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Diffuse panbronchiolitis

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ABSTRACT: Diffuse panbronchiolitis (DPB) is an idiopathic inflammatory disease, well recognised in Japan and principally affecting the respiratory bronchioles, causing a progressive suppurative and severe obstructive respiratory disorder. If left untreated, DPB progresses to bronchiectasis, respiratory failure and death.

It was first described in the early 1960s. Subsequently, in 1969, the disease was named DPB to distinguish it from chronic bronchitis. ''Diffuse'' refers to the distribution of the lesions throughout both lungs, and ''pan-'' refers to the involvement of inflammation in all layers of the respiratory bronchioles.

The distinctive imaging and histological features, the coexisting sinusitis, and the isolation of *Haemophilus influenzae* and *Pseudomonas aeruginosa* in the sputum enhance disease recognition. Histologically, DPB is characterised by chronic inflammation, localised mainly in the respiratory bronchioles and adjacent centrilobular regions, with characteristic interstitial accumulation of foamy histiocytes, neutrophils and lymphocyte infiltration. Neutrophils and T-lymphocytes, particularly CD8+ cells, together with the cytokines interleukin-8 and macrophage inflammatory protein-1, are believed to play key roles in the development of DPB.

A significant improvement in the prognosis of this potentially fatal disease has been recently reported thanks to the use of long-term therapy with macrolide antibiotics, the effect of which is attributed to an anti-inflammatory and immunoregulatory action.

KEYWORDS: Diffuse panbronchiolitis, erythromycin, foamy macrophages, human leukocyte antigen haplotype, macrolides

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In the early 1960s, a group of Japanese clinicians and lung pathologists described a hitherto-unreported chronic airway disease. In 1969, YAMANAKA and 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 lesions throughout both lungs, and ''pan'' refers to the involvement of inflammation in all layers of the respiratory bronchioles.

DPB is an idiopathic inflammatory disease that is largely restricted to Japan, although, since the late 1980s, case reports and small series have confirmed that DPB may be encountered, rarely, in Western countries [4, 5]. It is characterised by progressive suppurative and obstructive airway disease, which, left untreated, progresses to bronchiectasis, respiratory failure and death [3, 4]. Its distinctive imaging and histological features, the coexisting sinusitis, and the isolation of *Haemophilus influenzae, Streptococcus pneumoniae* (and, in advanced stages of the disease, of *Pseudomonas aeruginosa*) in the sputum enhance disease recognition [3, 4]. A significant improvement in the prognosis of this potentially fatal disease has been recently reported thanks to the use of long-term therapy with macrolide antibiotics [4, 5].

EPIDEMIOLOGY

DPB is now recognised worldwide as a distinct clinical entity, usually occurring in the 2nd–5th decade of life (average age of onset: 40 yrs; range: 1st–7th decade of life) [1–6]. According to a population-based survey made in Japan on behalf of the Ministry of Health and Welfare in 1982, the prevalence of physician-diagnosed DPB

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was 11 cases per 100,000 people [7]. In Japan, the male:female ratio of cases is ~1.4–2:1 and, consequently, no remarkable sex predominance could be observed. Two-thirds of patients are nonsmokers and patients have no particular history of inhalation of toxic fumes. In the years following the initial description of DPB in Japan, cases were recognised in other parts of Asia, including Taiwan, Korea, China, Malaysia, Thailand and Singapore. More recently, DPB has been encountered in Caucasian, Hispanic and African-American populations in Italy, France, the UK, Germany, Norway and the USA [8–20]. One case has been reported in a child [21]. A European series reporting cases with radiographical and clinical aspects mimicking DPB, but without the entire pathological spectrum of the disorder, has recently been published, suggesting that any end-stage chronic bronchiolitis may show many of the clinical and radiological features of DPB, or that *forme fruste* cases of DPB might be observed in non-Asian subjects [22].

AETIOLOGY

Although nothing is known about the aetiology of the disease, the finding of DPB among East Asians, including Asian emigrants, indicates that disease susceptibility may be determined by a genetic predisposition unique to Asians. The human leukocyte antigen (HLA) system plays an essential role in the appropriate immune response mediated by T-cell receptors. Therefore, associations between HLA types and diseases, particularly those with a presumed immune aetiology, have been extensively studied [23]. In 1990, SUGIYAMA *et al.* [24] serologically typed the HLA-A, -B and -C antigens of 38 patients with DPB, and showed that 63% possessed the HLA-Bw54 antigen, compared with 11% of control subjects. Although the number of patients in the study was relatively small, it was noteworthy because HLA-Bw54 is a serotype that has been found predominantly in East Asians [25]. This connection was later confirmed in a more extensive case–control study where the odds ratio was 3.4 [26]. In contrast, in Korean patients suffering from DPB, a positive association with another HLA class I antigen, HLA-A11, has been found [27]. These observations have led to the suggestion that there is a major disease susceptibility gene for DPB, located between the HLA-A and HLA-B loci. KEICHO *et al.* [28] have suggested that an HLA-associated major susceptibility gene for DPB is probably located within a 200 kb segment in the HLA class I region, with its centre 300 kb telomeric of the HLA-B locus on chromosome 6p21.3.

Cystic fibrosis (CF), a common genetic disease in Caucasians, is frequently compared with DPB [29]. In DPB, however, neither pancreatic insufficiency nor any obvious abnormalities of the sweat electrolytes are seen, and the two are considered to be entirely different diseases. Reproductive failure in males with DPB is not observed. A large sputum volume, often >100 mL·day^{-1}, caused by hypersecretion from the inflamed airway, is a distinct feature of DPB but not of CF, where patients are often infected with mucoid strains of *P. aeruginosa* and mortality is secondary to chronic progressive lung disease [29]. The most common mutation in CF, ΔF508, has not been found in patients with DPB [30]. However, a possible contribution to DPB of minor mutations in the CF transmembrane regulator gene has not been excluded [31]. Primary ciliary dyskinesia (PCD) also shares some clinical features with DPB, but ultrastructural studies of the cilia in DPB have not shown the spectrum of abnormalities identified in PCD. Another genetic disorder, bare lymphocyte syndrome (BLS) type I, has close similarity to DPB in phenotype, including chronic sinobronchial infection and diffuse granular lesions: a Japanese patient suffering from BLS type I and DPB was successfully treated with erythromycin [32, 33]. BLS type I, a rare disease, is marked by a deficiency of HLA class I antigens caused by a defect in the transporter associated with antigen processing-1 or -2 [34, 35]. Although these similarities are significant, bare lymphocyte syndrome type I is considered separate and distinct from DPB. Finally, since the clinicopathological and immunopathogenic features of human T-cell lymphotropic virus type 1 (HTLV-1)-associated bronchiolitis and DPB are quite similar, it has been suggested that DPB is a chronic pulmonary manifestation of human HTLV-1 infection [36]. However, HTLV-1-associated bronchiolitis might be associated with conditions that are distinct from those of DPB based on its different response to macrolides and the difference in activated T-cells bearing CD25 in the lungs. Further studies of the mechanisms involved and a deeper understanding of the aetiologies of diffuse panbronchiolitis and HTLV-1-associated bronchiolitis will help to distinguish these two conditions. Clinical features, including computed tomography (CT) findings and pathological aspects mimicking those of DPB, have also been recognised in rheumatoid arthritis [37].

PATHOLOGY

At autopsy, lungs in DPB appear hyperinflated and often show bronchiectasis [2]. Cut sections show yellow nodules, 2–3 mm in diameter, centring on small airways. The lesions are widespread, but worse in the lower rather than in the upper lobes. Typical features are seen in the respiratory bronchioles, with transmural and peribronchial infiltration by lymphoctyes, plasma cells and histocytes (fig. 1a–d). The prominent involvement of respiratory bronchioles is a distinctive feature of DPB, as in other forms of obliterative bronchiolitis the main involved structures are membranous bronchioles [38]. Most of the histiocytes manifest as foamy macrophages, and interstitial accumulations of foamy macrophages in the wall of respiratory bronchioles and in the surrounding interalveolar septa represent one of the nearly unique histological features of DPB (figs 1b, 1c and 2a). The bronchiolar lumen contains neutrophils (fig. 1a) particularly in later phases of the disease. Proliferation of lymphoid follicles along the airways is also frequently noted (fig. 2b). The inflammatory infiltrate destroys the bronchiolar epithelium (fig. 1d) and extends to peribronchiolar spaces, but most of the alveoli are unaffected. Occasionally, intraluminal centrilobular granulation tissue tufts are seen. Respiratory bronchiolar narrowing and ectasia of proximal membranous bronchioles, and, ultimately, widespread bronchiectasis occur as the disease advances [4, 38].

PATHOGENESIS

Neutrophils and T-lymphocytes, particularly CD8+ cells, together with the cytokines interleukin (IL)-8 and macrophage inflammatory protein-1 are believed to play key roles in the development of DPB (fig. 2a and c) [4, 5]. An accumulation of activated neutrophils in the airways appears to be an

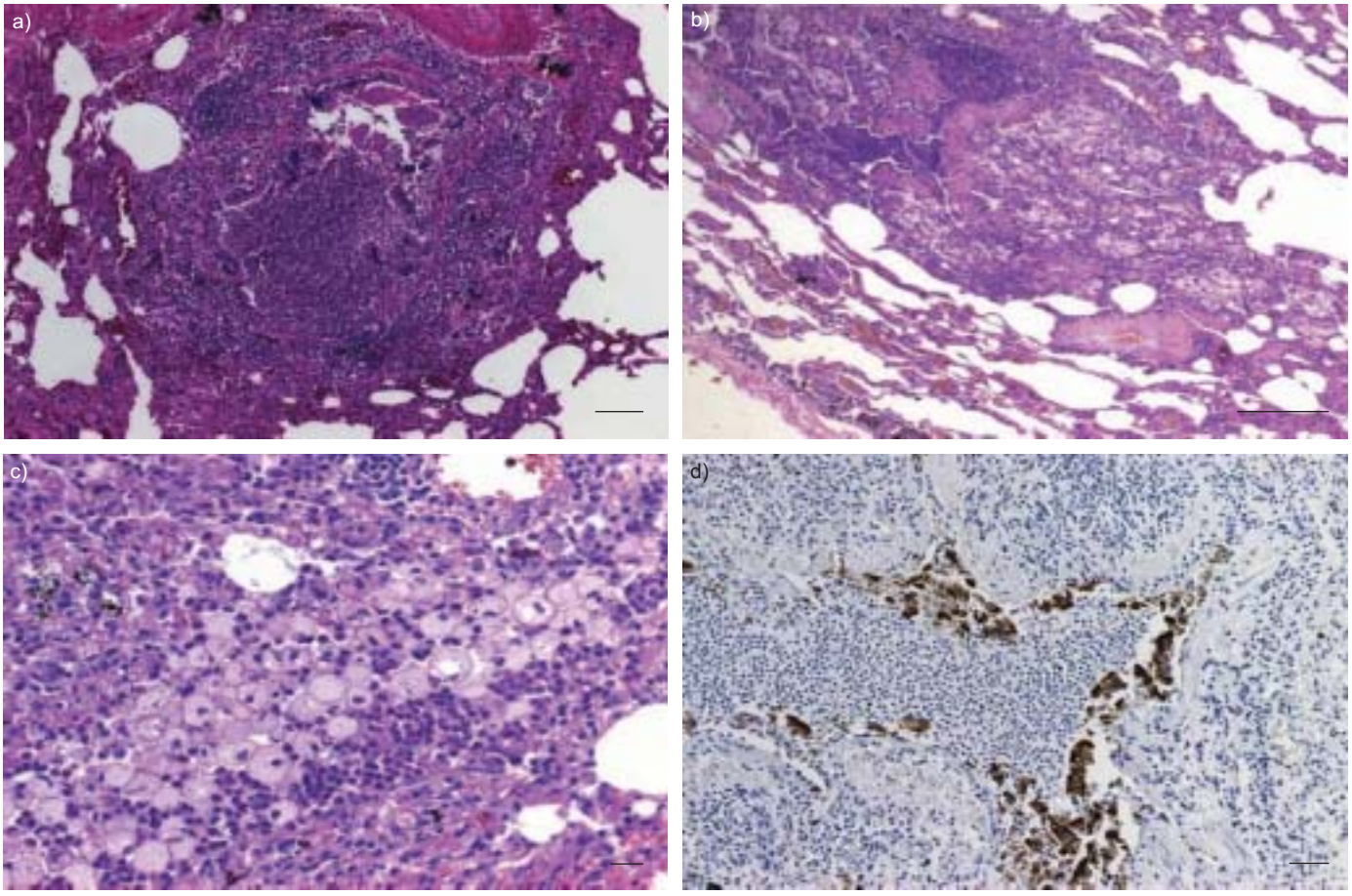

FIGURE 1. a) A respiratory bronchiole with thickened wall infiltrated by mononuclear inflammatory cells and with the lumen filled by neutrophils (haemotoxylin and eosin stain). b) Foamy cells infiltrating the interstitial alveolar wall surrounding a respiratory bronchiole. c) Foamy macrophages with small lymphocytes in the interstitial wall. d) Bronchiolar epithelium is partly destroyed as shown by anti-cytokeratin 8–18 polyclonal antibody staining. Scale bars=100 μm (a, b), 20 μm (c) and 50 μm (d).

important mechanism of injury in this disease. Previous reports have shown the presence of numerous neutrophils in the broncheolar lavage fluid (BALF) of DPB patients, associated with high concentrations of IL-8, suggesting that the accumulation of neutrophils and IL-8 secretion in the airway lumen plays an important role in the pathogenesis of the disease (fig. 2d) [39–41]. High concentrations of leukotriene B4 and defensins in BALF have also been shown [42]. There is a considerable increase in neutrophil chemotactic activity in bronchial fluid from DPB patients, compared with that from healthy volunteers [43–46]. It is possible to speculate that neutrophil chemotactic factors at the site of inflammation and upregulation of adhesion molecules, such as the macrophage antigen Mac1, in the circulation can promote the ingress of neutrophils into the airways [47, 48]. Recent reports have shown that neutrophil apoptosis seems to be prevented by survival-enhancing factors, including granulocyte macrophage-colony stimulating factor (GM-CSF), in the airways of DPB patients [49]. The accumulation of activated neutrophils in the airways may eventually damage epithelial cells, by releasing oxidative and proteolytic products, and promote the development of extensive bronchiectasis, a pathogenetic mechanism similar to that proposed in CF. Accordingly, the activity of elastase, a neutrophil product with relevant injurious potential, is increased in the bronchial fluid of patients with DPB [44]. DPB is also a hypersecretory airways disease, although the mechanism of mucus hypersecretion in DPB is poorly understood. Marked mucus hypersecretion observed in DPB patients may partly be explained by increased and aberrant expression of the MUC5B gene [50]. Moreover, mucin synthesis in the airways has been reported to be regulated by neutrophilic inflammation-induced epidermal growth factor receptor (EGFR) expression, and the degranulation of goblet cells is known to be mediated by neutrophilic elastase. A study by KIM *et al*. [51] proposes that mucus hypersecretion due to goblet cell metaplasia is closely associated with neutrophilic inflammation and the expression of EGFR.

The pathogenetic significance of bronchus-associated lymphoid tissue (BALT) is less clear [52], as is that of the observed increase, in absolute number, of CD3+ γ/δ cells [53]. In addition, a significant increase in the percentage and absolute number of activated cytotoxic (CD8+, HLA-DR+, CD11b+) cells has been observed [54, 55]. The number of CD4+ cells is also increased, with a predominance of CD4+CD29+ memory T-cells [53]. All these findings, taken together, suggest that cell-mediated immunity is also involved in the pathogenesis of DPB. BALT hyperplasia (consisting of B-cells), around the bronchioles may be partially responsible for airflow limitation,

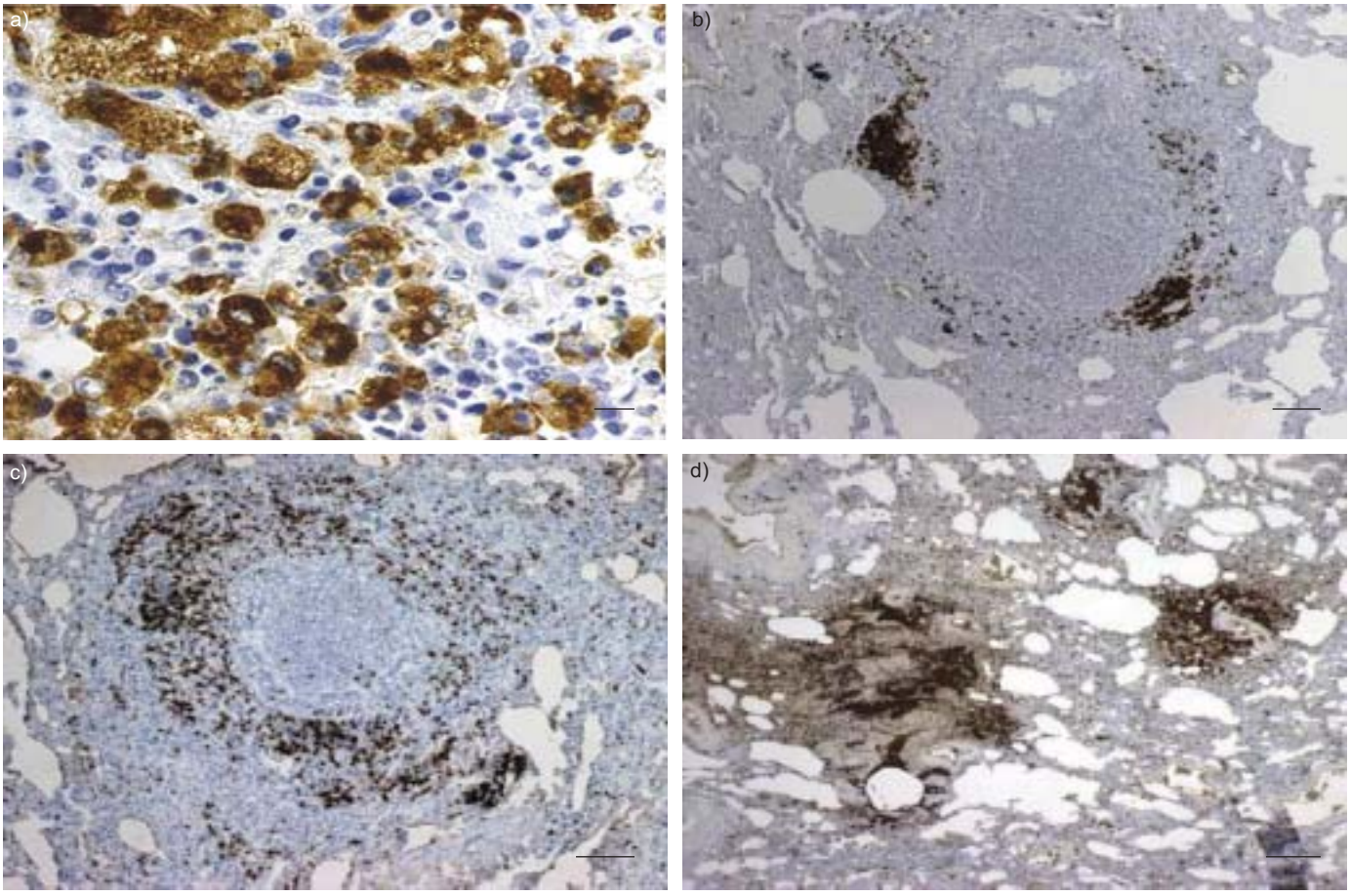

FIGURE 2. a) Foamy cells clearly depicted by a staining procedure specific for macrophages (anti-CD68 monoclonal antibodies). b) Hyperplastic peribronchiolar follicles, shown by a staining method using anti-CD20 monoclonal antibodies. c) Mature T-cell lymphocytes are the main part of the inflammatory infiltrate in the bronchiolar wall (anti-CD3 staining). d) Neutrophils are mainly in the lumen of the respiratory bronchioles (anti-CD15 immunohistochemical staining). Scale bars=20 μm (a), 100 μm (b, c) and 300 μm (d).

but it may also contribute to mucosal defence mechanisms, through local production of immunoglobulin (Ig)G and IgA. Marked increases in the number of CD1a+, CD1c+ and CD83+ dendritic cells (DCs) are found in both the bronchiolar epithelium and submucosal tissues of patients with DPB, as compared with control subjects with normal lungs [56]. DCs are the most potent antigen-presenting cells (APC) and they play a central role in initiating primary immune responses. The observed increase and activation of DCs in DPB may be related to the strong expression of GM-CSF by bronchiolar cells [56]. Accordingly, this important cytokine is crucial for the differentiation and function of DCs. The effect of acute and chronic inflammation on bronchiolar epithelium is a progressive modification of its structures, owing to the abnormal balance between injury and repair. In fact, necrotic bronchioles alternate with hyperplastic bronchioles in the same affected tissue regions. The significance of foamy macrophages is still a matter of speculation. These peculiar cells are mainly located within interstitial spaces, a situation at variance with other diseases such as hypersensitivity pneumonitis or amiodarone parenchymal lung injury, where foamy cells are mainly intraluminal. Foamy cell accumulation is generally considered a consequence of abnormal uptake of surfactant proteins by macrophages, caused by airway obstruction or metabolic impairment [57, 58]. The interstitial location of foamy macrophages in DPB renders these causes unlikely, as also suggested by the lack of surfactant protein-1 immunoreactivity.

DIAGNOSIS

Clinical profile

The development of symptoms (cough and sputum) typically occurs in the 2nd–5th decade of life. Exertional dyspnoea usually follows. Physical examination reveals crackles, wheezes or both. In half of the untreated patients, sputum volume exceeds 50 $mL \cdot day^{-1}$. A large majority (>80%) of patients with DPB have a history of chronic paranasal sinusitis or still suffer from the disease [1–6].

Radiological findings

Plain chest radiography reveals bilateral, diffuse, small nodular shadows with pulmonary hyperinflation. In advanced cases, ring-shaped or tram-line shadows can be observed, and these suggest bronchiectasis (fig. 3). High-resolution (HR)CT findings, coupled with the features seen on histological examination, serve best to distinguish DPB from better-recognised sinobronchial disorders [59]. Nodular shadows are distributed in a centrilobular fashion, often extending to small, branching linear areas of attenuation (''tree-in-bud''

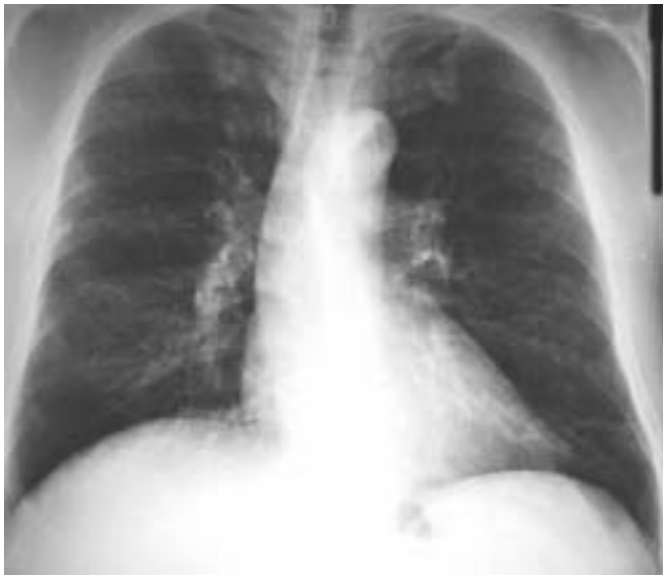

FIGURE 3. Chest radiograph of an Italian male with histologically proven diffuse panbronchiolitis, showing bilateral, diffuse, small nodular shadows with pulmonary hyperinflation.

pattern). Peripheral air trapping is usually confirmed in expiratory films. In addition, dilatation of airways and bronchial wall thickening are present. Mosaic oligoemia is usually absent (fig. 4). A system for grading these HRCT scan changes has been described [59]. These features have been used to diagnose, stage and assess the severity of the disease [60]. In stage 1, small nodules, <5 mm in diameter, are seen at the end of bronchovascular branching structures. In stage 2, these centrilobular nodules are seen connected to distal branching bronchovascular structures in a Y-shaped configuration, which provides the tree-in-bud appearance. These nodules represent bronchioles filled with secretions. Cystic dilatations of these nodules representing early-stage bronchiectasis are seen in stage 3, while stage 4 is characterised by large cysts that are connected to dilated proximal bronchi. Although characteristic of DPB, these changes are not, by themselves, diagnostic. Similar but not identical changes have been described in patients with hypogammaglobulinaemia, CF, primary ciliary dyskinesis, allergic bronchopulmonary aspergillosis, Wegener's granulomatosis, tuberculosis, sarcoidosis, diffuse aspiration bronchiolitis, bronchiolitis obliterans, collagen vascular-related bronchiolitis and bronchiolitis occurring in patients with ulcerative colitis (table 1) [38, 61–63].

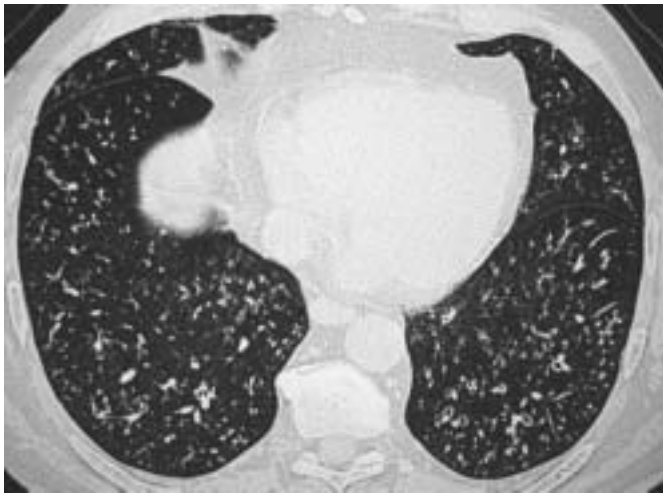

FIGURE 4. High-resolution computed tomography scan of an Italian male with histologically proven diffuse panbronchiolitis. Nodular shadows are distributed in a centrilobular fashion, often extending to small branching linear areas of attenuation (tree-in-bud pattern).

TABLE 1 Differential diagnoses for diffuse panbronchiolitis

Chronic bronchitis
Bronchiectasis
Infectious bronchiolitis
Primary ciliary dyskinesia
Cystic fibrosis
Hypogammaglobulinaemia
Rheumatoid arthritis-related bronchiolitis
Inflammatory bowel disease-related bronchiolitis
Idiopathic chronic bronchiolitis

Microbiological and laboratory findings

Microbiological analysis of 81 histologically proven cases showed that 44% had *H. influenzae* in their sputum at presentation and 22% had *P. aeruginosa* [1]. Less frequently in the early stage, *S. pneumoniae* and *Moraxella catarrhalis* are also present. On average, the *P. aeruginosa* detection rate rises to 60% after 4 yrs of clinical treatment. DPB patients do not usually have *Staphylococcus aureus* in their sputum, as is often detected in the early stage of CF. The most characteristic laboratory feature associated with DPB is the persistent elevation of cold agglutinins, but tests for *Mycoplasma pneumoniae* are negative [38]. In the early stages of the disease, the sputum generally contains normal flora or *H. influenzae*. Colonisation with *P. aeruginosa* eventually occurs, which appears to accelerate the destructive process [1–4]. Serum IgA is elevated and positive rheumatoid factor may frequently be noted. Among the remaining laboratory abnormalities that suggest nonspecific inflammation, mild neutrophilia, raised erythrocyte sedimentation rate and positive findings for C-reactive protein can be mentioned [6]. Markedly high levels of the ''tumour-associated'' carbohydrate antigens sialyl stage-specific embryonic antigen-1 and sialyl Lewis (a) have been demonstrated in the serum and BALF of patients with DPB [64]. This increase may be the result of bronchiolar damage, as commonly observed in DPB. Nasal nitric oxide (NO) is low in DPB patients, and its measurement may serve as a noninvasive test. NO is only this low in two other disorders, CF and ciliary dyskinesia syndrome [65].

Pulmonary function

Pulmonary function tests show a significant airflow limitation, which is relatively resistant to bronchodilators [38, 66]. Simple cut-off points have been established for use in diagnosis, using decreased forced expiratory volume in one second/forced vital capacity <70%, vital capacity <80% predicted and residual volume >150% pred [6]. Analysis of arterial blood gas usually

TABLE 2 Diagnostic criteria for diffuse panbronchiolitis

1. Persistent cough, sputum and exertional dyspnoea
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. $FEV_1/FVC < 70\%$ and $P_{a,O_2} < 80$ mmHg
6. Titre of cold haemagglutinin ≥ 64

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; P_{a,O_2}: arterial oxygen tension. Cases definitely established should fulfil 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 [67]. 1 mmHg=0.133 kPa.

shows hypoxaemia (partial pressure of arterial oxygen <80 mmHg). It must be noted, however, that in the earlier stage of the disease, these cut-off points are too rigid to be applied. Occasionally, a restrictive ventilatory defect may be present. The diffusing capacity is variably reduced. In advanced DPB, *P. aeruginosa* is superinfected, reducing the lungs' capacity for gas exchange, which brings about the progression of hypoxaemia and, later, hypercapnia. Pulmonary hypertension develops, which is linked to the development of cor pulmonale with consequent death due to chronic respiratory failure in most cases. Finally, the diagnostic criteria laid down by a working group of the Ministry of Health and Welfare of Japan in 1998 are reported in table 2 [67]. A lung biopsy is usually necessary in Western countries, where the disease is rare and clinicians are not familiar with it.

A recent European series of patients with many similarities to those with DPB has been reported [22]. In this study, patients exhibited sputum production, tree-in-bud pattern on HRCT and marked increase in serum sialyl Lewis (a). In these patients, diffuse pansinusitis was not evident and histology showed chronic inflammatory and constrictive bronchiolitis, centering mainly on membranous bronchioles. Few cases had foamy histiocytes in the peribronchiolar alveolar septa. These cases might represent a *forme fruste* of DPB or a limited/variant form of DPB in Caucasian subjects. Alternatively, they may represent examples of end-stage bronchiolitis from a variety of causes (including idiopathic) that share some of the clinical, radiological and histological features of DPB. Interestingly, in these forms, when diagnosis was made in the early phase, low-dose erythromycin proved to be beneficial.

PROGNOSIS

The prognosis of patients with DPB was poor, with 5- and 10-yr survival rates in 1983 of 62.1 and 33.2%, respectively. However, long-term treatment with erythromycin has increased the 10-yr survival rate to >90% [68]. Furthermore, TANIMOTO *et al.* [69] showed that the 10-yr survival rate for those infected with *P. aeruginosa* was only 12%, while this was 73% for those who remained uninfected [2, 6, 69].

TREATMENT

In the 1970s, none of the available treatments for DPB helped to avoid fatality. DPB pharmacotherapy served only to alleviate symptoms or complications. In the early stage, oral glucocorticosteroids and antibiotics such as β-lactams against *H. influenzae* and other bacteria were tried, but these were unsuccessful in changing the clinical outcome. Mucolytic agents were also applied, together with bronchodilators. These, however, did not ameliorate the airflow limitation caused by bronchiolar inflammation [66]. In the advanced stage, traditional oxygen therapy and ventilator support to chronic respiratory failure were central elements of disease management.

Erythromycin therapy

Many studies have established the efficacy of erythromycin therapy in improving symptoms, lung function, CT scan changes and survival rates [70–74]. It was observed that

TABLE 3 Clinical guidelines for diffuse panbronchiolitis therapy#

Macrolides should be applied soon after the diagnosis is made, as there is a better clinical response in the earlier stage

- First choice: erythromycin 400 or 600 mg orally
- When it is no longer effective or if administration should be stopped because of adverse effects or drug interactions
- Second choice: clarithromycin 200 or 400 mg orally or roxithromycin 150 or 300 mg orally¶

Assessment of response and duration of treatment

- Although clinical response can usually be noted within 2–3 months, the treatment should be continued for ≥6 months, after which time the overall response should be assessed
- Treatment should be completed after a period of 2 yrs when clinical manifestations, radiological findings and pulmonary function measurements have improved and stabilised and without any significant impairment of daily activity
- Treatment should be resumed if symptoms reappear after the cessation
- In cases of an effective cure in advanced cases with extensive bronchiectasis or respiratory failure, treatment should be continued for >2 yrs

#: developed by a working group of the Diffuse Lung Disease Committee of the Ministry of Health and Welfare of Japan [67]; ¶: 16-member ring macrolides do not seem to be effective.

600 mg erythromycin administered daily for 2 yrs had a curative effect. All reports recorded a clinical and satisfactory efficacy. The duration of treatment remains unclear, but most patients in Asia have been treated for >2 yrs. A logical point at which to stop therapy is on the resolution of symptoms and the disappearance of centrilobular nodules from HRCT scans [74]. Once treatment is stopped, the patient must be followed-up for relapse by symptoms and HRCT, as recurrence has been documented even after lung transplantation [75]. The efficacy of long-term macrolide therapy is not explained by genetic susceptibility [76].

Macrolide antibiotics are known for their efficacy in treating acute airway infections, but, just as importantly, they are also effective anti-inflammatory and immunoregulatory agents [77, 78]. The mechanisms of action for the anti-inflammatory properties of the macrolides are still being investigated, but they are clearly multifactorial. Macrolides inhibit the production of many pro-inflammatory cytokines, such as IL-1, IL-6, IL-8 and tumour necrosis factor-α, perhaps by suppressing the transcription factors nuclear factor-κB or activator protein-1. Inhibition of cytokine production has been seen *in vitro* and also in BALF. Macrolides also inhibit formation of leukotriene B4, which attracts neutrophils, and inhibit the release of superoxide anions by neutrophils that may be present in the airway. Levels of leukotriene B4, IL-8 and human defensins in BALF are significantly reduced in patients with DPB after erythromycin treatment [79–81].

A further important aspect of inflammation is extravasation of neutrophils into the tissues. Macrolides block the formation of adhesion molecules necessary for neutrophil migration. It has been demonstrated that erythromycin treatment is associated with a reduction in absolute number and percentage of neutrophils in the BALF of patients with DPB, and the antibiotic decreases the number of neutrophils in BALF following challenge with gram-negative bacteria [77, 78, 82, 83]. Together, these anti-inflammatory effects result in improved pulmonary function and fewer airway infections. In patients with DPB, the anti-inflammatory effects lead to a significant increase in survival [84]. One major effect of erythromycin therapy is a decrease in sputum volume [1, 6, 68, 69, 72]. The change is supported by *in vitro* experimental evidence that erythromycin and clarithromycin inhibit mucin secretion [85, 86] and may inhibit water secretion by inhibiting chloride secretion in airway epithelial cells. TAMAOKI *et al.* [87] showed that chloride secretion is inhibited by erythromycin, which consequently leads to suppression of water secretion into the airway lumen.

New macrolides

Clarithromycin and roxithromycin, semisynthetic 14-member ring macrolides with modifications in their structures, have also been widely used in the treatment of DPB [88–91]. These new macrolides have sometimes been effective in cases where erythromycin was ineffective [92]. Josamycin, a 16-member ring macrolide, has been empirically shown to be ineffective in treating the disease [86].

Recommended treatment protocol

Based mainly on evidence from the previously mentioned non-randomised trials, observational studies and expert opinion, a working group of the Diffuse Lung Disease Committee of the Ministry of the Health and Welfare of Japan submitted clinical guidelines on macrolide therapy for DPB in 2000 (table 3) [67].

CONCLUSION

Over 30 yrs ago, the first case of DPB was described in Japan. Since then, considerable research has focused on the aetiology of the disease, and it has been suggested that there is a genetic predisposition unique to Asian populations. The advent of macrolide therapy has changed the prognosis and clinical outcome of the disease to a remarkable extent, and the beneficial effects have also been tested on other chronic inflammatory diseases [92]. Cases mimicking DPB in Caucasians have recently been reported. However, they have a different genetic background, so these cases may be *forme fruste* cases of DPB or cases without the full-blown morphological and clinical expression, and may be more frequent in this population than previously thought. The beneficial effects of macrolides have been documented in some of these cases [93].

The diffuse panbronchiolitis saga is interesting because it has demonstrated therapeutic effects of macrolides beyond those related to antimicrobial properties and has opened new therapeutic opportunities in other chronic airway diseases.

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