Clinical profiles of Chinese patients with diffuse panbronchiolitis

Kenneth W T Tsang, Clara G C Ooi, Mary S M Ip, Wah-kit Lam, Henry Ngan, Eric Y T Chan, Brian Hawkins, Chu-shak Ho, Ryoichi Amitani, Eisaku Tanaka, Harumi Itoh

Abstract

Background—Diffuse panbronchiolitis (DPB), characterised by progressive sinusobronchial sepsis, is well characterised in Japanese subjects but not in other ethnic groups. The experience with DPB in seven Chinese patients is described and the clinical profiles compared with those of Japanese subjects.

Methods—Seven Chinese patients (three women; mean (SD) age 48 (18.6) years, all never smokers) who attended a teaching hospital centre and fulfilled the diagnostic criteria for DPB were assessed prospectively for clinical, radiological, lung function, microbiological, and other “characteristic” laboratory parameters.

Results—Lung function assessment showed a typical obstructive pattern (n = 5) and air trapping (n = 7). Typical bronchiolar infiltration by lymphocytes and plasma cells and accumulation of foamy macrophages in the intraluminal tissue were detected in open lung biopsy specimens (n = 2). Chest radiographs and high resolution computed tomographic scans revealed hyperinflation, diffuse nodules, bronchial thickening and dilatation, peripheral hypoattenuation, and bronchiolectasis. Radiological improvement, manifest as a reduction in nodular density and bronchial thickening, and persistence of other abnormalities such as air trapping were not accurately depicted by the classical Nakata or Akira classifications. The other “characteristic” features such as HLA-B54, IgG subclass deficiency, raised CD4/CD8 T lymphocyte ratio, cold haemagglutinaemia, raised IgA, IgG, and rheumatoid factor were not present. Treatment with erythromycin led to excellent responses in symptoms, lung function indices, and the radiological picture. A review of the non-Japanese cases in the literature reveals that this absence of typical “additional features” in DPB might also be applicable to non-Japanese patients.

Conclusions—We report the only series of non-Japanese Mongoloid patients with well characterised DPB who had uncharacteristic investigation profiles. This experience should help other clinicians in the investigation and management of DPB in non-Japanese patients.

(Thorax 1998;53:274–280)

Keywords: diffuse panbronchiolitis; chronic bronchial sepsis; macrolides; Chinese

Diffuse panbronchiolitis (DPB) is a relatively newly recognised idiopathic chronic progressive suppurative airways disease originally described in Japan on necropsy cases. It typically presents with wheezing, chronic bronchial sepsis, and often rapidly progresses to respiratory failure and death before the introduction of low dose erythromycin therapy. Pathologically, thickening of the bronchiolar wall due to infiltration by lymphocytes, plasma cells and histiocytes, and peribronchiolar accumulation of foamy macrophages occur. DPB is distinct from asthma, bronchiectasis, and chronic obstructive pulmonary disease pathologically and radiologically although some of the clinical symptoms can overlap.

Although DPB is not an uncommon disease amongst Japanese subjects, only sporadic cases have been reported in Caucasians, Koreans, Indians, black subjects, and Hispanics. HLA-B54 is found in 63.2% of Japanese patients with DPB (relative risk 13.3) and has been reported in a widely quoted study to be prevalent in 10.4% of Chinese subjects. This suggests that the Chinese might also be susceptible to developing DPB. However, there has been no systematic study on DPB in Chinese subjects in whom it is still rarely reported and poorly defined. Under-recognition of this condition, which mimics primary ciliary dyskinesia, bronchiectasis, and cystic fibrosis, has serious consequences as DPB is highly responsive to treatment with low doses of erythromycin but is fatal if untreated.

Although firmly established, the diagnostic criteria for DPB were constructed according to the characteristics of Japanese patients and have not been validated for other ethnic groups. We therefore report our experience with DPB in seven well characterised Chinese patients and compare the clinical profiles of our patients with those of the Japanese.

Methods

PATIENT POPULATION

Between October 1994 and October 1996 seven patients (pure southern Chinese) were diagnosed to have DPB at the Department of Medicine, University of Hong Kong. Diagnosis was made according to established diagnostic criteria and after consultation with clinicians and radiologists experienced in DPB. An informal survey through the clinical practice of
Table 1  Diagnostic criteria for diffuse panbronchiolitis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung symptoms</td>
<td>Nocturnal cough, persistent productive cough, recurrent wheezing, dyspnoea on exertion and hypoxaemia</td>
</tr>
<tr>
<td>CXR</td>
<td>Baseline hypoxia, partly or completely occluded, ill-defined nodules in the periphery, bronchiectasis and broncho-pulmonary cysts.</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>Endobronchial thickening of the terminal respiratory bronchioles, with alveolar or bronchiolar epithelial hyperplasia.</td>
</tr>
<tr>
<td>Bronchial biopsy</td>
<td>Transbronchial or open-lung biopsy with histological findings of panbronchiolitis</td>
</tr>
</tbody>
</table>

Table 2  Characteristics of patients at presentation

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age at onset (years)</th>
<th>Age at assessment (years)</th>
<th>No. of months on treatment</th>
<th>Nasal symptoms (years)</th>
<th>Sputum pathogen</th>
<th>Physical examination</th>
<th>Histologic examination</th>
<th>HLAtyping</th>
<th>IgG against Cold hemagglutinin</th>
<th>CD4/CD8 ratio (0.63–3.24)*</th>
<th>Serum IgA (90–450 mg/dl)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(M)</td>
<td>54</td>
<td>15</td>
<td>15</td>
<td>30</td>
<td>H influenzae</td>
<td>Wheeze</td>
<td>TBB+OLB</td>
<td>A24, A11, B27,</td>
<td>Negative</td>
<td>1.2</td>
<td>268</td>
</tr>
<tr>
<td>2(M)</td>
<td>57</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>P aeruginosa</td>
<td>Wheeze</td>
<td>Nil</td>
<td>A2, A33, B17,</td>
<td>Positive</td>
<td>1.4</td>
<td>224</td>
</tr>
<tr>
<td>3(F)</td>
<td>30</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>H influenzae</td>
<td>Wheeze/crackles</td>
<td>TBB</td>
<td>B27, DR12, DR9, DR16</td>
<td>Negative</td>
<td>1.5</td>
<td>614</td>
</tr>
<tr>
<td>4(M)</td>
<td>32</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>P aeruginosa</td>
<td>Wheeze/crackles</td>
<td>TBB</td>
<td>B5, DR9, DR12, DR3, DR6, DR8</td>
<td>Positive</td>
<td>1.6</td>
<td>420</td>
</tr>
<tr>
<td>5(M)</td>
<td>60</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>H influenzae</td>
<td>Wheeze/crackles</td>
<td>TBB</td>
<td>B5, DR9, DR12, DR3, DR6, DR8</td>
<td>Negative</td>
<td>1.7</td>
<td>368</td>
</tr>
<tr>
<td>6(F)</td>
<td>63</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>P aeruginosa</td>
<td>Wheeze/crackles</td>
<td>TBB</td>
<td>B5, DR9, DR12, DR3, DR6, DR8</td>
<td>Negative</td>
<td>1.8</td>
<td>365</td>
</tr>
<tr>
<td>7(F)</td>
<td>72</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>H influenzae</td>
<td>Wheeze/crackles</td>
<td>TBB</td>
<td>B5, DR9, DR12, DR3, DR6, DR8</td>
<td>Negative</td>
<td>1.9</td>
<td>465</td>
</tr>
</tbody>
</table>

No. of months on treatment refers to duration since onset of symptoms. Nasal symptoms include rhinorrhea, sneezing, and postnasal drip. Sputum pathogen includes bacteria and fungi. Physical examination includes wheezes, crackles, and rhonchi. Histologic examination includes transbronchial and open-lung biopsies. HLAtyping includes HLA-A, -B, and -C. IgG against Cold hemagglutinin refers to presence or absence of antibody. CD4/CD8 ratio is measured in lymphocyte subsets. Serum IgA concentration is measured in milligrams per deciliter.

*Normal range for data.

**Notes:**
- **CD4/CD8 ratio:** The CD4/CD8 ratio is a measure of the balance between CD4+ and CD8+ T lymphocytes. A ratio above 1.5 is considered within normal limits. Ratios below 0.63 or above 3.24 are considered abnormal.

Investigative Profiles

Lung function indices were measured using a Sensor-Medics 2200 Lung Function package and standard protocol as per routine clinical practice. Nasal mucosa was obtained from the inferior turbinate of subjects with a cytology brush (without anaesthetic) and resuspended in medium 199 (Flow Laboratory, Paisley, Scotland, UK) before examination of ciliary movement and beat frequency with a Leica DM LB phase contrast microscope (Leica, Wetzlar, Germany) and a MPV-COMBI (Leica, Wetzlar, Germany) photomultiplier system as described previously. Ciliated epithelium was fixed in 2.5% glutaraldehyde (in osmium tetroxide buffer) and embedded in araldite for ultrastructural examination by a trained electron microscope technician. Evaluation of routine haematological indices and renal and liver biochemical profiles; serum immunoglobulin (IgG, IgA, and IgM) autoantibody titres (for rheumatoid factor, antinuclear factor, and IgG against Ro, La, Jo1, mitochondrial, and smooth muscle); arterial blood gases; serum IgG subclasses; lymphocyte subset analysis; α1-antitrypsin level; viral titres (measles, mumps, influenza, parainfluenza, respiratory syncytial, adenovirus, rotavirus, and enterovirus); blood CD4/CD8 lymphocyte ratio; IgG against *Pseudomonas*
Table 3  Investigation profiles at presentation and re-assessment

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood leucocyte count (x10^9/ml)</td>
<td>11.7 (11.8)</td>
<td>7.6 (6.5)</td>
<td>8.3 (7.2)</td>
<td>9.6 (7.0)</td>
<td>13.9 (9.1)</td>
<td>6.1 (6.4)</td>
<td>9.0 (5.8)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>12 (20)</td>
<td>37 (22)</td>
<td>63 (54)</td>
<td>86 (3)</td>
<td>45 (32)</td>
<td>48 (6)</td>
<td>26 (39)</td>
</tr>
<tr>
<td>C reactive protein (&lt;1 mg/dl)</td>
<td>&lt;0.3 (&lt;0.3)</td>
<td>1.0 (&lt;0.3)</td>
<td>6.4 (&lt;0.3)</td>
<td>6.4 (&lt;0.3)</td>
<td>&lt;0.3 (&lt;0.3)</td>
<td>&lt;0.3 (&lt;0.3)</td>
<td></td>
</tr>
<tr>
<td>Auto-antibodies</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Complement 3 and 4</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>24 hour sputum production (ml/24 h)</td>
<td>60 (20)</td>
<td>30 (0)</td>
<td>10 (0)</td>
<td>20 (0)</td>
<td>30 (20)</td>
<td>20 (5)</td>
<td>100 (50)</td>
</tr>
<tr>
<td>FEV1 (%predicted)</td>
<td>23 (47)</td>
<td>84 (142)</td>
<td>41 (64)</td>
<td>57 (98)</td>
<td>22 (25)</td>
<td>53 (54)</td>
<td>44 (86)</td>
</tr>
<tr>
<td>FVC (%predicted)</td>
<td>61 (92)</td>
<td>95 (143)</td>
<td>52 (85)</td>
<td>67 (114)</td>
<td>35 (42)</td>
<td>45 (109)</td>
<td>101 (87)</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>29 (39)</td>
<td>74 (83)</td>
<td>69 (77)</td>
<td>63 (63)</td>
<td>47 (60)</td>
<td>80 (44)</td>
<td>38 (71)</td>
</tr>
<tr>
<td>RV (%) predicted</td>
<td>212 (180)</td>
<td>147 (116)</td>
<td>167 (131)</td>
<td>270 (164)</td>
<td>101 (90)</td>
<td>144 (156)</td>
<td>164 (185)</td>
</tr>
<tr>
<td>VC (%) predicted</td>
<td>64 (76)</td>
<td>93 (140)</td>
<td>66 (110)</td>
<td>70 (119)</td>
<td>37 (55)</td>
<td>39 (97)</td>
<td>96 (70)</td>
</tr>
<tr>
<td>RV/LTC</td>
<td>58 (48)</td>
<td>38 (24)</td>
<td>57 (36)</td>
<td>64 (37)</td>
<td>57 (55)</td>
<td>62 (42)</td>
<td>56 (55)</td>
</tr>
<tr>
<td>Kco (%predicted)</td>
<td>84 (101)</td>
<td>101 (82)</td>
<td>105 (106)</td>
<td>111 (90)</td>
<td>101 (100)</td>
<td>98 (138)</td>
<td>140 (138)</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>8.3 (10.2)</td>
<td>12 (11.4)</td>
<td>9.3 (10.3)</td>
<td>8.2 (10.5)</td>
<td>8.0 (9.8)</td>
<td>8.1 (10.0)</td>
<td>9.0 (11.0)</td>
</tr>
<tr>
<td>PaO2 (kPa)*</td>
<td>23 III (III)</td>
<td>II (II)</td>
<td>III (III)</td>
<td>IV (II)</td>
<td>IV (IV)</td>
<td>III (III)</td>
<td>II (II)</td>
</tr>
<tr>
<td>Nakata radiographic grading</td>
<td>3 (0.3)</td>
<td>1.8 (0.8)</td>
<td>2 (1.7)</td>
<td>2.3 (1.3)</td>
<td>2.3 (2)</td>
<td>2.7 (1.4)</td>
<td>1.7 (1.2)</td>
</tr>
<tr>
<td>Akira HRCT grading</td>
<td>2 (22)</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>4 (4)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Nodular profusion, overall score</td>
<td>2 (0.7)</td>
<td>1.8 (0.8)</td>
<td>2 (1.7)</td>
<td>2.3 (1.3)</td>
<td>2.3 (2)</td>
<td>2.7 (1.4)</td>
<td>1.7 (1.2)</td>
</tr>
<tr>
<td>Nodular symmetry</td>
<td>Asymmetrical</td>
<td>Asymmetrical</td>
<td>Symmetrical</td>
<td>Symmetrical</td>
<td>Symmetrical</td>
<td>Symmetrical</td>
<td>Symmetrical</td>
</tr>
<tr>
<td>Nodular distribution</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Airway dilatation, overall score</td>
<td>1.5 (1.8)</td>
<td>1.0 (0.8)</td>
<td>1.1 (0.8)</td>
<td>0.8 (0.3)</td>
<td>2.0 (2.0)</td>
<td>1.6 (1.0)</td>
<td>0.7 (0.7)</td>
</tr>
<tr>
<td>Airway thickening</td>
<td>1.5 (1.3)</td>
<td>1.0 (0.8)</td>
<td>1.3 (0.7)</td>
<td>0.7 (0.3)</td>
<td>1.3 (1.3)</td>
<td>2.0 (0.4)</td>
<td>1.7 (1.3)</td>
</tr>
<tr>
<td>Hypoattenuation, overall score</td>
<td>2 (3)</td>
<td>0.2 (0.2)</td>
<td>0.8 (1.2)</td>
<td>0.2 (0.2)</td>
<td>1.7 (2.7)</td>
<td>1.7 (2.6)</td>
<td>1.0 (1.0)</td>
</tr>
<tr>
<td>Air trapping,* overall score</td>
<td>1.9 (5.5)</td>
<td>1.3 (1.1)</td>
<td>1.6 (1.2)</td>
<td>1.0 (1.0)</td>
<td>1.7 (2.6)</td>
<td>1.7 (2.6)</td>
<td>1.0 (1.0)</td>
</tr>
</tbody>
</table>

Data shown are measurements made at presentation and re-assessment (in parentheses).  
*Normal range for arterial blood gases when breathing room air 10.6–14 kPa.  
†Assessment made at expiratory HRCT scanning of the thorax.  
**Assessment made at inspiratory HRCT scanning of the thorax.  
NP=not performed.  
Please refer to text for the scoring systems.

Table 4  Radiological assessment at presentation and re-assessment

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakata radiographic grading</td>
<td>III (III)</td>
<td>II (II)</td>
<td>III (III)</td>
<td>IV (II)</td>
<td>IV (IV)</td>
<td>III (III)</td>
<td>II (II)</td>
</tr>
<tr>
<td>Akira HRCT grading</td>
<td>3 (4)</td>
<td>3 (2)</td>
<td>3 (3)</td>
<td>3 (2)</td>
<td>4 (4)</td>
<td>2 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Nodular profusion, overall score</td>
<td>2 (0.7)</td>
<td>1.8 (0.8)</td>
<td>2 (1.7)</td>
<td>2.3 (1.3)</td>
<td>2.3 (2)</td>
<td>2.7 (1.4)</td>
<td>1.7 (1.2)</td>
</tr>
<tr>
<td>Nodular symmetry</td>
<td>Asymmetrical</td>
<td>Asymmetrical</td>
<td>Symmetrical</td>
<td>Symmetrical</td>
<td>Symmetrical</td>
<td>Symmetrical</td>
<td>Symmetrical</td>
</tr>
<tr>
<td>Nodular distribution</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Airway dilatation, overall score</td>
<td>1.5 (1.8)</td>
<td>1.0 (0.8)</td>
<td>1.1 (0.8)</td>
<td>0.8 (0.3)</td>
<td>2.0 (2.0)</td>
<td>1.6 (1.0)</td>
<td>0.7 (0.7)</td>
</tr>
<tr>
<td>Airway thickening</td>
<td>1.5 (1.3)</td>
<td>1.0 (0.8)</td>
<td>1.3 (0.7)</td>
<td>0.7 (0.3)</td>
<td>1.3 (1.3)</td>
<td>2.0 (0.4)</td>
<td>1.7 (1.3)</td>
</tr>
<tr>
<td>Hypoattenuation, overall score</td>
<td>2 (3)</td>
<td>0.2 (0.2)</td>
<td>0.8 (1.2)</td>
<td>0.2 (0.2)</td>
<td>1.7 (2.7)</td>
<td>1.7 (2.6)</td>
<td>1.0 (1.0)</td>
</tr>
<tr>
<td>Air trapping,* overall score</td>
<td>1.9 (5.5)</td>
<td>1.3 (1.1)</td>
<td>1.6 (1.2)</td>
<td>1.0 (1.0)</td>
<td>1.7 (2.6)</td>
<td>1.7 (2.6)</td>
<td>1.0 (1.0)</td>
</tr>
</tbody>
</table>

Data shown are measurements made at presentation and re-assessment (in parentheses).  
*Assessment made at inspiratory HRCT scanning of the thorax.  
NP=not performed.  
Please refer to text for the scoring systems.
of these features an overall score was obtained by dividing the sum of the scores from all lung zones by six.

Chest radiographs corresponding in time to the HRCT scans were graded from types I to V as described by Nakata et al. Types I, II, III, IV, and V were assigned when there was overinflation without nodular shadows, disseminated small nodular shadows confined to one lung, small nodular shadows in both lungs, ring-shaped or tramline shadows in the lower lungs with nodular shadows, and large ring-shaped and nodular shadows, respectively.

Results

DEMOGRAPHIC DATA

The mean (SD) ages at onset of symptoms and at initial assessment were 48 (18.6) and 50 (17.8) years. None of the seven patients (three women) had ever smoked cigarettes and they received treatment with erythromycin (250 mg twice daily) for 8.6 (9.4) months before re-assessment. Three patients had travelled to Japan 15, 11, and 10 years before the onset of symptoms (table 2).

CLINICAL FEATURES

Six patients had had nasal symptoms (obstruction and rhinorrhoea) for a mean of 22.5 (15.1) years. All seven patients presented with copious purulent sputum production (38.6 (31.2) ml/24 hours), cough, and dyspnoea on exertion. At the initial assessment six patients were found to have wheezes and five had crackles in their chest on physical examination. After 8.6 (9.4) months of treatment with erythromycin the presenting symptoms of dyspnoea on exertion, cough, sputum production, and nasal symptoms improved in all seven patients. The mean sputum volume reduced to 13.6 (18.4) ml/24 hours and patients 2, 3, and 4 had no further sputum production at re-assessment (table 3). Examination of the chest revealed no further wheezing in five and persistence of crackles in five patients.

INVESTIGATION PROFILES

All the patients underwent the investigation profiles listed above and repeated measurements were made on some selected parameters as shown in table 3. At initial presentation the mean (SD) forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), residual volume (RV), vital capacity (VC), carbon monoxide transfer coefficient (Kco), and arterial oxygen tension (Pao₂) were 46.3 (21.4)%, 65.1 (24.8)%, 172.1 (54.4)%, 66.4 (23.2)%, 105.7 (17.2)%, and 9.0 (1.4) kPa, respectively, which changed to 73.7 (38.7)%, 95.7 (31.3)%, 146 (35.0)%, 95.3 (30.0)%, 107.9 (22.1)%, and 10.5 (0.6) kPa after erythromycin therapy. Tests for ciliary beat movement and frequency, ciliary ultrastructure, HLA typing, α₁-antitrypsin, viral titres, IgG against P pseudomallei, L pneumophilia, C psittaci, M pneumoniae, and HTLV-1, Aspergillus precipitins, complements 3 and 4, and routine haematological and biochemical indices were negative or normal at initial presentation. Serum IgA and IgG3 levels were persistently raised in two and three patients, respectively, although the levels of other immunoglobulins were normal. Antinuclear factor was positive in six patients and anti-smooth muscle in two, while anti-dsDNA, anti-extractable nuclear antigen, rheumatoid factor, and anti-mitochondrial antibodies were negative in all patients. ANCA (cytoplasmic) was positive in six patients, none of whom had anti-proteinase...
III antibody. Lymphocyte subset distribution was normal in three patients but the remaining four displayed an increase in CD4 T cells, a decrease in CD3 T cells, an increase in CD3 and CD8 T cells, and a decrease in CD3 and CD8 T cells, respectively. The CD4/CD8 ratio was raised in two patients, reduced in one, and normal in four patients.

*P. aeruginosa* was isolated from the sputum of two patients and *Haemophilus influenzae* from three patients at initial presentation. The remaining case had no identifiable pathogen in her sputum. The sputum of patient 6 yielded only *Mycobacterium tuberculosis* on culture (negative Ziehl-Neelsen staining), although repeated bronchoscopic, bronchial and transbronchial biopsies and bronchoalveolar lavage had not yielded any other evidence of tuberculous infection (endobronchial and parenchymal). In addition, a two month supervised course of rifampicin, isoniazid, ethambutol, and pyrazinamide did not alter her symptoms or produce any improvement in lung function or radiology (HRCT and plain radiography). This was followed by open lung biopsy which confirmed the diagnosis of DPB.

**RADIological ASSESSMENT**

At the initial assessment nodular distribution with lower lobe predominance was bilateral and diffuse in all except two cases, in whom it was asymmetrical (table 4). After treatment with erythromycin there was an overall improvement in both bronchial thickening and dilatation, but not in hypoattenuation of the peripheral areas. Air trapping was confirmed on expiratory scans in only two cases at initial presentation and in all seven cases after erythromycin treatment. The serial Akira and Nakata classifications remained unchanged in four and six patients, respectively, and did not appear to reflect the reduction in nodular perfusion which was the most significant response to treatment (figs 1 and 2).

**Discussion**

All our patients presented with typical chronic sinobronchial sepsis and most had persistence of *P. aeruginosa* or *H. influenzae* in their sputum, characteristic radiological features, and excellent clinical and radiological response to macrolide therapy (tables 1–4). However, our cases differ from the Japanese patients (table 1) in several respects, primarily the absence of HLA-B54 type. The Chinese patient mentioned briefly by Iwata et al did not possess HLA-B54 but shared a common feature with most of our patients in possessing HLA-A2.4 The 10% prevalence of HLA-54 in Chinese subjects quoted in the literature14 does not agree with our finding of a prevalence of 3% in patients from southern China.23 If HLA-B54 has a pathological role in DBP, then this low incidence of HLA-54 would explain the relative scarcity of DBP in the Chinese population, in addition to the probable underdiagnosis and reporting. Five of the seven patients in this series had HLA-DR9 compared with 29.2% in the normal population in Hong Kong. Although the number of patients tested is small, our preliminary results suggest that future patients should also be tested for HLA-DR9 and HLA-A2. Two of our patients also had HLA-B55, which has also been reported to be increased in a Japanese study.14

Three of our cases had raised IgG4 levels but IgG levels were normal, whereas 30.8% of Japanese patients were reported to have IgG4 deficiency.25 The other “atypical” features include normal or low CD4/CD8 lymphocyte ratio in five patients, absence of raised serum IgA in five, and absence of raised serum IgG, cold haemagglutinin and rheumatoid factor in seven patients.2 A review of the cases in the literature of DBP in non-Japanese subjects revealed a total of 19 Mongoloid (14 Chinese and five Koreans) and 13 non-Mongoloid cases who generally had not been systematically evaluated.4 8 10 11 12 15 16–18 27 Of these, HLA-B54 was detected in only two cases in the former and either not checked or not detected in the latter group. In addition, raised levels of cold haemagglutinin were found in two Hispanic patients but not in the rest of the aforementioned 32 cases.6 13 The other investigation profiles that were considered to be characteristic and helpful in the diagnosis (table 1), including CD4/CD8 lymphocyte ratio, serum IgA level, IgG subclass analysis, and *M. pneumoniae* serology, were not evaluated in these non-Japanese patients. Our results suggest that these “additional” features (table 1) might not be applicable in the diagnosis of DBP in non-Japanese patients. The finding of a positive ANCA in six of our patients is also interesting and needs confirmation by other workers, as this has not been reported previously in DBP.

The value of HRCT scans in assessing small airways disease in DBP is clear and is substantiated by a pathological-radiological correlation.24 25 29 This experience, however, is limited to Japan, largely due to the relative confinement of DBP to that country. Peripheral areas of hypoattenuation on HRCT scanning26–28 are a non-specific indicator of air trapping and reflect an underlying hyperinflation caused by narrowing of the small airways.29 In the only other series of patients with DBP followed up by HRCT scanning after treatment with erythromycin there was an improvement in nodular perfusion but not airway dilatation and peripheral hypoattenuation.30 In contrast, our findings suggest that there was partial reversibility in bronchiolar dilatation in our patients, although no corresponding improvement in the peripheral areas of hypoattenuation was evident. This might be due to selective and more severe injury to the peripheral airways resulting in sustained distal air trapping, whilst the less affected central larger airways recovered with erythromycin treatment. However, in agreement with Akira et al,10 there was a universal reduction in nodular perfusion in all our patients after erythromycin treatment. This important feature in the radiological follow up of these patients, which appears to parallel the improvement in lung function and clinical improvement, could not be accurately represented in the Nakata...
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Our study also highlights the relative insensitivity of plain radiography compared with HRCT scanning in assessing disease activity, particularly in small airway pathology. The usefulness of the Nakata radiographic and Akira HRCT classifications in this study therefore appears to be limited.

As with Japanese patients, our patients responded very well in terms of lung function indices, blood oxygenation, symptomatic relief, sputum production, and radiological evaluation to low dose, long term treatment with erythromycin.7 Whilst the efficacy of macrolides in treating DPB is well established, the mechanism(s) is still largely unknown. One possible mechanism is the reduction of pulmonary levels of interleukin 8 and leukotriene B4, which are potent chemotactic agents.8 9 This leads to a reduction in neutrophil influx into the airways and alveolar space10 which is known to cause airway destruction in chronic bronchial sepsis by various processes such as the release of human neutrophil elastase.11 12 It is also possible that erythromycin interferes with the formation of Pseudomonas biofilms which are important in its persistence in the airways.13 14 Until the precise mechanism is known, more specifically targeted treatment cannot be planned other than empirical treatment with macrolides.15 There appears to be a “class effect” in that most of the available macrolides including erythromycin, clarithromycin, roxithromycin, and azithromycin, are efficacious in DPB.16 For resistant cases recent in vitro and clinical evidence suggests that inhalation of indomethacin and oxitriptol bromide might be effective in reducing sputum production.17

Interestingly, three of our patients had travelled to Japan prior to the onset of symptoms, similar to the Hispanic man who developed DPB after extensive travels to Japan and South East Asia.18 However, the long interval between the journey to Japan and the onset of symptoms makes an aetiological link very unlikely in our patients. As in the cases in the Japanese literature, there was no identifiable aetiology for the onset of chronic bronchial sepsis or DPB in our patients. Our investigations have also effectively excluded all the known differential diagnoses for DPB including primary ciliary dyskinesia, bronchiectasis, chronic bronchitis and emphysema, bronchiolitis obliterans, cystic fibrosis (not known to occur in Chinese), Wegener’s granulomatosis, malignant lymphoma, and bare lymphocyte syndrome.4

Whilst we have demonstrated characteristic features of DPB in all our cases, only four patients were examined histologically for features of DPB. Open lung biopsy specimens of patients who fulfilled the clinical diagnostic criteria for DPB might very occasionally show unclassified bronchiolitis and bronchiolectasis.19 However, in most instances the pathological changes in DPB correlate well with HRCT features20 and HRCT scanning is advocated and frequently used as the diagnostic tool in this condition,21 especially in Japan where clinicians and radiologists have considerable relevant experience. In practice, most patients with DPB in Japan are routinely diagnosed using high quality thoracic HRCT scans. The clinical and radiological response to erythromycin also gives very good circumstantial evidence to support the diagnosis of DPB.

We have reported seven cases of DPB who, despite typical clinical features, appear to have different investigation profiles from their Japanese counterparts. More experience needs to be gathered on non-Japanese patients to evaluate further the clinical characteristics of this macrolide responsive but otherwise progressive idiopathic pulmonary disease.

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