Diffuse panbronchiolitis in rheumatoid arthritis


ABSTRACT: The association of progressive obliterative bronchiolitis (OB) with rheumatoid arthritis (RA) is uncommon but has been reported previously. Diffuse panbronchiolitis (DPB) is a unique inflammation principally affecting the respiratory bronchioles and has been reported mainly in Japanese adults. Recently, DPB has also been noted in patients with RA in Japan. Therefore, there might be considerable overlap in clinical features between DPB and OB associated with RA in Japan. The aim of this study was to evaluate the clinicopathological characteristics of bronchioli-tis in patients with RA.

Three RA patients clinically diagnosed as having DPB were evaluated. All patients underwent chest radiographs, pulmonary function tests (PFT) and post mortem examination. Clinical features in all patients were a history of productive cough, exertional dyspnoea, wheezing and/or coarse crackles. Chest radiographs showed small nodular shadows up to 2 mm in diameter with bronchiectasis throughout both lungs in all patients. The PFT revealed marked obstructive impairment in all patients. All patients died of progressive respiratory failure. Pathologically, two out of the three cases were confirmed as DPB, while the remaining one case was confirmed as OB, because the primary obstructive lesions were in the respiratory bronchioles in the former and in the membranous bronchioles and the proximal small bronchi in the latter. Thus, the clinical features of DPB and OB were strikingly similar, but the histopathological features revealed distinct differences.

This study demonstrated that there was considerable overlap in clinical features between diffuse panbronchiolitis and obliterative bronchiolitis associated with rheumatoid arthritis, suggesting that diffuse panbronchiolitis might be a new manifestation of rheumatoid arthritis. The differentiation of these two disease entities is significant in making decisions on their therapeutic modality and is possible by analysing the precise histopathological findings of the lung.


The pulmonary manifestations of rheumatoid arthritis (RA), including pleuritis, rheumatic nodules, pneumonitis and vasculitis [1], are well known. However, progressive airway obliteration related to obliterative bronchiolitis (OB) with a concentric narrowing of the lumina of the membranous bronchioles producing fatal obstructive lung disease is uncommon and has been noted in a small number of patients with RA, mainly female patients in Europe [2, 3] and America [4]. In contrast, diffuse panbronchiolitis (DPB), a disease primarily affecting the respiratory bronchiole and causing a severe obstructive respiratory disorder, has been reported mainly in Japan [5–7]. Recently, the first autopsy case of DPB accompanying RA has been recognized in Japan [8], suggesting that DPB may be another manifestation of RA. There may be considerable overlap between DPB and OB associated with RA in Japan, but only little is known about the nature and evolution of these airway diseases [9]. In fact, one of the three cases after autopsy in the present study turned out to be OB after histopathological examination. The aim of this study was to clarify the clinicopathological characteristics of bronchiolitis in patients with RA.

Subjects and methods

Between May 1977 and November 1996, six patients (four males and two females) with RA were clinically diagnosed as having DPB. Three out of these six patients underwent post mortem examination. These three cases are presented and the association of DPB and OB with RA is discussed. DPB was diagnosed using the clinical diagnostic criteria established with the aid of the Ministry of Health and Welfare of Japan [10]: 1) cough, sputum and shortness of breath on exertion; 2) moist and dry rales on the chest; 3) chest radiographic findings of diffuse scattered granular shadows in bilateral lung fields and hyperinflation [11]; and 4) pulmonary function tests of diminution in forced expiratory volume in one second (FEV1)% (below 70%), diminution of vital capacity (below 80% of predicted value), increase in residual air above 150% of predicted value and hypoxaemia (below 10.6 kPa (80 mmHg)). To establish the diagnosis, at least three of these criteria must be met. Additional features such as chronic parainfluenza, elevation of cold haemagglutinin titre, CD4/CD8 ratio, immunoglobulin (Ig)A and proof of human
leukocyte antigen (HLA)-B54 antigen are frequently present. Such clinical findings can be used in making the diagnosis of DPB. Histological studies, when possible, can confirm the diagnosis. Chronic bronchitis, bronchial asthma and chronic emphysema should be carefully ruled out. RA was diagnosed based on the revised criteria of the American Rheumatism Association in 1987 [12]. The new criteria are as follows: 1) morning stiffness in and around joints lasting for at least 1 h before maximal improvement; 2) soft tissue swelling (arthritis) of three or more joint areas observed by a physician; 3) swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal or wrist joints; 4) symmetric swelling (arthritis); 5) rheumatoid nodules; 6) the presence of rheumatoid factor; and 7) radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints. RA is defined by the presence of four or more of these criteria.

Radiography

Chest radiographs and/or chest computed tomographic (CT) images before treatment were evaluated.

Pulmonary function tests

Lung volume, FEV1, maximal midexpiratory flow and blood gas studies were carried out according to standard methods. 

Morphological analysis

All the patients underwent post mortem examination and one patient also underwent transbronchial lung biopsy performed as an initial diagnostic procedure. At autopsy, the lungs were inflated with a fixative (10% formaldehyde) at 30 cmH2O via a tracheal cannula. After fixation for 48 h, 5 mm serial sections along each bronchus were obtained from all segments of both lungs for the reconstruction studies of the primary obstructive lesions of the bronchioli. Tissue samples were embedded in paraffin, from which 3 µm thick sections were cut and stained with haematoxylin-eosin (H&E) and Elastica van Gieson. Sections were mounted in aqueous mounting medium and observed by light microscopy to determine the characteristics of bronchiolitis.

Clinical findings, radiographic images, results of pulmonary function tests and pathological findings were analysed and compared according to the diagnosis of DPB associated with RA.

Table 1. – Clinical features (1)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age yrs</th>
<th>Sex</th>
<th>Clinical diagnosis</th>
<th>Pathological diagnosis</th>
<th>Respiratory symptoms</th>
<th>RA to respiratory symptoms yrs</th>
<th>Respiratory symptoms to death yrs</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>F</td>
<td>DPB (RA)</td>
<td>DPB (RA)</td>
<td>Cough</td>
<td>-12</td>
<td>30</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>M</td>
<td>DPB (RA)</td>
<td>DPB (RA)</td>
<td>Sputum</td>
<td>0</td>
<td>4</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>F</td>
<td>DPB (RA)</td>
<td>OB (RA)</td>
<td>Cough</td>
<td>13</td>
<td>6</td>
<td>Respiratory and renal failure</td>
</tr>
</tbody>
</table>

Table 2. – Clinical features (2)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>SI</th>
<th>Dust</th>
<th>Chronic paranasinusitis</th>
<th>CHA</th>
<th>Sputum g·day⁻¹¹</th>
<th>Sputum culture</th>
<th>Treatment</th>
<th>HLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>-</td>
<td>(+)</td>
<td></td>
<td>512</td>
<td>H. influenzae</td>
<td>Steroid</td>
<td>B54</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>-</td>
<td>(-)</td>
<td></td>
<td>512</td>
<td>P. aeruginosa</td>
<td>Gold</td>
<td>NE</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>-</td>
<td>(+)</td>
<td></td>
<td>2048</td>
<td>P. aeruginosa</td>
<td>Penicillin</td>
<td>NE</td>
</tr>
</tbody>
</table>

SI: smoking index; CHA: cold haemagglutinin; HLA: human leukocyte antigen; DPB: diffuse panbronchiolitis; RA: rheumatoid arthritis; OB: obliterative bronchiolitis; H. influenzae: Haemophilus influenzae; P. aeruginosa: Pseudomonas aeruginosa; NE: not examined.

Results

Clinical findings

The clinical features of the two patients with DPB and one patient with OB (one male and two females; mean age 62.3±2.3 yrs) in association with RA are shown in tables 1 and 2. The duration between the onset of RA symptoms and respiratory symptoms was 0–13 yrs in two cases and respiratory symptoms preceded RA symptoms in one case (case 1). All patients died of progressive respiratory failure within 4–30 yrs after the onset of respiratory symptoms. There was no close relationship with smoking or inhalation of toxic dust. Chronic paranasinusitis was diagnosed in two out of three patients. Initial respiratory symptoms were cough and tenacious sputum in all patients.

Table 3. – Chest radiographic findings

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Small nodular shadows</th>
<th>Tramlines</th>
<th>Bronchiolitis</th>
<th>Hyperinflation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (DPB with RA)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2 (DPB with RA)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3 (OB with RA)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

DPB: diffuse panbronchiolitis; RA: rheumatoid arthritis; OB: obliterative bronchiolitis.
The mean amount of sputum production was as large as 107 g·day⁻¹. Physical signs of wheezing and/or coarse crackles were auscultated on the chest in all patients. *Haemophilus influenzae* or *Pseudomonas aeruginosa* superinfection appeared in the sputum of all patients. Elevated cold haemagglutinin titre by more than 512-fold was observed in all three patients. Corticosteroid or gold therapy for RA was applied in all patients and penicillamine therapy was applied in one patient.

**Radiography**

Chest radiographic and/or CT images showed small nodular shadows up to 5 mm in diameter with tram lines and bronchiolectasis throughout both lungs in all patients. The incidence of hyperinflation were found in two out of three patients (table 3).

**Pulmonary function tests**

Pulmonary function tests at the first visit revealed marked obstructive impairment, slight restrictive impairment and hypoxaemia in all patients (table 4).

**Pathological findings**

All three patients died of progressive respiratory failure within 4–30 yrs after the onset of respiratory symptoms and underwent post mortem examination. Post mortem examination of the lungs in two patients (cases 1 and 2) showed thickening of the walls of the respiratory bronchioles with infiltration of lymphocytes, plasma cells and histiocytes associated with secondary ectasis of the proximal terminal bronchioles. The lungs in the other patient (Case 3) showed obliteration and destruction of the membranous bronchioles by granulation tissues, but the distal respiratory bronchioles were spared. Therefore, two of the three patients with a clinical diagnosis of DPB (cases 1 and 2) were confirmed as having DPB while the third was found to have OB (case 3). The primary obstructive lesions were in the respiratory bronchioles in those confirmed to have DPB and in the membranous bronchioles and the proximal small bronchi in the patient with OB (table 5).
Case reports

Characteristic clinical and pathological features in the two patients who were finally diagnosed as having DPB and OB associated with RA are demonstrated.

Case 2. A 61 yr old woodworker visited our hospital because of dyspnoea on exertion, cough and sputum. There was no history of chronic parasinusitis, toxic fume inhalation or cigarette smoking. At the age of 57 yrs, the patient experienced generalized joint pains and was then diagnosed as having RA. The patient was admitted for the first time in 1982 because of progressive dyspnoea on exertion and was diagnosed as having DPB associated with RA, which was confirmed by transbronchial lung biopsy. In 1983, the patient was admitted for the second time because of progressive dyspnoea. Physical examination showed coarse crackles and wheezing in the bilateral lower lung fields. The clinical course of the patient with a duration of 4 yrs from the patient's first visit to death, is shown in figure 1. Pulmonary function tests revealed a marked mixed ventilatory impairment and early hypoxaemia, later accompanied by hypercapnia. Sputum culture revealed *H. influenzae* infection in the initial stage, later followed by *P. aeruginosa* superinfection. In spite of intensive treatment, including the administration of antibiotics and corticosteroids, oxygen inhalation and the use of a respirator, the patient died of refractory respiratory failure in 1985. Chest radiography on admission showed hyperlucency associated with tramlines and scattered fine nodular densities in both lung fields (fig. 2). On autopsy, the macroscopic appearance of the cut surface of the lung showed multiple fine, yellowish nodules in the centrilobular lesions up to 2–3 mm in diameter (arrows), representing respiratory bronchiolitis and peribronchiolitis associated with proximal bronchiectasis (fig. 3).
Microscopy at a low magnification showed that the lesion was exclusively limited to the area of the respiratory bronchioles accompanying proximal bronchiolectasis. The alveolar spaces were slightly overinflated, but without destruction (fig. 4). The appearance of the primary lesions under higher magnification showed thickening of the respiratory bronchioles by the infiltration of lymphocytes and plasma cells, accompanied by an accumulation of lipid-laden macrophages (foamy cells) (fig. 5). These lesions correspond to the fine, yellowish nodules observed macroscopically on the cut surface of the lung. A schematic reconstruction of the serial sections focusing on the primary lesions showed respiratory bronchiolitis and peribronchiolitis associated with ectasis of the proximal membranous bronchioles (fig. 6).

Clinical symptoms

- PFT: pulmonary function test
  - VC (%VC)
  - FEV1 (FEV1 %)
  - RV/TLC
  - Pao₂ (torr)
  - Paco₂ (torr)

- VC: vital capacity
- FEV1: forced expiratory volume in one second
- RV: residual volume
- TLC: total lung capacity
- Pao₂: arterial oxygen tension
- Paco₂: arterial carbon dioxide tension

- H. influenzae: Haemophilus influenzae
- P. aeruginosa: Pseudomonas aeruginosa

Treatment

- Gold
- Operation
- Corticosteroids
- Antibiotics
- Cefoperazone sodium
- Piperacillin sodium
- Cefsulosim sodium
- Cefuroxime sodium
- Doxycycline hydrochloride

Sputum culture: H. influenzae, P. aeruginosa

Sputum culture: 100 mL/day

Respirator: DOXY: doxycycline hydrochloride

1 torr: 0.133 kPa
Case 3. A 65 yr old nonsmoking female homemaker attended because of dyspnoea on exertion, cough and sputum. The patient had a history of chronic paranasalitis. Since the age of 46 yrs, the patient had had joint pains in the hands and was diagnosed as having RA in 1972. The patient underwent knee replacements in 1979, and was admitted to the hospital for the first time in 1982 because of a productive cough and was diagnosed as having DPB associated with RA. In 1983, the patient was admitted for the second time because of progressive dyspnoea. Physical examination showed coarse crackles in the bilateral lower lung fields and swelling of the hands with ulnar deviation. The clinical course of the patient, with a duration of 19 yrs from initial joint symptoms to death, is shown in figure 7. Pulmonary function tests revealed obstructive impairment with early hypoxaemia. Sputum culture revealed *H. influenzae* infection followed by *P. aeruginosa* super-infection. In spite of intensive treatment, the patient died of refractory respiratory failure in 1983, 6 yrs after the onset of respiratory symptoms. Chest radiography on admission showed hyperinflation associated with tramlines and scattered fine, nodular shadows in the both lung fields (fig. 8).
The highly magnified macroscopic appearance of the right upper lobe showed multiple white-yellowish nodules in the centrilobular lesion corresponding to the obliteration of the small bronchioles along the pulmonary arteries (fig. 9). The microscopic appearance under low magnification showed that the lesions were exclusively limited to the area of the membranous bronchioles associated with proximal bronchiolectasis, but the distal respiratory bronchioles were spared (fig. 10). The higher magnification revealed that the primary lesion obliterated the lumen of the membranous bronchiole and its wall was destroyed by granulation tissues with an accumulation of foamy cells (figs. 11 and 12). This corresponds to the fine, yellowish nodules observed macroscopically on the cut surface of the lung. The schematic reconstruction of the serial sections focusing on the primary lesions showed that the lumina of membranous bronchioles were obliterated by granulation tissues, but the distal respiratory bronchioles were spared and alveolar spaces were slightly overinflated (fig. 13). According to these pathological findings, this case was diagnosed as OB, instead of the DPB clinically diagnosed prior to death.

**Discussion**

**Pathogenesis of diffuse panbronchiolitis**

DPB is characterized by chronic inflammation localized mainly in the region of the respiratory bronchiole just distal to the terminal bronchiole, known as the transitional zone between the airway and the pulmonary parenchyma. This transitional zone features its own particular structure, respiratory mechanics, gas transport and defence mechanism. The lesions are characterized by respiratory bronchiolitis and peribronchiolitis, which are diffusely disseminated throughout both lungs, especially in the lower lobes. The existence of this disease, as distinguished from bronchial asthma, chronic bronchitis, chronic pulmonary emphysema, bronchiectasis or alveolitis, has been noted since 1969 in Japan [5]. More than 1,000 cases of probable DPB and 82 histologically confirmed cases have been reported in Japan [7]. DPB shows a predilection for males, typically in the fourth to fifth decades of life. At onset, affected patients present with subacute signs and symptoms of progressive airway obstruction.

The aetiology of DPB is as yet unknown. However, there have been increasing reports on cases of DPB observed in the same family [13, 14]. It is well known that there is a high incidence of chronic sinusitis affecting various members of the same family. Analysis of HLA in patients with DPB demonstrated that HLA-B54 was found more frequently in 38 DPB cases (63.2%) than in 184 healthy controls (11.4%) [15]. According to histocompatibility testing, HLA-B54 was found specifically in Japanese (14.1%), Chinese (10%) and Korean (2.8%) subjects but not in Caucasians [16, 17].

Therefore, DPB may be an ethnically specific disease with a gene controlling susceptibility linked with a Japanese...
The association of RA with HLA-DR4 is well established in various ethnic groups including the Japanese [18, 19]. Since HLA-B54 is correlated with DR4 as an extended haplotype, both DPB and RA have the same HLA haplotype correlation which includes B54 and DR4 [20]. Therefore, it is likely that these two diseases may occur together. Although HLA-B54 and -DR4 were not examined in this study, further analyses are necessary to clarify the correlation between HLA typing and DPB associated with RA.

Pathogenesis of obliterative bronchiolitis

Although it is widely accepted that DPB is a discrete and unique syndrome, there is considerable overlap between DPB and other obstructive lung diseases including OB. OB is characterized by narrowing or obliteration of the membranous bronchioli but the distal respiratory bronchioli are spared [21]. OB shows a predilection for females and sometimes has a more severe and rapidly progressive dyspnoea than DPB. Geddes et al. [2] reported the association of progressive airway obliteration in female adults in association with RA and demonstrated that this process was related to OB. Several other reports have demonstrated this association and have further suggested a role for penicillamine in the pathogenesis of this disorder [22, 23].

Clinical diagnostic criteria

In this study, two patients with DPB and one patient with OB, associated with RA were analysed with regard to clinical features, radiographic images, pulmonary function tests and pathological findings. According to the diagnosis made on the basis of clinical features, DPB was dominant in males and OB was found in one female. Penicillamine therapy for RA was applied in one patient with DPB but not in the patient with OB. In the radiographic images, small, nodular shadows, tramlines and bronchiolectasis were found throughout both lungs in both patients with DPB and OB. With regard to pulmonary function, obstructive impairment was prominent in both DPB and OB. Thus, there were striking similarities between DPB and OB in clinical features, radiographic images and the pulmonary function tests, however, histopathological features obtained by reconstructing the lung specimens demonstrated distinct differences between these two diseases. The primary obstructive lesions were in the respiratory bronchioli in DPB and in the membranous bronchioli in OB.

The radiographic and CT features of OB associated with RA, with or without β-penicillamine, are similar to those seen with idiopathic OB. Hyperinflation is the most common abnormality and small nodules may be seen [24]. Although follicular bronchiolitis (FB) has also been described in RA and is said to be associated with reticulonodular opacities of the chest radiograph [25, 26], no lesions consistent with FB were found in the three autopsy cases. Thus, this study suggested that the airway involvement in patients with RA could be divided into three kinds of bronchiolitis: DPB, OB and FB.

Five patients (four Whites and one Hispanic) in the USA were identified as having DPB in a recent report [27]. Therefore, increased awareness of DPB associating with or without underlying diseases in the differential diagnosis of bronchiolitis would probably increase the diagnostic yield in the West.

Treatment and prognosis

The 5-yr survival from the onset of respiratory symptoms in patients with DPB has improved markedly from 62.8% to 91.4% since the introduction of erythromycin therapy for DPB in the past 10 yrs in Japan [28, 29]. It is not likely that erythromycin has an antibacterial mechanism. Other mechanisms have been proposed, such as anti-inflammatory or immunomodulatory effects, decreased polymorphonuclear leukocyte-directed migration and suppression of hypersecretion [30–32]. In this study, erythromycin was not applied to all patients because they died before the introduction of macrolide therapy for DPB. Corticosteroids rather than erythromycin may be of benefit in patients with OB. It may be important to institute these treatments early in the course of the illness, before irreversible structural changes can develop. However, if a patient with OB does not respond to corticosteroids, lung transplantation may be a new therapeutic modality for such end-stage patients and has been applied to one patient with OB, as reported recently [33].

Conclusions

Although it has been established that obliterative bronchiolitis is associated with rheumatoid arthritis, the association of diffuse panbronchiolitis in these patients may simply be coincidental, but the striking similarities between obliterative bronchiolitis and diffuse panbronchiolitis suggest that a real interrelationship may exist between diffuse panbronchiolitis lesions and rheumatoid arthritis. The differentiation of these two disease entities, although very difficult according to the present clinical diagnostic criteria, is very significant for deciding the appropriate methods of treatment in bronchiolitis associated with rheumatoid arthritis, and such differentiation is only possible by analysing the histopathological findings of the affected lung.

References

5. Yamanaka A, Saiki S, Tamura S, Saito K. The problems


