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Diffuse panbronchiolitis: A progressive fatal lung disease that is curable with azithromycin, but only if diagnosed!

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Abstract

Diffuse panbronchiolitis (DPB) is a rare progressive and eventually fatal pulmonary disease first identified in Japan and initially seen predominantly in Southeast Asia. Macrolide antibiotics rapidly reverse symptoms and pathology, and their use increased the 5 and 10-year survival from 50 and 30 percent, respectively, to over 90%. Review of 181 case reports from previous publications found patients with DPB commonly had their pulmonary symptoms preceded by rhinosinusitis, frequently by many years. Long delays in diagnosis for many years were common. The review further identified DPB in all ethnic groups and multiple areas outside of Southeast Asia. Although diagnosis was most commonly made in adults, 13% of the diagnoses were made in children and nine of the adult cases described onset in childhood. Few cases of relapse were reported, but extended periods of monitoring after treatment were not generally present.

KEYWORDS
diffuse lung disease, diffuse panbronchiolitis, international health, Interstitial Lung Disease (ILD), lung pathology

1 | INTRODUCTION

Diffuse panbronchiolitis (DPB), first observed in Japan in the mid-1960s, was described as a progressive, eventually fatal, respiratory disease of unknown etiology.[1] Initially considered incurable, the 5-year survival was reported as 51% and only 8% in those with advanced disease.[2] The outlook was changed by the serendipitous observation that erythromycin substantially altered the course of disease by an unexplained non-antibiotic effect.[3] Subsequent to the practice of long-term treatment with erythromycin in 1984, the reported 10-year survival increased from 33% in 1983, to 90%.[4] Azithromycin, better tolerated, and requiring less frequent administration than erythromycin, eventually became the agent of choice for treating DPB. A retrospective examination of 51 cases of DPB treated with azithromycin in Shanghai China reported a 5-year survival of 94%.[5] The dramatic effect of azithromycin for DPB led to a study of its mechanism of action. It is hypothesized to function as an anti-inflammatory agent through inhibition of IL-1β.[6] Because of the impressive effect of azithromycin for DPB, clinical trials have occurred for cystic fibrosis (CF),[7] COPD,[8] non-CF bronchiectasis,[9] and asthma.[10] While some positive effect has been seen for those diseases, the effect does not match the dramatic benefit seen for DPB.

In 2015, we reported a 10-year-old American child of Korean descent in whom we made the diagnosis of DPB.[11] Using azithromycin as monotherapy, we successfully relieved him of all clinical and physiologic manifestation of the disease. After 3 years without treatment while remaining free of any symptoms or signs of DPB, he experienced a relapse. A major component of the relapse was severe rhinosinusitis (RSS) with complete nasal obstruction. RSS with nasal obstruction had also preceded by 2 years his previous pulmonary symptoms. RSS and the pulmonary symptoms of DPB were completely resolved with azithromycin on both occasions. The experience with this patient was the rationale for the current review to assess the role of DPB in pediatric respiratory disease, the relationship of severe RSS to DPB, and the frequency of relapse.

To address these observations, we systematically reviewed all English language published descriptions of DPB. This was accomplished by first searching PubMed for publications in English using the

search term, "diffuse panbronchiolitis." This produced 687 articles. After reviewing abstracts of those articles, 67 of the articles were found to contain specific clinical details of individual or multiple patients. A detailed review was performed of those identified clinical details of 181 patients diagnosed with DPB. A complete list of patients is in Table S1 in the Supplementary material. This provided us with the ability to review epidemiological characteristics of DPB, age, ethnicity, presenting symptoms, response to treatment, and reports of relapse.

2 | CHARACTERISTICS OF DPB

2.1 | Epidemiology

The review of available case reports found that DPB has a broad geographical and ethnic distribution. While the predominance of the 181 patients were Southeast Asians, 22 case reports included Caucasians from North and South America, Europe, Australia, and Turkey[12–24] There was also one instance of a patient of African descent,[25] one Samoan,[26] and one Australian Aborigine.[27] Males were 64 percent of published cases. Ages at diagnosis ranged from 10 to over 70 years. Where data for individual patients were present, 13% were in the pediatric age range (Figure 1).

2.2 | Clinical presentation

Productive cough and/or dyspnea were the most common symptoms that would be brought to the attention of a physician. Those symptoms were often present for years prior to diagnosis. Nine of the adults diagnosed with DPB indicated onset of symptoms in childhood. For one publication of 51 cases,[5] symptoms were present a median of 10 years, with a range of 10 days to 40 years, prior to diagnosis. Of 69 patients where individual patient data was available, only 10% were diagnosed within 1 year of symptoms onset, 41% between 1 and 5 years, 30% between 5 and 10 years, and 19% only after 10 years of symptoms.

Sixty-four percent of the cases reported chronic RSS, variably described as parasinusitis, pansinusitis, paranasal sinusitis, or just nasal symptoms; 6% of the cases specifically commented on the absence of sinusitis. In a single report of 51 Chinese cases, paranasal sinusitis was diagnosed in 96%.[5] Sinusitis was frequently indicated as present at the time of diagnosis. Twenty percent of the cases in Table S1 provided information indicating that RSS preceded pulmonary symptoms. Half of those reported the specific duration of sinusitis prior to cough and dyspnea as being from 1 to 48 years with a median of 6 years. When details of nasal symptoms were provided, severe nasal blockage was mentioned. Alternative diagnoses, including bronchiectasis, asthma, and COPD commonly preceded the diagnosis of DPB. Treatment with antibiotics, corticosteroids, and bronchodilators prior to the use of macrolide antibiotics had provided little benefit.

Physical findings most commonly mentioned were wheezing and crackles. When details were provided, wheezing was indicated as expiratory, and crackles were on inspiration, generally at the lung bases. Cough was frequently described as producing profuse amounts of sputum. In a report of 51 Chinese patients, lung crackles were the most consistent auscultatory finding, present in 96%, with wheezing described in 65%. Digital clubbing was uncommon, present in only 10%.[5] Bronchiectasis was present in 51%. Cultures of the sputum were only variably reported, but Pseudomonas aeruginosa was frequently indicated as present and had been present in our previously reported case.[11]

2.3 | Diagnostic testing

Pulmonary function generally showed a mixed obstructive and sometimes a restrictive pattern. Mild hypoxemia was common as was a decrease in the diffusing capacity (DLCO), when reported. Radiologic findings included diffuse small nodules on chest films. CT scans of the chest, generally identified as high resolution CT (HRCT), characteristically showed multiple centrilobular nodules (described in 1 case as 2–3 mm in diameter). Tree-in-bud appearance was frequently described (Figure 2). Dilated bronchioles and bronchiectasis were reported in many cases.

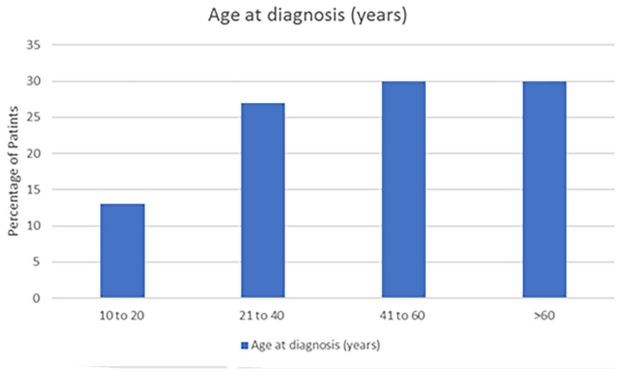

FIGURE 1 Distribution of ages at diagnosis of DPB in the case reports where that data was available (some reports had only ranges of multiple patients)

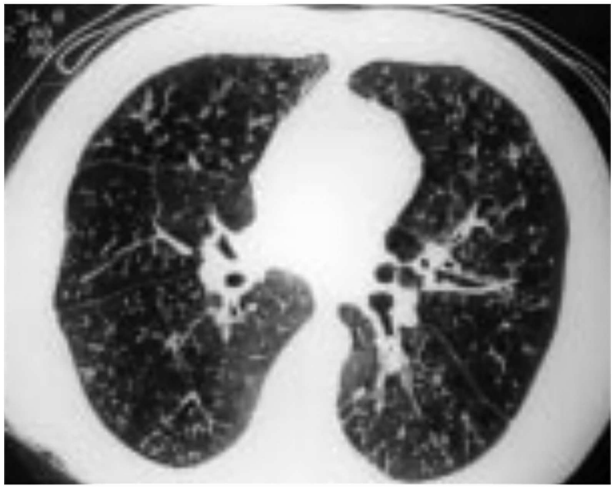

FIGURE 2 HRCT showing centrilobular nodules with tree-in-bud appearance in the lower lobes of a patient with DPB. (from Tsang et al. Thorax 1998;53:274-280)[28]

Lung biopsies were characterized by the presence of fine nodules in the centrilobular regions. Nodules consisted of thickened walls of the respiratory bronchioles with infiltration of lymphocytes, plasma cells, and histiocytes. Accumulation of foamy histiocytes in the walls of the respiratory bronchioles and alveolar ducts was a prominent histopathological sign of the disease (Figure 3).[28]

2.4 | Treatment

Because of the prolonged period of symptoms prior to diagnosis as DPB, patients were treated with medications used for asthma or other obstructive pulmonary diseases. Antibiotics, even when directed at the bacteria associated with DPB including Pseudomonas had little or no effect on the clinical course. Monotherapy with azithromycin for DPB provided cure or substantial improvement with apparent cessation of disease progression (Figure 4).[5]

2.5 | Prognosis

The extent of improvement with azithromycin varies with the degree of permanent lung damage from DPB. Treatment early in the course, such as in the 10-year-old boy described in our previously published case report with pulmonary symptoms for less than a year,[11] was associated with complete absence of symptoms and normal pulmonary function. He subsequently experienced a relapse at age 16, 3 years after stopping azithromycin. Other studies report varying degrees of improvement.[5] Noteworthy, not only the pulmonary symptoms improved but resolution of the RSS symptoms also resulted from the macrolide antibiotic. Only two reports of relapse were reported, both in one published report.[5]

3 | DISCUSSION

Examination of the previously published case reports of DPB confirmed the presence of RSS as part of the disease process of DPB for all but a few patients. RSS frequently preceded pulmonary symptoms of DPB by many years. While relapse of the disease in the published reports was described in only two patients,[5] it's not apparent that long term monitoring was sufficient to address the question.

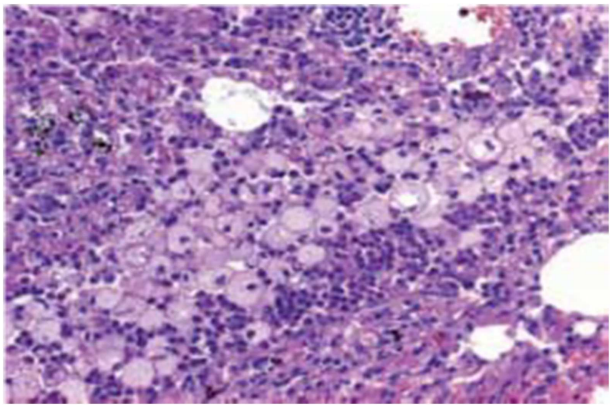

FIGURE 3 Foamy macrophages with lymphocytes in the interstitial wall. (from Poletti et al. Eur Resp J 2006;28:862-871)[36]

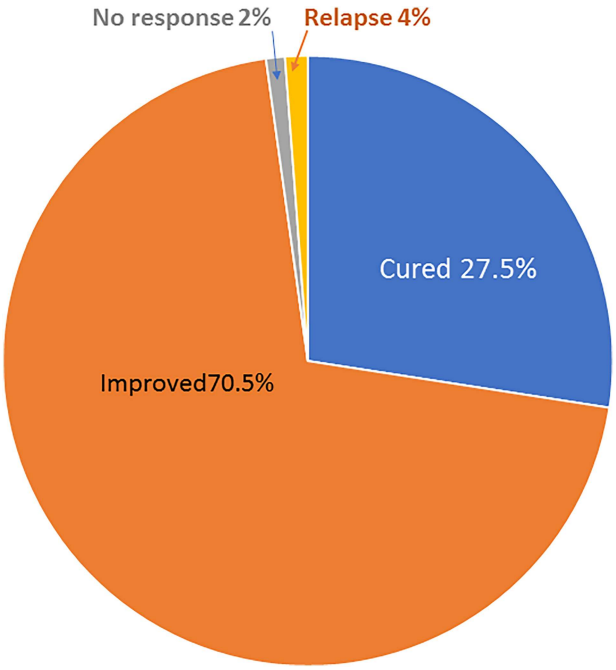

FIGURE 4 Outcome of DPB from azithromycin in 51 patients with DPB. (adapted from Li et al. Intern Med 2011:50:1663-1669)[5]

Previously reported cases were predominantly in adults, but onset beginning in childhood has been described in several publications. One report indicated a 38-year-old man diagnosed with DPB with age of onset at 1 year of age.[29] Another patient in that report indicated a man diagnosed at age 60 Year-old with onset of DPB symptoms at 10 years of age.[29] An Indian man diagnosed at with DPB at age 45 years was described as having productive cough since age 10 years.[30] In addition to our previous report of a 10-year-old boy of Korean ancestry,[11] a Caucasian Turkish 12 year old girl had a prior 5 year history of pulmonary symptoms consistent with DPB and an even longer prior history of RSS.[20] In nine of the reviewed cases of adult diagnoses, onset of symptoms was reported as occurring in childhood..[5,31–35] Thus, DPB can present at all ages from childhood to the elderly and is neither limited to Southeast Asian ethnic populations nor limited to that region.

3.1 | Diagnosing DPB

There is no specific diagnostic test for DPB. However, the clinical symptoms of chronic productive cough and dyspnea on exertion, though not exclusive to DPB, are sufficiently characteristic to include DPB in a differential diagnosis. Pulmonary function can include some degree of air trapping, airway obstruction, decreased diffusing capacity, and hypoxemia. If asthma is initially considered in a patient with those symptoms, as is often the case, the absence of at least transient clearing with a course of systemic corticosteroid warrants further evaluation that would include consideration of DPB.

Examination of the previously published case reports (Table S1) provides relevant information for clinicians seeing patients with

respiratory disease. Long delays, often for years, in diagnosing DPB appear to have been the rule rather than the exception. Misdiagnoses as other lung diseases was usual during that period. Since there are no specific diagnostic tests for DPB, clinicians need to consider clinical characteristics that point to possible DPB in the differential. Those include prolonged productive cough and dyspnea on exertion, most commonly preceded by RSS.

Examination of how diagnosis was eventually made in the case reports suggests that high resolution cat scan (HRCT) is the most useful initial test. The presence of multiple centrilobular nodules and tree-in-bud pattern, while not absolutely diagnostic, is sufficiently consistent with DPB that the diagnosis should be seriously considered if the clinical symptoms fit (Figure 2).[36] However, somewhat similar findings have been reported in other lung diseases.[37] Open lung or thoracoscopic lung biopsy is regarded as providing the highest likelihood to make a definitive diagnosis of DPB. The less invasive transbronchial route has shown utility in some cases[28] but is reported to have a lower yield compared with methods that obtain a larger sample such as open lung or video-assisted thorocoscopy[32] Microscopic examination of an adequate biopsy of a patient with DPB typically shows interstitial accumulation of foamy macrophages in the wall of respiratory bronchioles and the surrounding interalveolar septa. This represents one of the nearly unique histological features of DPB (Figure 3).[36] However, somewhat similar findings can be seen with other lung diseases.[38] Consequently, the biopsy is justified only if the clinical characteristics are consistent with DPB. A patient with the clinical and radiologic characteristics of DPB may forego a biopsy and instead be given a trial of azithromycin for 2-3 months with close assessment of the clinical course.

The criteria for diagnosis of DPB is based primarily on data accumulated in Japan since its identification there.[2] They include the following:[36]

1. Persistent cough productive of sputum
2. Exertional dyspnea
3. History of chronic paranasal sinusitis (with occasional exceptions)
4. Coarse inspiratory crackles
5. FEV_1/FVC <70
6. PaO_2 <80 mmHG
7. Titer of cold hemagglutinin >64

Numbers 1 and 2 are the primary symptoms that bring the patient to the attention of a physician. Number 3 is usually present and characteristically is part of DPB, but several cases of diagnosed DPB have not had sinusitis.[17,29,39,40] If at least 2 of 4-7 are also present, the index of suspicion is greatly increased. Those clinical criteria are sufficient to justify a radiologic exam. If characteristic findings of the characteristics of DPB are present in a HRCT (Figure 2), a trial of azithromycin may be justified without confirmation by a biopsy.

3.2 | Unresolved questions

Both the etiology of the disease and the specific mechanism by which macrolide antibiotics substantially alter the course of DPB are unknown. Another unknown aspect is the relationship of the generally long-standing chronic RSS that precedes, in all but a few patients, the chronic productive cough, exertional dyspnea, and pulmonary physiologic abnormalities. Interestingly, nonallergic RSS in children with frequent recurrences has been reported to be prevented with azithromycin.[41] Additionally, macrolide antibiotics have also been reported to have benefit in persistent post-surgical non-eosinophilic rhinosinusitis.[42]

Are some cases of chronic rhinosinusitis a form fruste of DPB? Without further knowledge of the long-term clinical course of treatment-resistant chronic rhinosinusitis, that question can not currently be answered. Confirmation of clinical response to azithromycin of some phenotypes of chronic rhinosinusitis could prevent the current empirical but often ineffective pharmacological and surgical approaches to that disease.[43]

Limitations of this report include primarily the absence of cases from Japan since case reports from that literature were not available in English. However, it is unlikely that inclusion of translated Japanese reports would alter the conclusions that can be derived from the current data in Table S1. While an early estimate of DPB prevalence among the Japanese had been about one in 10 000,[44] we have no information about the prevalence in other countries. Consequently, we cannot estimate how many diagnoses are being missed.

The prevalence of relapse remains unknown because of absence of long term monitoring. Our previous experience with relapse in a 16-year-old boy after 3 years of previous remission suggests that patients diagnosed and treated for DPB should be monitored for an indefinite period.

4 | CONCLUSION

Based on this review, the diagnosis of this highly treatable disease is likely to continue being delayed and even completely missed unless DPB is included in a differential diagnosis when chronic productive cough and exertional dyspnea cannot be convincingly attributed to other diseases. This is especially true outside of Southeast Asia where respiratory physicians have had less experience with the disorder. However, there are likely more than the 22 Caucasian cases included in this report (Table S1). And we would not know the prevalence until physicians consider, identify, and treat DPB. Ideally that treatment would be sufficiently early in the clinical course of the disease to prevent permanent lung damage and fatal outcome. Once the diagnosis is made and DPB is successfully treated, long-term monitoring is essential since relapse can occur.

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CONFLICTS OF INTEREST

Neither author has any conflict of interest related to the contents of this manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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