CASE REPORT

Diffuse panbronchiolitis in a Caucasian man in Canada

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Diffuse panbronchiolitis (DPB) is a rare, chronic bronchiolar disease in non-Asian populations and is therefore commonly overlooked in Western countries. It usually affects nonsmokers and manifests as persistent air flow obstruction, chronic cough and interstitial nodular opacities. Untreated, the prognosis is poor. In this report the authors describe a Caucasian man of Canadian descent who presented with progressive clinical and lung function impairment despite three years of bronchodilator and corticosteroid treatment with presumed asthma. His chest computed tomography scan showed diffuse centrilobular opacities. Lung biopsy revealed chronic bronchiolitis characterized by infiltration of lymphocytes, plasma cells and foam cells in respiratory and terminal bronchioles, compatible with a diagnosis of DPB. After two months of therapy with clarithromycin, the patient had already shown improvement. Physicians should be aware that DPB may occur in Western countries, and that DPB should be considered in the differential diagnosis of patients with persistent air flow obstruction and nodular shadows on chest radiograms.

Key Words: Clarithromycin; Diffuse panbronchiolitis; Macrolide;
Refractory asthma

A 27-year-old white man from Toronto, Ontario was referred to the Asthma and Airway Centre, Toronto Western Hospital, University Health Network (Toronto, Ontario) in 1999 with a diagnosis of refractory asthma. He presented with a three-year history of cough, moderate amounts of purulent sputum production and exertional dyspnea after a viral-like illness. His previous diagnosis of asthma had been based on his symptoms and some spirometric results that showed an obstructive ventilatory defect with some bronchodilator response. Treatment with short acting beta2-agonist bronchodilators, inhaled steroids, long acting bronchodilators and a leukotriene receptor antagonist did not result in significant improvement. Indeed, his symptoms and obstructive defect worsened progressively. He had lost 14 kg since his symptoms began. He was a lifetime nonsmoker with no other medical problems. His work as a salesperson had not exposed him to any known occupational respiratory hazards. He had enjoyed a healthy childhood and had not travelled to Asia at any time in his life. Physical examination revealed inspiratory and expiratory wheezes throughout both lungs. There was no cyanosis or clubbing. Pulmonary function tests showed a moderate obstructive ventilatory defect with gas trapping and no significant response to bronchodilators (Table 1). His carbon monoxide diffusion capacity was normal. A chest x-ray showed mildly increased interstitial markings. A high resolution computed tomography scan revealed diffuse multiple nodular shadows on chest radiograms.

CASE PRESENTATION

A 27-year-old white man from Toronto, Ontario was referred to the Asthma and Airway Centre, Toronto Western Hospital, University Health Network (Toronto, Ontario) in 1999 with a diagnosis of refractory asthma. He presented with a three-year history of cough, moderate amounts of purulent sputum production and exertional dyspnea after a viral-like illness. His previous diagnosis of asthma had been based on his symptoms and some spirometric results that showed an obstructive ventilatory defect with some bronchodilator response. Treatment with short acting beta2-agonist bronchodilators, inhaled steroids, long acting bronchodilators and a leukotriene receptor antagonist did not result in significant improvement. Indeed, his symptoms and obstructive defect worsened progressively. He had lost 14 kg since his symptoms began. He was a lifetime nonsmoker with no other medical problems. His work as a salesperson had not exposed him to any known occupational respiratory hazards. He had enjoyed a healthy childhood and had not travelled to Asia at any time in his life. Physical examination revealed inspiratory and expiratory wheezes throughout both lungs. There was no cyanosis or clubbing. Pulmonary function tests showed a moderate obstructive ventilatory defect with gas trapping and no significant response to bronchodilators (Table 1). His carbon monoxide diffusion capacity was normal. A chest x-ray showed mildly increased interstitial markings. A high resolution computed tomography scan revealed diffuse multiple nodular shadows on chest radiograms.

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linear and nodular densities, and some areas of consolidation, mainly in the lower lobes. The nodules had a centrilobular distribution and a peripheral predominance (Figure 1). Bronchiolitis obliterans with organizing pneumonia was considered a potential diagnosis. Sputum cultures were negative. Results of tests of serum immunoglobulins, *Aspergillus* precipitins, rheumatoid factor and erythrocyte sedimentation rate were normal. Nitric oxide levels (an airway inflammatory marker) present in the nose were decreased. The patient was started on oral prednisone 50 mg/day followed by a dose reduction to 25 mg/day, and had partial radiological and symptomatic improvement. Attempts to reduce his prednisone dose resulted in worsening of symptoms and lung function, and a brisk response to an inhaled bronchodilator was detected (Table 1). An increase in dose of prednisone, as well as initiation of therapy with a combination of salmeterol 50 µg/fluticasone 500 µg twice daily, resulted in functional improvement (Table 1). However, a productive cough and moderate airflow obstruction persisted. An open lung biopsy was performed. Lung tissue from the right upper and lower lobes revealed chronic bronchiolitis consistent with DPB (Figure 2). There was transmural inflammation with mixed mononuclear inflammatory cells confined to membranous and terminal bronchioles, as well as peribronchiolar interstitial histiocytosis. Segmental areas of bronchiolectasis with mucus stasis were also observed. The absence of cystic fibrosis transmembrane conductance regulator gene mutation excluded the unlikely diagnosis of cystic fibrosis. Human leukocyte antigen typing was negative for antigens previously reported to be associated with DPB. A sinus x-ray confirmed the presence of previously unsuspected chronic maxillary sinusitis. Bronchoalveolar lavage collected one month after the patient’s lung biopsy revealed 97% alveolar macrophages, 1% neutrophils, 2% lymphocytes and moderate growth of *Pseudomonas aeruginosa*. He was treated for three weeks with ciprofloxacin, and clarithromycin (250 mg bid) was then...
Diffuse panbronchiolitis in a white man in Canada

We report the findings and clinical course of a 27-year-old white male born in Canada, who had been diagnosed with refractory asthma but who was indeed suffering from DPB. To our knowledge, this is the first case of DPB described in a Caucasian man in Canada. DPB was considered, for many years, to be a disease seen exclusively in Japanese, Chinese and Korean populations. DPB was not described outside of Asia before 1990 (3,4), and although rare, it is now a recognized disease in Western countries. It is defined as a chronic bronchiolitis characterized by infiltration of lymphocytes, plasma cells and foam cells in the walls of membranous, terminal and respiratory bronchioles, with extension of this inflammation toward the peribronchial area (1,5). In DPB, chronic inflammation and foamy macrophages can be seen accumulated in the walls of membranous and terminal bronchioles, adjacent alveolar ducts and alveoli (5). These abnormalities were detected in our patient’s lung biopsy. Neutrophils may be seen, with mucus, in the lumen of the bronchioles and may be demonstrated by bronchoalveolar lavage. In the advanced stages, there is narrowing and constriction of respiratory bronchioles due to the inflammatory infiltration, lymphoid tissue hyperplasia, accumulation of histiocytes and secondary ectasies of proximal terminal bronchioles.

The onset of the disease is usually between the second and fifth decades of life. The natural history of the disease is dismal if not treated, with only a 25% 10-year survival rate. The clinical symptoms in some ways resemble cystic fibrosis, but there is no exocrine system dysfunction. Chronic cough, copious sputum production and exertional dyspnea are characteristic and may appear at the onset of the disease or following several years of chronic sinusitis, which is present in 75% of patients (1). Weight loss may be present (3). The physical examination may reveal wheezing or coarse crackles. Our patient was typical in demonstrating these clinical findings. With disease progression, cor pulmonale develops. Sputum cultures may initially not reveal anything of note, but frequently, infection with Haemophilus influenzae and Streptococcus pneumoniae appear during the course of the disease, followed commonly by P aeruginosa in advanced stages of the disease. Chest radiographs in patients with DPB usually show small, nodular shadows throughout both lungs; as well, they often show hyperinflation. The high resolution computed tomography scan reveals poorly defined centrilobular nodules, centrilobular branching opacities and intralobular secretions (6), corroborating our findings in the present case. Air trapping may be present and bronchiectasis appears in advanced stages of the disease. There are no specific laboratory abnormalities in DPB. The typical abnormality in pulmonary function tests is air flow limitation with gas trapping. In some patients, especially in progressive cases, a mixed obstructive-restrictive pattern may be observed (1). The diffusion capacity may be reduced or normal. Some bronchodilator responsiveness may be seen but not as typically as it is seen in patients with asthma. In our patient, the presence of bronchodilator response, partial improvement of lung function with high doses of inhaled steroid and long acting bronchodilators, as well as positive allergy skin testing for several allergens, suggest that he had an ‘asthmatic component’ to his disease.

The etiology of DPB remains unknown. It is possible that genetic susceptibility and environmental factors each contribute to the development of the disease. Association with HLA-B54 in Japanese patients with DPB has been demonstrated (7), yet Asian descendents living in Western countries do not have a high frequency of DPB.

Long term treatment with low dose (600 mg/day) erythromycin improves the prognosis of the disease significantly, decreasing symptoms, improving lung function and increasing survival (8). The time of response to therapy is variable and may take several months (4,8,9). The mechanism of action of macrolides in DPB is contentious. The known anti-inflammatory effects of macrolides are more likely to be responsible for their beneficial effects in DPB than are their antibacterial properties. Macrolides inhibit inflammatory cells (neutrophils) and cytokine activity (10). In addition, macrolides exert an inhibitory effect on bronchial secretion. The reported patient showed improvement after two months of macrolide therapy. Although rare in non-Asians, DPB does occur outside the Far East, and should be considered in the differential diagnosis of patients with persistent air flow obstruction and nodular shadows on chest roentgenograms, particularly if associated with a history or radiological evidence of chronic sinusitis.

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REFERENCES

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