A Case of Diffuse Panbronchiolitis Complicated by Peripheral T Cell Lymphoma Not Otherwise Specified

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Established Facts
- Diffuse panbronchiolitis is a distinctive form of small airway disease. Its pathogenesis is unclear.

Novel Insights
- A very rare case of diffuse panbronchiolitis complicated by non-Hodgkin’s lymphoma is reported, and the relationship of diffuse panbronchiolitis with T cell tumors is discussed.

Key Words
Diffuse panbronchiolitis • Lymphoma • T cell lymphoma

Abstract
We report a case of diffuse panbronchiolitis (DPB) complicated by peripheral T cell lymphoma not otherwise specified. A 40-year-old Chinese man presented with intermittent fever, cough and significant white sputum production for more than 9 years, in addition to dyspnea and chest congestion that worsened after exercise. A chest CT scan indicated diffuse centrilobular fine nodular opacities with a ‘tree-in-bud’ appearance in both lungs. An open-lung biopsy was performed, and DPB was diagnosed by histopathological analysis. Three months later, the patient’s pulmonary symptoms worsened. A chest CT of both lungs revealed multiple patchy opacities as well as enlargement of the hilar, mediastinal and multiple superficial lymph nodes. A whole-body bone scan revealed multiple osteolytic lesions located in the thoracic, lumbar and sacral spine. A biopsy of the right supraclavicular lymph node was performed, and peripheral T cell lymphoma not otherwise specified was diagnosed histopathologically. Cases of DPB complicated by non-Hodgkin’s lymphoma are a rare occurrence. To our knowledge, there is only one earlier report of such a case in the literature (in Japanese). However, the prevalence of DPB complicated by T cell tumors is relatively high, indicating a possible association in pathogenesis of T cell disorders and DPB.

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Diffuse panbronchiolitis (DPB) is a rare and distinctive form of small airway disease, which is relatively common in Asian populations. DPB was first reported and described by Japanese researchers [1]. It predominantly affects the respiratory bronchioles and is characterized by prominent interstitial foamy macrophages in peribronchilolar distribution.

Cases of DPB complicated by non-Hodgkin’s lymphoma are relatively uncommon. We report the case of a male Chinese patient with this diagnosis. Lung and the right supraclavicular lymph node biopsy were performed. DPB complicated by peripheral T cell lymphoma not otherwise specified (PTCL-NOS) was diagnosed by histopathological analysis. We also review DPB complicated by T lymphocyte diseases and discuss the possibility of association in pathogenesis of T cell disorders and DPB.

**Case Profile**

A 40-year-old Chinese man presented with intermittent fever, cough and sputum production of significant yellow-white purulent sputum for more than 9 years. He also had chest congestion and dyspnea, which worsened after exercise. His highest fever reached 39.5°C. Cephalosporin, erythromycin, azithromycin and rifampin had been administered. The symptoms were alleviated with this regimen but recurred. On average, an acute attack occurred every 3–6 months and lasted approximately 10 days. The patient had a 25-year history of chronic sinusitis and had undergone three surgical treatments for it. He had also been treated for pulmonary tuberculosis 6 years prior.

**Physical Examination**

Multiple cervical lymph nodes were palpable bilaterally. The nodes were 0.5 cm in diameter and were tender with free movement, but no pain was elicited on palpation. Aspiratory coarse sounds with some wet rales could be heard in both lower lung bases.

**Laboratory Examination**

Complete blood count was performed: WBC 19.82 × 10^9/liter with 58.9% neutrophils, Hg 137 g/liter, PLT 370 × 10^9/liter blood, CD4/CD8 = 26.17 (reference: 1.536 ± 0.589), erythrocyte sedimentation rate = 7 mm/h (normal range: 0–15), C-reactive protein level = 0.242 g/dl (reference: 0–0.08).

**Bronchoscopic Examination**

The carina of the bronchial tubes were sharp with a clear opening bilaterally. Viscous secretions were noticeable in the lumens. The bronchial mucous membrane was smooth, and no new growths were found. Pulmonary function test showed obstructive defects with FVC (3.55 liters, 80% of predicted) and FEV\textsubscript{1} (2.38 liters, 55.5% of predicted), and FEV\textsubscript{1}/FVC ratio was at 67.06%, but the diffusing capacity of the lung was normal.

**Radiological Examination**

A high-resolution CT (HRCT) chest scan showed diffuse centrolobular opacities, and a ‘tree-in-bud’ appearance was seen in both lungs (fig. 1), particularly in the lower lobes. Fiber-like high-density regions were seen in both upper lobes.

After admission, the patient underwent an open-lung biopsy. Lung tissue from the right upper and right middle lobes was taken for biopsy. Microscopic lesions were observed to be distributed predominantly along the respiratory bronchioles, the accumulation of foamy cells in the peribronchial interstitium was revealed and DPB was pathologically diagnosed (fig. 2). In addition, epithelial granulomas with central caseous necrosis were visualized.

**Fig. 1.** A chest CT scan performed prior to open lung biopsy. Bilateral diffuse centrilobular opacities with a tree-in-bud appearance are visible.

**Fig. 2.** A histopathology specimen from the open lung biopsy reveals diffuse panbronchiolitis, chronic inflammation and large amount of foam cells in the interstitium are present. HE stain.
locally in the biopsy specimen. The condition was considered a local complication of tuberculosis. Levofloxacin combined with antituberculosis medications (0.3 g isoniazid, 0.45 g rifampicin, 1 g pyrazinamide and 0.75 g ethambutol) were administered after surgery.

Three months after lung biopsy, the patient was readmitted due to a sudden high fever (40 °C) associated with accomass fatigue, sweating and cough with yellow purulent sputum for 10 days. A chest HRCT showed multiple shades of patchy consolidation in both lungs (fig. 3). The hilar and mediastinal lymph nodes were enlarged and were significantly more aggravated than during the exam 3 months prior. Physical examination revealed 1 palpable left submandibular lymph node (1 × 1 cm), 2 palpable left cervical lymph nodes (both 0.5 × 0.5 cm), 1 palpable right supraclavicular node (1 × 1 cm) and 1 inguinal lymph node on each side (both 0.5 × 0.5 cm). The above-noted lymph nodes were tender with free movement, but none were tender to palpation.

Complete blood count was performed: WBC 16.50 × 10⁹/liter with 82.5% neutrophils and 9.2% lymphocytes, Hg 144 g/liter, PLT 449 × 10⁹/liter, lactate dehydrogenase 876 U/liter (normal range: 97–270), CA125 = 102.4 U/liter (normal range: 0–35). A whole-body bone scan revealed multiple osteolytic lesions located in the thoracic, lumbar and sacral spine. A bone marrow biopsy revealed reactive granulocytic hyperplasia, although the erythroid and lymphoid lines were morphologically normal. A pathological diagnosis of PTCL-NOS was confirmed via a biopsy of the right supraclavicular lymph nodes (fig. 4). Immunohistochemical staining showed that the tumor cells are positive for CD3 and negative for CD20 and CD79a. Gene rearrangement analysis using a polymerase chain reaction with primers specific for TCR Vγ1–8, Vγ9, Vγ11, β and IgH-VH gene segments was performed and revealed the following result: TCR (+) [γ1–8/A (–); γ10 (–); γ11 (+); β (–)]; IgH (–) [VH (–)].

CHOP chemotherapy was administered for 6 cycles upon diagnosis. The abnormal chest shadows and the patient’s symptoms were improved for follow-up 14 months at this writing.

Discussion

DPB is a distinct clinicopathological syndrome characterized by chronic sinopulmonary inflammation in the paranasal sinuses and the respiratory bronchiolae of the lung. It was originally described in Japan in 1969[1], and reported mainly from Asia. Clinically, patients typically have a history of chronic sinusitis, dyspnea, cough and purulent sputum production. Elevation of serum cold agglutinins and obstructive pulmonary function defects are usually present. On HRCT scan, DPB is characterized by the presence of diffuse centrilobular nodulars along with thickened bronchioles throughout both lungs. Pathologically, interstitial foamy macrophages around respiratory bronchioles is the most distinctive feature. Treatment with low-dose macrolides has been shown to significantly improve survival [2, 3].

We have reported a rare case of DPB complicated by PTCL-NOS. The patient was a middle-aged Chinese male with a long history of chronic sinusitis and a recurrent chronic cough lasting at least 9 years. A chest CT scan revealed diffuse bronchiolar opacities in both lungs. The pathological diagnosis of DPB was confirmed.
by open lung biopsy. Three months after surgery, the patient was readmitted due to aggravated pulmonary symptoms, and a chest CT scan showed enlarged hilar, mediastinal and multiple superficial lymph nodes. The pathological diagnosis of PTCL-NOS was confirmed by a biopsy of the right supravacular lymph node, and TCR gene rearrangement was detected in this patient. Gene rearrangement analysis has been most frequently used to obtain objective evidence for clonality of a lymphoid proliferative process. Because each antigen-specific T cell and its clonal progeny has a unique rearrangement of its TCR gene, rearrangement of TCR gene is essential to establish monoclonality. The presence of clonal rearrangement of TCR has been used to define malignant T cell lymphoma.

HRCT manifestation of DPB is characteristic. In this reported case, a chest CT scan revealed diffuse centrilobular opacities in both lungs during the patient’s first hospitalization, these findings were consistent with DPB. At the second hospitalization 3 months later, a chest CT scan showed significantly different results: there were multiple shades of patchy consolidation in both lungs. Although no lung biopsy was performed during the second hospitalization, we suspected that the aggregated symptoms and changes in the CT results were caused by lymphoma involving the lung. DPB complicated by lymphoma is rare. To our knowledge, this is only the second report of such a case in the literature. Minura et al. [4] reported a singular case of DPB complicated by non-Hodgkin’s lymphoma in 1987 in a Japanese patient (report in Japanese).

In addition to having an elevated rate of chronic sinusitis, the percentage of DPB patients with leukemia and thymoma is greater than that of the general population. A total of 6 cases of DPB complicated by thymoma have been reported in the literature [5–8]. In addition, Ono et al. [9] retrospectively studied 43 cases of adult T cell leukemia in Japanese patients and found 3 cases complicated by DPB. There were a total of 13 DPB cases confirmed by histopathological diagnosis in our hospital records from 1996 to 2010. Among them, 3 cases were complicated by thymoma (2 of these cases have been reported in the literature [8]), and 1 case was complicated by T cell lymphoma (this report). All 3 thymomas were lymphocytic dominated (B1 type) with a large amount of immature T lymphocytes in the tumor tissue. Interestingly, all of the above thymomas, leukemias and lymphomas were T cell tumors, which suggests that there may be an association between the pathogenesis of DPB and T cell tumors.

The reason for the high incidence of DPB patients associated with T cell tumors is still unclear. It is also well known that T cells are important cells in the component of bronchial inflammation in DPB [10]. So it is speculated that there may be some common etiology for both diseases. For example, impaired immunity might be a reason for the development of DPB as well as T cell malignancies. It had been reported [11] that the concentration of β-defensins was higher in BALF of DPB patients than in patients with idiopathic pulmonary fibrosis and healthy subjects. Human β-defensins are widely expressed in epithelial cells and can participate in all phases of an immune response in the lung. Furthermore, T cell lymphoma and DPB are diseases that are more prevalent in Asia, so environmental factors and racial predisposition might play a role in it.

Human T cell lymphotropic virus type 1 (HTLV-1) is a retrovirus that suppresses T cell function and immune response. It is associated with the pathogenesis of adult leukemia and lymphoma. Similarly, HTLV-1 may also cause panbronchiolitis. Kadota et al. [2] compared HTLV-1-associated bronchiolitis and DPB. Their findings showed similarities among the clinical, radiologic and histopathological features of the two diseases. Therefore, they suggested that some DPB cases were a pulmonary manifestation of HTLV-1 infection [2]. DPB cases that are HTLV-1 positive have also been reported in the literature [12]. However, PTCL-NOS was a distinct subtype of lymphomas different from adult leukemia and lymphoma, and the patient in this report was negative for serum antibodies to HTLV-1. So further studies of the etiology of DPB, the role of HTLV-1 as a contributing factor in DPB and the reason for high incidence of DPB patients associated with T cell tumors are needed.

References


