Lung Cancer with Focal Lymphocytic Interstitial Pneumonia
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Abstract
A 65-year-old man was found to have a mass lesion surrounded by ground-glass attenuation in the left upper lobe on chest radiography. He was diagnosed with stage IA adenocarcinoma of the lung. The resected lung specimen revealed papillary adenocarcinoma associated with infiltration of numerous lymphocytes in the alveolar septa, which was consistent with focal lymphocytic interstitial pneumonia (LIP). However, it was not associated with Sjögren’s syndrome or any other immunologic abnormalities. Immunohistochemical study disclosed that CD8 positive T-cells constituted the major element of the infiltrated lymphocytes in the tumor, and were also found in the enlarged alveolar septa, suggesting an association between lung cancer and LIP. To our knowledge, this is the first description of an association between LIP and lung cancer. In addition, the focal LIP in this case probably reflected local immune response to an antigenic stimulus caused by lung cancer.

Key words: anti-tumor immunity, T-cell, CD8

Introduction
Lymphocytic interstitial pneumonia (LIP) is a benign lymphoproliferative disorder characterized by a diffuse and exquisitely interstitial proliferation of small lymphocytes and plasma cells (1). LIP occurs most commonly in patients who have Sjögren’s syndrome, autoimmune thyroid disease, acquired immunodeficiency syndrome (AIDS), or Castleman disease (2–8). LIP with Sjögren’s syndrome is now regarded both clinically and histopathologically as a wide spectrum of lymphoproliferative disorders ranging from benign to malignant. In fact, malignant lymphoma has supervened in some patients with LIP (9). However, lung cancer associated with LIP has not been reported previously.

Case Report
A 65-year-old man with no symptoms was found to have a mass shadow in the left upper lobe of the lung on chest radiography. He received an implantable cardioverter-defibrillator (ICD) with ventricular fibrillation due to hypertrophic cardiomyopathy (HCM) in 1997. Battery depletion necessitated a generator exchange in June 2001. At that time, an abnormal shadow was found by chest X-ray. He had smoked 30 cigarettes daily for about 40 years. He was a truck driver, who had not experienced any risk factors for occupational or environmental exposure to toxic materials, nor did he have hypersensitivity pneumonia. There were no abnormal findings on the chest X-ray which was taken in 1999.

At our hospital, physical examination revealed fine crackles over the left anterior mid-lung field. An abdominal examination was normal. There was no peripheral edema, digital clubbing, cyanosis, or sicca syndrome. In a laboratory examination, the white blood cell count was 3,900/μl with a normal differential. Hemoglobin and hematocrit were normal. CRP was not increased. Arterial blood gas analysis showed PO2 of 74.8 mmHg, PCO2 of 41.2 mmHg and pH 7.449. Lung function studies showed a vital capacity of 89.3% and forced expiratory volume in 1s (FEV1) was 75.3%. Quantitative immunoglobulin assay yielded: IgG, 794 mg/dl (normal 870–1,700); IgA, 201 mg/dl (normal 110–410); and IgM, 81 mg/dl (normal 46–260). Rheumatoid factor and antinuclear antibodies were negative. Both anti-SS-A and SS-B antibody were also negative. Human immunodeficiency virus (HIV) and human T-cell lymphocytotropic virus-1 (HTLV-1) antibodies were negative. A tuberculin skin test (PPD) was negative. Tumour markers investigated (CEA, SLX, SCC, NSE), were within the normal limit.

A chest radiograph showed a unilateral ground-glass infiltrate in the left upper lobe (Fig. 1A). A nodule, about 2.5 cm in
Figure 1. Chest X-ray and high resolution computed tomography (HRCT) findings on admission. (A) Chest X-ray shows a coin lesion with ground-glass attenuation. (B) High resolution CT shows diffuse ground-glass infiltrate in left lung, and an irregularly outlined nodular lesion in the left upper lobe.

Figure 2. Histological findings of the resected lung. (A) The coin lesion was a moderately differentiated papillary adenocarcinoma with lymphocyte infiltration (HE stain, original magnification, x40). (B) The adjacent lung tissue demonstrated a lymphocytic infiltration in the interstitium with preservation of normal lung architecture, which was consistent with LIP. Many lymphoid follicles were present (HE stain, original magnification, x10).

A nodular lesion was present in the ground-glass infiltrate. A high resolution computed tomographic (HRCT) scan of the chest confirmed diffuse ground-glass infiltrate in the left lung, and an irregularly outlined nodular lesion in the left upper lobe (Fig. 1B). Neither hilar and mediastinal lymphoadenopathy, nor pleural thickening was present. Bronchoscopic examination revealed no endobronchial lesions. A nodular lesion was diagnosed as adenocarcinoma by transbronchial lung biopsy. He was diagnosed with stage IA (T1N0M0), and therefore surgery was indicated. On the 24th hospital day, a left upper lobectomy was performed. The resected lung specimen contained a well-circumscribed, subpleural nodule. It was 25×25×20 mm in size. Microscopically, the papillary adenocarcinoma (moderately differentiated) was associated with infiltration of mononuclear cells, mainly composed of lymphocytes (Fig. 2A). The adjacent lung tissue demonstrated a lymphocytic infiltration in the interstitium with preservation of normal lung architecture, which was consistent with LIP (Fig. 2B). Many lymphoid follicles were present around the bronchioles. There was no interstitial fibrosis. The hilar lymph nodes had no evidence of cancer metastasis nor malignant lymphoma.

Representative sections of formalin-fixed, paraffin-embedded tissue were analyzed using monoclonal antibodies and the
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Figure 3. Photomicrographs of immunostaining of lung tissue. (A) Immunostaining for CD8 demonstrates positive staining of the lymphocytes in adenocarcinoma (original magnification, ×40). (B) Immunostaining for CD8 demonstrates positive staining of the lymphocytes in the alveolar septa (original magnification, ×40). Immunostaining for CD4 demonstrates negative staining of the lymphocytes in both adenocarcinoma and alveolar septa (data not shown).

avidin-biotin immunoperoxidase technique. Monoclonal antibodies to both B-cell (CD20) and T-cell (CD3, CD45RO, CD4 and CD8) were used. The immunophenotyping studies disclosed a greater prevalence of cells reacting with the pan-B-cell (anti-CD20) antibody than cells reacting with the pan-T-cell (anti-CD3) antibody in the lymphoid aggregates. However, cells reacting with the pan-T-cell (CD3 and CD45RO) were more prevalent than cells reacting with the pan-B-cell in the enlarged alveolar septa and tumor (data not shown). In addition, cells reacting with the anti-CD8 antibody were more prevalent than cells reacting with the anti-CD4 antibody in the enlarged alveolar septa and tumor (Fig. 3A, B). Therefore, CD8 positive T-cells constituted the major element in the tumor, and were also found in the enlarged alveolar septa. There was no evidence of malignant lymphoma in the lymph nodes or resected lung tissue. Pathological findings including immunohistochemical studies in a surgically resected lung revealed adenocarcinoma in focal LIP which was mainly composed of CD8 T-cells.

Discussion

Bronchogenic carcinoma has frequently been associated with para-neoplastic phenomena, ranging from mild systemic or cutaneous disease to neuromyopathic disorders and interstitial pneumonia (10). It has been reported that lung cancer is frequently associated with usual interstitial pneumonia (UIP) and an excess relative risk of lung cancer has been found in patients with UIP compared with the general population (11). Recently, Yamadori et al also reported a case of primary lung cancer associated with non-specific interstitial pneumonia (NIP) (12). In this report, we describe a case of lung cancer complicated with focal LIP. The lung cancer was surrounded by LIP in the same lobe, and infiltrated by CD-8 positive T-cells as well as alveolar septa in LIP, suggesting an association between lung cancer and focal LIP.

As first described by Liebow and Carrington in 1973, LIP is a pathological term used to describe diffuse interstitial infiltration of mature lymphocytes and plasma cells. It is well known that LIP is associated with systemic disorders, particularly Sjögren’s syndrome (1–8). Liebow and Carrington suggested that LIP is analogous to Sjögren’s syndrome in which the lungs rather than salivary glands are involved in the first instance (1). Recently, it has been reported that LIP is often associated with HIV infection, autoimmune thyroiditis, and multicentric Castleman’s disease. However, the present case was not associated with Sjögren’s syndrome or any other immunologic abnormalities. To our knowledge, this is the first description of an association between LIP and lung cancer. Takabatake et al reported a case of adenocarcinoma of the lung in LIP in 1999, but their case was associated with primary Sjögren’s syndrome (13).

The cause of LIP remains obscure, however an immune process is believed to be essential in most reports (14–17). Since it is commonly associated with hypergammaglobulinemia or hypogammaglobulinemia and since polyclonal B cell proliferation and hyper-secretion or hyposecretion of immunoglobulins may be secondary to defects in regulatory T-cell subsets (18, 19), it is important to clarify the mechanism of immunoregulatory pathways in patients with LIP. The present patient also showed hypogammaglobulinemia (IgG, 794 mg/dl), a finding consistent with a defect in the immunoregulatory system. Joshi et al reported that immunologic abnormalities are related to the pathogenesis of LIP associated with AIDS in children (20). When LIP occurs as part of a systemic disorder (such as AIDS), LIP probably reflects local response to an antigenic stimulus, possibly a kind of circulating antigen. In addition, Yamadori et al reported a case of lung cancer associated with NIP (12). They described the existence of circulating anti-human lung cancer cell antibodies including anti-cytokeratin 8 and 19 antibodies and emphasized the importance of these antibodies in the patho-
genesis of NIP.

Some studies have detailed the immune cell infiltration in lung cancer and the surrounding lung tissue (21–23). Previous studies suggest a beneficial effect of an enhanced immune cell infiltrate in lung cancer. Most of the infiltrating lymphocytes consist of T cells, and NK cells constitute a small portion of the tumor infiltrating lymphocytes (21, 24–27). One study has immunohistochemically determined that an excess of CD3 (pan-T cell) in lung tumors is associated with a good prognosis (25). Another study described the prognostic benefit of tumor-infiltrating CD45RO (memory T cell) in lung cancer (26). Watanabe et al reported that lymphocytic infiltration is marked in adenocarcinoma, particularly in well-differentiated papillary adenocarcinoma, less in squamous cell carcinoma, and least in small-cell carcinoma (28). Erickson reported that the extent of lymphocytic infiltration of tumors and the surrounding lung tissue can reflect the host immune response or tumor antigenicity (29).

Considering that the occurrence of lymphocyte infiltration in lung cancer may be related to the cytotoxic T-cell immunity of the host, infiltrated lymphocytes in LIP in our case may have reflected the host immune response or anti-tumor immunity against the lung cancer. In fact, CD8 positive T-cells infiltrated both the lung cancer and surrounding alveolar septa. This leads to speculation that LIP in our case probably occurred under the antigenic stimulus of lung cancer. Similarly, Travis et al demonstrated that the lymphocytes in LIP in adult HIV-infected patients are predominantly CD8 positive T-cells (5). This leads to speculation that interactions between HIV-specific cytotoxic T lymphocytes and infected macrophages may play a major role in the pathogenesis of LIP in patients with AIDS.

In contrast to our case and HIV-infected patients with LIP, Barbera et al have shown in a previous study that B-cells are the main constituent of pulmonary lymphocytic infiltrates in patients with LIP associated with Sjögren’s syndrome (30). The reason why pulmonary lymphoid infiltrates in some LIP patients consist of B-cells rather than T-cells or vice versa is unknown. However, it is possible that variations in the host immune response would affect the type of immune cell infiltrates in LIP. Host differences could be due to dissimilar mechanisms of lymphocyte recruitment to the lung, which might involve lymphocyte-endothelial interactions, such as vascular addressing, as well as lymphocyte chemoattractant factors, such as interleukins and lymphocyte chemoattractant factor. These represent potential areas for future research to further investigate the pathogenesis of LIP.

In summary, we present a case of lung cancer associated with focal LIP. In addition, the focal LIP in this case probably reflected the local immune response to an antigenic stimulus caused by lung cancer.

### References

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