Diffuse panbronchiolitis, a potentially misdiagnosed sinopulmonary syndrome

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Diffuse panbronchiolitis (DPB), a rare sinopulmonary syndrome characterized by chronic inflammation of respiratory bronchioles of unknown etiology, is an important cause of progressive obstructive lung disease.¹⁻³ It mainly occurs in East Asia and sporadic cases have been reported in other parts of the world.²⁻⁴ The diagnosis may easily be made by clinical and radiological features in countries where the disease is common, but in other countries the diagnosis may need to be confirmed by transbronchial or open lung biopsy.³ In many countries outside of East Asia, DPB is often unrecognized, underdiagnosed or misdiagnosed, which leads to mistreatment or lack of appropriate treatment. In this report, we describe the second case of DPB in Turkey.⁵

Case

The patient was a 36-year-old housewife who presented to our outpatient clinic in January 2002 with a 2-year history of productive cough with night sweats, anorexia and mild exertional dyspnea. The cough was worse in the evening. She had a daily expectoration of 1 tablespoon of green sputum and also complained of chronic postnasal drip. The patient had not been febrile. Nine months prior to presentation she experienced an episode of hemoptysis and gave a history of weight loss of about 20 kg over 3 years. She had a 1-pack-year history of smoking and had discontinued cigarettes 10 years earlier. There was no history of tuberculosis (TB) or TB contact. She had not travelled outside Turkey. Other medical history was noncontributory. The hemoglobin level was 10.9 g/dL, hematocrit was 30%, the WBC count was 5.67×10^3 cells/ μ L, and platelets were 282×10^3 cells/ μ L. The erythrocyte sedimentation rate was 40 mm per hour. Urinalysis and routine serum chemistry findings were normal. Electrocardiogram (ECG) revealed sinus tachycardia. The measurement of arterial blood gas levels on room air found the following: pH 7.51, $p\text{CO}_2$ 25.0 mm Hg, $p\text{O}_2$ 62.1 mm Hg, HCO_3^- 23.4 mmol/L, and arterial O_2 saturation, 91.6%. Results were negative or normal at initial presentation for sputum microscopy and culture for bacteria, acid fast bacilli and fungi, α_1 -antitrypsin level and serum levels of IgE, IgA, IgG and complement, serological tests for the anti-nuclear antibodies, rheumatoid factor, circulating immune complexes, cold agglutinins, and *Mycoplasma pneumoniae*. Sweat and tuberculin skin tests (Mantoux test) were negative. Her pulmonary function test revealed a restrictive pattern: FEV₁ of 2.06 L (71.5% of predicted); FVC, 2.30 L (65.0%); and FEV₁/FVC, 89.6%. On physical examination, she appeared ill and was in mild respiratory distress. She was afebrile with a pulse rate of 116 beats/min, BP of 120/80 mm Hg and a respiratory rate of 24 breaths/min. Coarse inspiratory crackles were heard in the mid- and lower lung zones on chest auscultation. The rest of the physical examination was normal. Her chest roentgenogram at hospital

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Accepted for publication

July 2004

Ann Saudi Med 2005;25(6):501-504

Figure 1. Initial chest radiograph showing diffuse ill-defined nodular opacities in both the mid- and lower lung fields.

Figure 2. Initial chest CT showing numerous centrilobular nodules with branching lines giving a tree-in-bud appearance and bronchial thickening and dilatation.

admission (Figure 1) showed diffuse reticulonodular infiltrations most markedly scattered in the lower lung fields. A thoracic computed tomography (CT) scan (Figure 2) demonstrated centrilobular nodules connected to branching lines, giving a tree-in-bud appearance, bronchial wall thickening and bronchiectasis and localized areas of decreased attenuation. Air trapping was confirmed on expiratory scans. Radiograph and CT scan of the paranasal sinuses showed opacification of the right maxillary sinus and mucosal thickening of the left maxillary sinus. Bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsies (TBB) were performed

with nondiagnostic results. BAL cultures were negative. Then the patient underwent open lung biopsy. Histopathologic examination of the tissue specimen (Figure 3) revealed chronic bronchiolar inflammation with infiltration of mononuclear cells spreading from the respiratory bronchioles to the peribronchiolar area and narrowing of the bronchiolar lumen in which lipid-laden macrophages and chronic inflammatory cells also accumulated. These findings were compatible with DPB. Blood human leukocyte antigen (HLA) typing was performed and showed the presence of HLA A2, A3, B27, B51(5), Bw4, Cw2, Cw14, DR14(6), DR16(2), DR51, DR52, and DQ5(1) antigens. HLA Bw54 and A11 antigens were not found. She was started on therapy with low dose oral erythromycin (500 mg/d). Symptoms subsided 1 week later. During the follow-up period, treatment produced a remarkable improvement in the clinical, physiological and arterial blood gas values (pulmonary function tests: FEV₁ of 2.24 L [81.7% of predicted]; FVC 2.41 L [76.2% of predicted]; and FEV₁/FVC 92.9%, pH 7.40, pCO₂ 39 mm Hg, pO₂ 91 mm Hg, HCO₃ 24 mmol/L, arterial O₂ saturation, 96%) and radiologic picture (Figure 4). The patient remained symptom free and has not experienced a recurrence.

Discussion

DPB is a rarely encountered clinicopathologic entity that is more prevalent in East Asia, especially in Japan.^{1,2} Although the pathogenesis of the disease is not well known, environmental and genetic factors might have important roles.^{2,3,6} Most patients are male and nonsmokers. Symptoms usually begin after age 40 or 50 years. DPB is characterized by chronic recurrent sinopulmonary infection and inflammation. Chronic productive cough, exertional dyspnea and wheezing are the chief clinical manifestations.^{1,2} Most of the patients have chronic sinusitis.^{1,2} The rarity of DPB and its nonspecific clinical presentations often lead to misdiagnoses as other obstructive lung diseases and inappropriate treatments. Clinical features and the diagnostic criteria are as follows:^{1-3,7}

- Symptoms of chronic cough, sputum, and dyspnea on exertion.
- Physical signs consisting of coarse crackles, rhonchi, or wheezes on auscultation of the chest.
- Bilateral fine nodular shadows, mainly in the lower lung fields often with hyperinflation of the lungs on chest radiograph.

- Forced expiratory volume in one second (FEV_1) < 70% of predicted on pulmonary function tests, diminution of vital capacity (below 80% of predicted value), increase in residual air above 150% of predicted value and PaO_2 < 80 mm Hg on blood gas analysis.
- Pulmonary function tests: usually obstructive and rarely restrictive ventilatory defect and hypoxemia with or without hypercapnia.
- Elevated cold hemagglutinin titers > 64 times without raised anti-*Mycoplasma pneumoniae* antibody (helpful if present).
- Past history or coexistence of chronic paranasal sinusitis (nearly all patients have chronic paranasal sinusitis).
- Transbronchial biopsies, if obtained, showing thickness of the wall of the respiratory bronchioles with infiltration of lymphocytes, plasma cells, and foamy histiocytes expanding into the peribronchiolar area.

A precise diagnosis is based on histology, which characteristically shows chronic inflammation exclusively located in the region of the respiratory bronchioles and thickening of the respiratory bronchiolar wall with infiltration of lymphocytes, plasma cells and histiocytes, and extension of the inflammatory changes toward peribronchiolar tissues, consequently causing obstruction or stenosis of respiratory bronchioles.^{1,2} Some familial cases and a strong association with human leukocyte antigen (HLA) Bw54 in Japanese and HLA-A11 in Korean patients with DPB points toward possible genetic predisposition.^{8,9} But the absence of these HLA antigens and cold haemagglutinaemia as seen in our case and in other reported cases outside of Japan and Korea does not exclude the diagnosis.^{3,7,10} Diffuse small nodules are seen on plain radiography. High-resolution CT findings are associated with the stage of the disease and consist of small centrilobular nodular and branching linear opacities that contact the nodules, and dilated airways with thick walls.¹¹⁻¹³ DPB must be considered in the differential diagnosis of sinopulmonary syndromes, which can include alterations in defense mechanisms (e.g. immotilia silia syndrome, immunodeficiencies), infections (e.g. HIV, invasive fungal diseases), idiopathic disorders (e.g. Wegener's granulomatosis, Churg-Strauss syndrome), and allergic or immunologic disorders (e.g. asthma and allergic rhinitis).¹⁴ Because of the poor prognosis and its treatable character, early diagnosis of DPB is

Figure 3 Chronic inflammatory cells in the wall and lumina of respiratory bronchioles (x 200 HE).

Figure 4 Control chest CT showing significant resolution of the nodular opacities and residual bronchiectasis and bronchiolectasis after treatment.

quite important. It often results in respiratory failure due to repeated episodes of respiratory infection, especially *Pseudomonas aeruginosa* infection in patients left untreated.¹⁻³ Macrolide antibiotic treatment is very effective in DPB.^{15,16} Most patients show good radiologic and physiologic responses to long-term (especially more than one month) administration of low-dose (400 to 600 mg/d) erythromycin therapy. Although the treatment may be ineffective as DPB progresses, this drug can improve the prognosis with its anti-inflammatory effects.¹⁵ Since DPB is seen not only in Asians, but also in other populations,²⁻⁴ pulmonary specialists should be familiar with this disease.

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