Diffuse Panbronchiolitis Associated with Adult T-cell Leukemia — A Case Report

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Diffuse panbronchiolitis (DPB) is a disease characterized by chronic inflammation exclusively located in the respiratory bronchioles. It has been previously reported to occur exclusively in East Asians, primarily in Japanese, Korean, and Chinese populations. The definite causative agent remains unclear; neither environmental factors nor infectious agents have been demonstrated. A significantly high frequency of anti-HTLV-I antibody in patients with DPB, higher than in those with other diseases and healthy controls, has been reported. Adult T-cell leukemia/lymphoma (ATL) is a category of lymphoid malignancy characterized histologically by malignant lymphocytes with flower-shaped nuclei, and HTLV-1 has been recognized as a causative agent of ATL. We present a case of DPB complicated by ATL and review the relationship between them. ***(Thorac Med 2006; 21: 94-100)***

Key words: diffuse panbronchiolitis (DPB), adult T-cell leukemia (ATL), human T-cell lymphotropic virus type I (HTLV-I)

Introduction

Diffuse panbronchiolitis (DPB), first described by Yamanaka *et al*. in 1969, is a disease characterized by chronic inflammation exclusively located in the respiratory bronchioles [1]. Histologically, chronic inflammation mainly affects the respiratory bronchioles, with distinctive interstitial accumulations of foamy cells in the wall of the bronchioles, adjacent alveolar ducts, and alveoli [2]. Diffusely disseminated bronchiolitis and peribronchiolitis cause obstructive respiratory disorders and early hypoxemia. The prognosis of patients with this disease has been poor, with a 10-year survival rate of 33.2% in 1983, but long-term treatment with erythromycin has increased the 10-year survival rate to > 90% [3]. DPB was previously reported exclusively in East Asians, primarily in Japanese, Korean, and Chinese populations. A few cases have been reported in Europe and North America [4]. The definitive causative agent remains unclear; neither environmental factors nor infectious agents have been demonstrated to be the cause. Genetic influence may play an important role in the development of DPB. A strong association

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with B54 human leukocyte antigen has been shown [5]. In addition, a significantly high frequency of anti-HTLV-I antibody in patients with DPB, higher than in those with other diseases and healthy controls, was reported by Kimura in 1992 [6].

Adult T-cell leukemia/lymphoma (ATL), identified by Takatuki in 1977, is a category of lymphoid malignancy characterized histologically by malignant lymphocytes with flower-shaped nuclei [7]. In 1980, HTLV-1 viral particles were found in the cells of a patient who had ATL, and these viral particles have been recognized as a causative agent of ATL ever since [8]. There are 4 subtypes of ATL: acute, chronic, smoldering, and lymphoma. Regardless of the subtype, ATL is refractory to therapy. The major cause of death in any subtype is respiratory complications [9]. DPB is 1 of the possible pulmonary complications [10]. We herein present a case of DPB complicated by ATL and review the relationship between them.

Case Presentation

A 53-year-old female complained of dyspnea on exertion and productive cough for several years. She was a non-smoker and denied having any allergy history. She had been diagnosed with chronic sinusitis and bronchiectasis 2 years prior to visiting our chest clinic. The first chest X-ray we obtained revealed diffuse micronodular infiltrative shadows and tram lines in both lung fields (Figure 1). Physical examinations revealed bilateral fine crackles on auscultation of the chest. Spirometry revealed an obstructive disturbance (FVC, 45%; FEV1, 30%; FEV1/FVC, 56%). Blood gas analysis showed mild hypoxemia. (pH 7.447, PO_2 89, PCO_2 33 mmHg under a nasal prong for 2 l/min). High-resolution computed tomography of the lung showed centrilobular nodules with distal branching bronchovascular structures, and dilated airways with thickened walls (Figure2). *Pseudomonas aeruginosa* and *Haemophilus influenzae* were cultured from the

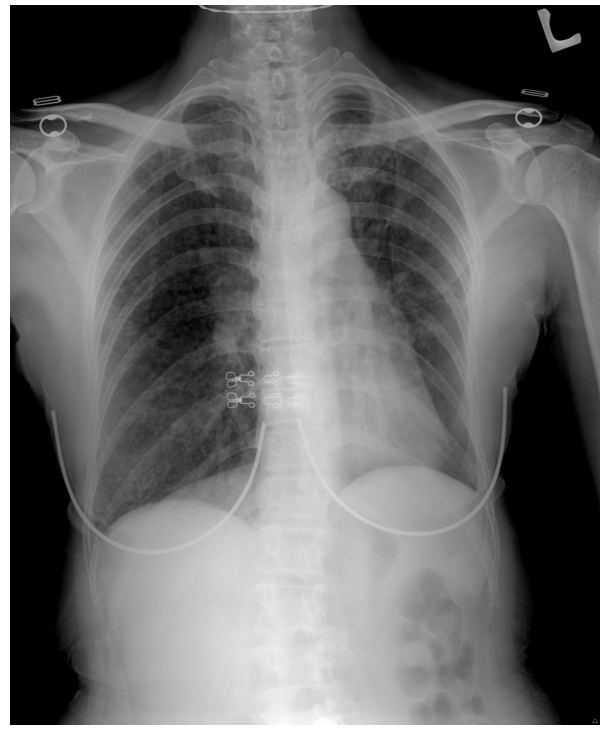

Fig. 1. Chest X-ray revealing diffuse micronodular infiltrative shadows and tram lines in both lung fields.

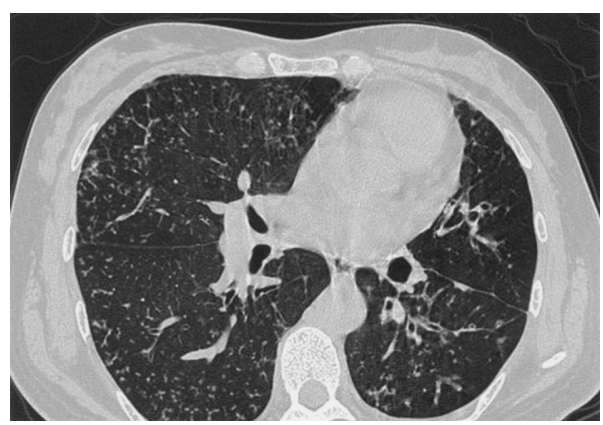

Fig. 2. High-resolution computed tomography of the lung showing centrilobular nodules with distal branching bronchovascular structures.

sputum. The leukocyte count was 8400/ul. Serum IgA was 108 mg/dl (normal range: 85-453 mg/dl). Cold hemagglutinin (CHA), rheumatoid factor and antinuclear antibody were both negative. On the basis of these data, a diagnosis of diffuse panbronchiolitis (DPB) was made, according to the clinical criteria established by Homma [1] in 1983.

The patient was then treated with low-dose erythromycin (500 mg/day) and followed up regularly at our clinic. Six months later, she was admitted to our hospital because of increasing dyspnea and fever for 8 days. The leukocyte count was 37,500/ul with 70.5% lymphocytes. A high C-reactive protein level (2.29 mg/dl, normal range, < 0.5 mg/dl) was noted. Chest X-ray showed diffuse micronodular shadows, patchy opacities and a wide mediastinum (Figure 3). Auscultation of the lungs revealed coarse crackles in the right lower lung and diffuse wheezing. An initial diagnosis of DPB and right lower lung pneumonia was made. At the beginning, empiric antibiotics with amoxicillin/clavulanic acid and gentamicin were administered. Mycoplasma Ab and urine legionella Ag were negative. *Pseudomonas aeruginosa* was cultured from the sputum 3 days later. Accordingly, the antibiotics were changed to piperacillin and gentamicin. The patient gradually became afebrile, however, persistent leukocytosis and a progressive change in the appearance of the lung infiltrates on the chest X-ray were noted. Antibiotics were then changed to piperacillin/tazobactam and erythromycin.

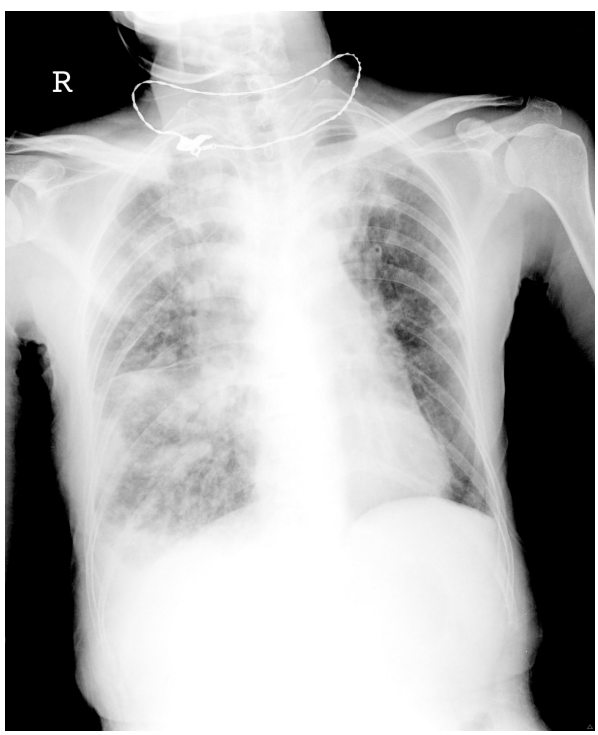

Fig. 3. Chest X ray showing diffuse micronodular shadows, patchy opacities, and a wide mediastinum.

Computed tomography of the chest was arranged, which revealed marked lymphoadenopathy in the bilateral axilla, hila, and the mediastinum; right-side pleural effusion was also noted. Several enlarged lymph nodes were palpable in the bilateral inguinal areas. Serum LDH was 425 mg/dl (normal range: 135-225 mg/dl). A chest echo was done, and a moderate amount of pleural effusion was found on the right side. The pleural effusion study revealed lymphocyte-predominant exudates with a WBC count of 12960/ul and LDH of 277 mg/dl. Pleural effusion cytology revealed abundant mature lymphoid cells. Lymphoma was highly suspected. A left inguinal lymph node excisional biopsy was done, and the result of the pathology report showed malignant T-cell lymphoma. The peripheral blood smear and bone marrow study showed lymphocytes with cloverleaf-shaped nuclear lobation. (Figure 4). Serologic examination also revealed that anti-HTLV-I antibody was positive by 128-fold. She was a carrier of human T-cell lymphotropic virus type I (HTLV-I). The diagnosis of adult T-cell leukemia (acute type) was finally made.

The patient began receiving chemotherapy with cyclophosamide, doxorubicin, vincristine,

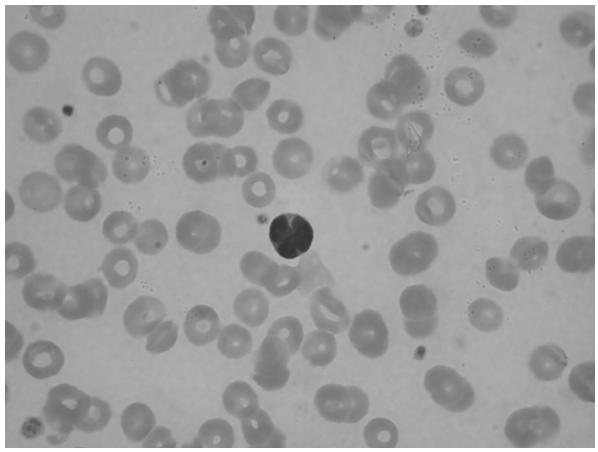

Fig. 4. Peripheral blood smear showing lymphocytes with clover-leaf-shaped nuclear lobation.

and prednisolone (the "CHOP" regimen). The patient's clinical symptoms, as well as the findings on chest-X rays, improved gradually. The patient was discharged 9 days later.

Discussion

The patient presented herein was a carrier of human T-cell lymphotropic virus type I (HTLV-I). She was diagnosed as having diffuse panbronchiolitis (DPB), based on the clinical criteria established by Homma [1] in 1983. These criteria included: (1) symptoms of chronic cough, sputum, and dyspnea on exertion; (2) physical signs consisting of coarse crackles, rhonchi, or wheezes on auscultation of the chest; (3) radiographic findings showing bilateral diffuse fine nodular shadows or chest CT scans revealing centrilobular micronodules; (4) pulmonary function studies showing at least 3 of the following 4 abnormalities: FEV1/FVC < 70%, VC < 80% of the predicted value, RV > 150% of the predicted value, PaO_2 < 80 mmHg; (5) additional clinical findings of chronic parasinusitis, increased cold hamagglutinin titers (x64 or higher), or increased immunoglobulin A. The clinical findings of our patient fulfilled most of the criteria, thus bronchoscopic biopsy or open lung biopsy was not arranged. However, the patient was also diagnosed as having the acute type of adult T-cell leukemia (ATL) 6 months later. Is there any relationship between DPB and ATL? HTLV-I retrovirus may be the key to the connection.

HTLV-I is the first human oncogenic retrovirus to be discovered, and is described as the causative agent of ATL [7]. Both HTLV-I and ATL have been shown to be endemic in some regions of the world, especially in southwest Japan [11], the Caribbean islands, and parts of Central Africa [12, 21]. Antibodies against HTLV-I have been found in over 1 million individuals [22], and more than 700 cases of ATL are diagnosed each year in Japan alone. The cumulative (life span of 70 years) incidence of ATL among HTLV-I carriers in Japan is estimated at 2.5% (3-5% in males and 1-2% in females), if competing risks for other diseases are disregarded [23].

The assertion that the clinical entity, TSP/HAM (tropical spastic paraparesis/HTLV-I associated myelopathy), is a non-neoplastic inflammatory process related to the HTLV-I infection, leads to the notion that HTLV-I may likely be the causative agent of some inflammatory disorders, such as arthritis, uveitis, and inflammatory pulmonary diseases [13-15]. DPB is 1 of the possibly-related inflammatory pulmonary diseases reported by Kikuchi *et al*. in 1996 [15]. Pulmonary complications in HTLV-I carriers have been reported to range from subclinical lymphocytic alveolitis and DPB, to lymphocytic interstitial pneumonia. [15, 19].

A nationwide histopathologic study in Japan to characterize pulmonary involvement in 32 HTLV-1 carriers with symptomatic chronic

pulmonary diseases demonstrated that 72% of the patients had bronchiolar involvement, rather than interstitial involvement, including DPB in 9 patients and chronic bronchiolitis in 14 patients [16]. Chronic bronchiolitis is pathologically characterized by the lymphocytic inflammation of small bronchi and membranous bronchioles without foamy cells, which are frequently characteristic of patients with DPB. Even so, could we say that HTLV-I-associated bronchiolitis (with a histological study revealing no foamy cells) is different from DPB? It is well-known that the diagnosis of DPB is based on clinical, functional, radiological, and histological findings. None of these is sufficient evidence by itself, since an isolated finding is nonspecific and could lead to a misdiagnosis. The current and popularly used diagnostic criteria are the clinical criteria described by Homma [1] in 1983.

The Ministry of Health and Welfare of Japan modified these criteria in 1995, yet histological proof is still deemed not necessary. In fact, Mukae *et al*. reported cases of HTLV-I carriers diagnosed with DPB using clinical criteria, yet whose histological findings showed no typical foamy cells [17]. This indicated that HTLV-I-associated bronchiolitis and DPB might overlap, under current diagnostic criteria. To assess whether these 2 conditions can be differentiated, Kadota *et al*., in 2004, reported on a study of 58 Japanese patients they had examined: 15 had HTLV-1-associated bronchiolitis and 43 had DPB (HTLV-1 was negative) [18]. Both conditions were compared using clinical symptoms, laboratory findings, radiological findings, histological findings, BAL fluid testing, and the treatment effect of macrolides. The study demonstrated that the clinical, laboratory, radiological, and bacterial features were strikingly similar in both patients with HTLV-1-associated bronchiolitis and those with DPB. Histological examinations also indicated an overlap between these 2 groups. However, long-term treatment with macrolides significantly improved mean PaO_2 in the DPB patients, more than in the HTLV-1-associated bronchiolitis patients. Therefore, HTLV-1-associated bronchiolitis might still be linked with conditions that are distinct from those of DPB, based on the different response to macrolides.

DPB complicated by ATL has been rarely reported. Ono *et al*. first reported a higher prevalence of DPB among patients with ATL, if compared with the general population [10]. He reported that 3 of their 43 patients with ATL were complicated by DPB in a follow-up study. In contrast, they encountered no DPB complication during the same period among the 129 cases of leukemia and non-HTLV-I-associated lymphoma. They posited 3 possible explanations for this relationship. First, slow viral infection via HTLV-I may induce the host's immune defense mechanism, resulting in chronic inflammation of the bronchioles. Second, HTLV-I may have an effect not only on lymphocytes but on bronchioles, as well as on the nervous system. Third, lymphocytes that are infected with HTLV-I may infiltrate the bronchioles. DPB may therefore increase the frequency of pulmonary infections, and subsequently interfere with the treatment of adult T-cell leukemia (ATL) and worsen the prognosis. As the prevalence of HTLV-I carriers in Taiwan is approximately 0.5% [20], the possibility of DPB co-existing with ATL should always be kept in mind.

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瀰漫性泛細支氣管炎併發成人 T 細胞白血病—病例報告

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瀰漫性泛細支氣管炎(Diffuse panbronchiolitis)是一呼吸性小支氣管慢性發炎之疾病。之前的報告病例多集中在東亞地區，主要在日本、韓國、中國。此病的致病因仍然不清楚，並未有確定的環境或感染因素被證實。曾有報告提出瀰漫性泛細支氣管炎的病人比一般健康人或有其他疾病的人有較高的機會發現人類嗜 T 淋巴球第一型病毒之抗體。成人 T 細胞白血病 / 淋巴瘤(Adult T-cell leukemia/lymphoma)是一個淋巴性惡性腫瘤，其組織特徵為具有花瓣狀細胞核的惡性淋巴球。而人類嗜 T 淋巴球第一型病毒被認為是成人 T 細胞白血病 / 淋巴瘤的致病因素。我們在此提出一個瀰漫性泛細支氣管炎合併成人 T 細胞白血病之病例報告，並且回顧此兩者之間相關的文獻。一位 53 歲的女性因活動性喘?及咳嗽有痰到胸腔科門診求診，經過檢查後她被診斷有瀰漫性泛細支氣管炎。然而 6 個月之後這個病人因發燒，白血球增多及身上多處淋巴結腫大入院，最後診斷患有成人 T 細胞白血病。 Ono *et al.*在 1989 年最先報告成人 T 細胞白血病的病人比一般人有更高的瀰漫性泛細支氣管炎盛行率。瀰漫性泛細支氣管炎會使成人 T 細胞白血病的病人更容易併發肺部感染，影響成人 T 細胞白血病的治療使愈後更差。在台灣，人類嗜 T 淋巴球第一型病毒的帶原者比非流行區高，因此也需留意瀰漫性泛細支氣管炎合併成人 T 細胞白血病的可能性。*(胸腔醫學* ***2006; 21: 94-100)***

關鍵詞：瀰漫性泛細支氣管炎，成人 T 細胞白血病，人類嗜 T 淋巴球第一型病毒

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