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Primary Malignant Lymphoma of the Lung (Low-grade B-cell Lymphoma of MALT Type) Occurring in a Patient with Bronchiolitis Obliterans Organizing Pneumonia

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Summary. **In May 1986, a 71-year-old woman was found by chest X-ray to have a nodular shadow in the right middle lobe, which later disappeared spontaneously. In June 1990, her chest X-ray showed wandering shadows diagnosed as bronchiolitis obliterans organizing pneumonia (BOOP) by trans-bronchial lung biopsy (TBLB); this was resolved by October 1990 without steroid therapy. During the follow-up period a nodular shadow of the right upper lobe appeared in December 1994, and gradually enlarged. To determine the diagnosis, a right upper lobectomy was performed in May 1995. Histological examination revealed low-grade B-cell lymphoma of the MALT type. Among defects of autoimmune disorders including Sjögren's syndrome, B-cell activation in BOOP was suspected to be inducing B-cell lymphoma in this case.**

Key words—bronchiolitis obliterans organizing pneumonia (BOOP), non-Hodgkin's lymphoma of the lung, mucosa-associated lymphoid tissue (MALT) lymphoma.

INTRODUCTION

Primary malignant lymphoma of the lung, a very rare type of lymphoma, is sometimes associated with autoimmune diseases, especially Sjögren's syndrome. Bronchiolitis obliterans organizing pneumonia (BOOP) is an interstitial lung disease of unknown etiology which is characterized by lymphocytic alveolitis and organization in the brochiole to intra-alveolar lumen. We observed a case of pulmonary low-grade B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type with a history of BOOP which had been diagnosed 4 years earlier. We here present this case, and discuss the relation between the two disorders.

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CASE REPORT

A 71-year-old woman was admitted to our hospital for further examination of an abnormal lung shadow in May 1995. She had no remarkable past history, but her family history revealed apoplexy in her father, vertebra caries in a younger sister, and tuberculous pleuritis in her husband. Prior to this, a medical examination in May 1986 had detected a nodular lesion of the right middle lobe (2×2 cm) on a chest X-ray. The shadow resolved spontaneously without therapy by August 1986. In May 1990, fever, a non-producing cough, and a right chest pain appeared. She was admitted to our hospital with the diagnosis of pneumonia. Her chest X-ray on admission showed pneumonic infiltrations in the right upper lobe and right S^6, and chest CT showed air-bronchogram (Fig. 1). In laboratory examination, CRP was 3.2 mg/dl, erythrocyte sedimentation rate was 101 mm/hr, and leucocyte count was 6400/mm^3 with 73% neutrophils, 20% lymphocytes, 6% monocytes, and 1% eosinophil. Suspecting a diagnosis of pneumonia, various antibiotics including Cefotiam (CTM), Ceftazidime (CAZ), Clindamycin (CLDM), Tobramycin (TOB), and Ofloxacin (OFLX) were administered; these, however, were not effective and a chest X-ray showed

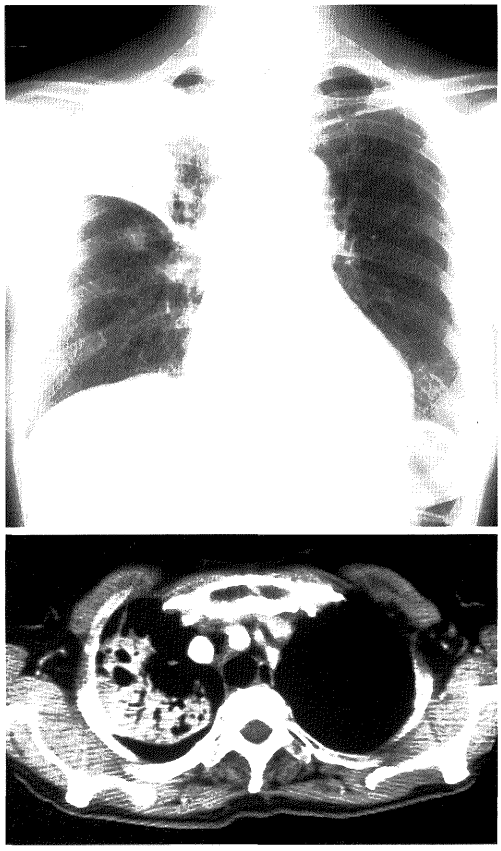

Fig. 1. Chest X-ray and CT film on admission (May, 1990) show shadows of an alveolar pattern in the right upper lobe and right S^6.

wandering shadows (Fig. 2). A trans-bronchial lung biopsy (TBLB) was performed from the right S^8a on August 6, 1990, and histological examination revealed lymphocytic alveolitis and organization in the alveolar duct to alveolar lumen (Fig. 3). In consideration of the chest CT findings, bronchiolitis obliterans organizing pneumonia (BOOP) was offered as a rational diagnosis. Bronchoalveolar lavage (BAL) was not performed. Chest X-ray shadows were almost resolved by October 1990. Thereafter, chest X-rays were taken every 6 months, with no abnormal shadow observed. In December 1994, a chest X-ray showed a nodular shadow in the right S^2b. Bronchofiberscopic examination disclosed no malignant cell nor acid-fast bacillus; still, the shadow grew gradually. A diagnosis of lung cancer was suspected, and the patient was again admitted to our hospital in May 1995.

At this admission, body temperature was 36.8°C, body weight was 49 kg, and height was 143 cm. Blood pressure was 140/80 mmHg, and pulse rate was 72/min regular. Palpebral conjunctiva was not anemic, and bulbar conjunctiva was not icteric, neither was there lymphadenopathy nor struma. There was no clubbed finger nor cyanosis. Pulmonary auscultation was normal, and there was no hepatosplenomegaly. Neurological findings were normal. Laboratory data on admission revealed that erthrocyte sedimentation rate was 19 mm/hr and PPD skin reaction was positive (20×14 mm). Hemoglobin concentration was 13.2 g/dl, leucocyte count was 4200/mm^3 with 66% neutrophils, 29% lymphocytes and 4% monocytes, and

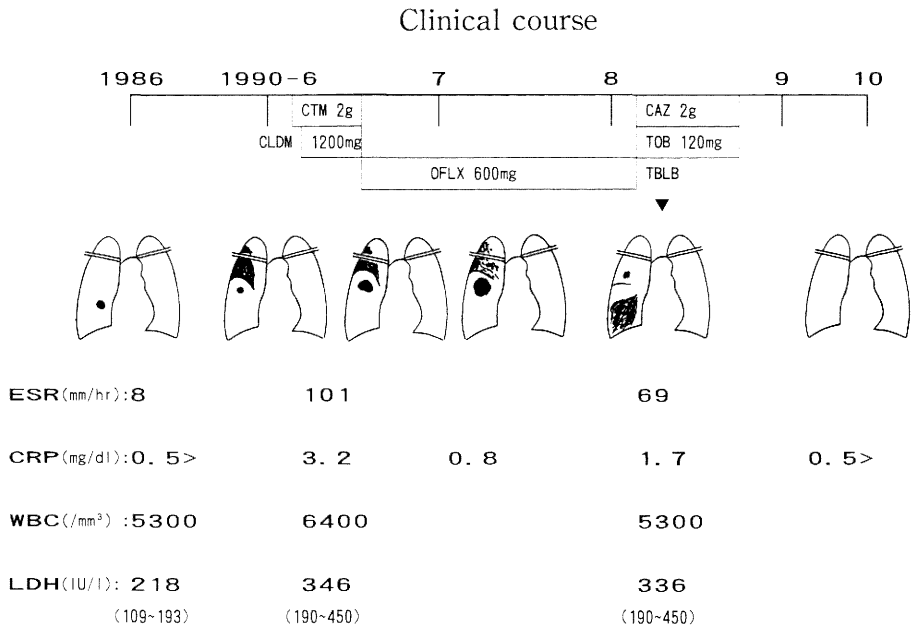

Fig. 2. Clinical course of first admission (1990).

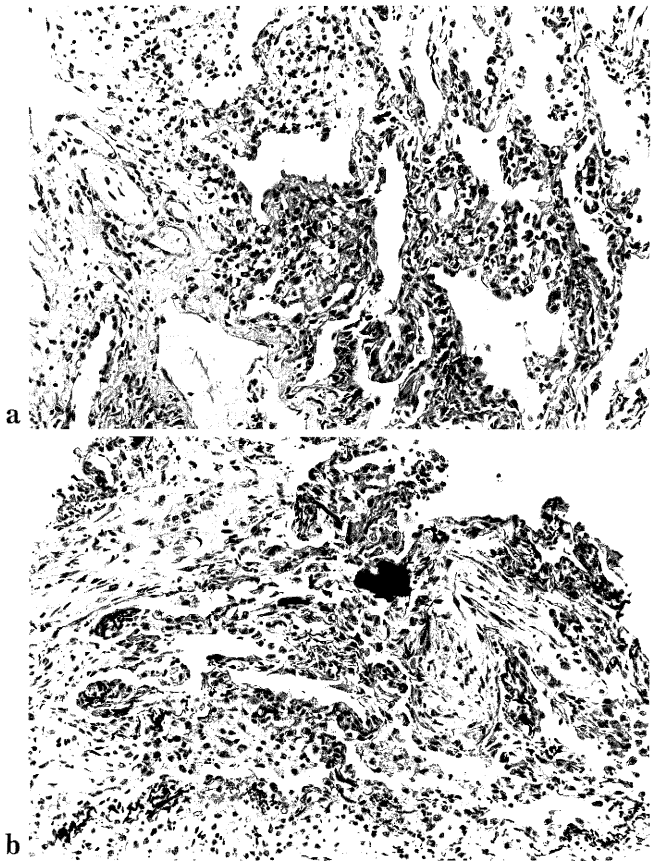

Fig. 3. Histology of trans-bronchial lung biopsy (right S^8a) in August, 1990. **a.** Lymphocytic alveolitis (H.E. stain, ×128). **b.** Organization in alveolar duct to alveolar lumen (E.M.G. (Elastica Masson Goldner) stain, ×128).

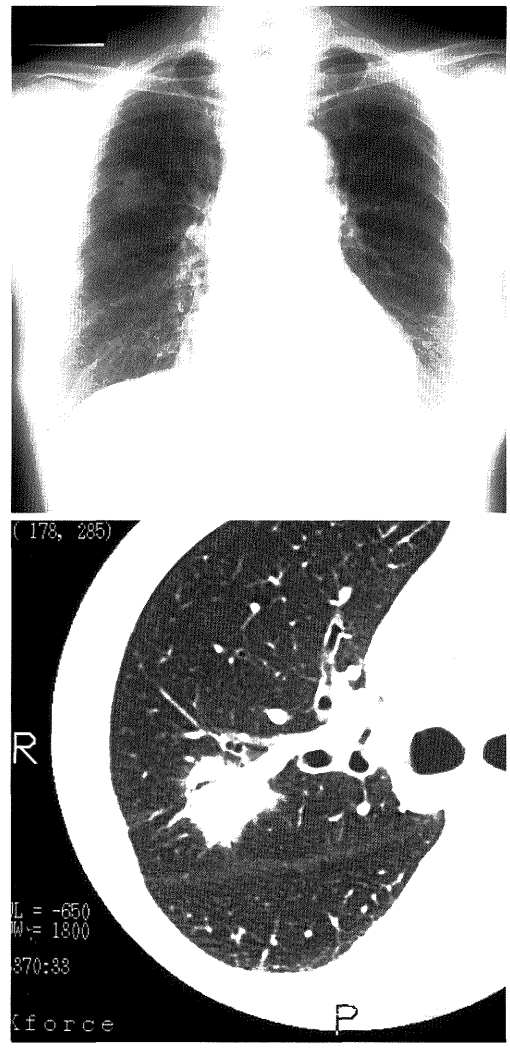

Fig. 4. Chest X-ray on second admission (May, 1995) shows a nodular shadow in the right S^2b; CT film shows air-bronchogram in the nodule.

thrombocyte count was $20.4\times10^4/mm^3$. Electrolytes and renal function were normal. The liver function was normal except for LDH (517 IU/l, normal: 190-450 IU/l). There was no hyper γ-globulinemia, and the immunoglobulin level was normal. CRP was 0.3 mg/dl, and auto-antibodies (ANF, SSA, SSB) were negative. Tumor markers (CEA, SCC, NSE) were not elevated. Sputum bacteriology was negative for bacteria and acid-fast bacillus.

Her chest X-ray on admission showed a nodular shadow with an irregular margin (2.3×3 cm) in the right S^2b, which was enlarged compared with that in December 1994. Chest CT-film showed a spicular formation and air-bronchogram in the nodule (Fig. 4). The mediastinal lymphnode was not enlarged. Cytology by bronchofiberscope did not detect malignant cells, but the possibility of lung cancer was not dismissed. Therefore, a right upper lobectomy and mediastinal lymphnode dissection were performed in June 1995. Macroscopically, the resected lesion was a yellowish white colored with an irregular margin. Histologically, monocytoid cells, centrocyte-like cells, and partially, plasma cells infiltrated between well developed lymphfollicles around the bronchus. The neoplastic lymphoid cells were stained with a B-cell marker (L-26). There were also lympho-epithelial lesions (intraepithelial infiltration) (Fig. 5). Plasma cells were stained with λ-light chain and IgM, which proved to be a monoclonality of the plasma cells (Fig. 6). From the above histological findings, a diagnosis of pulmonary (extra nodal) low-grade B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type was made. There was no invasion in the media-

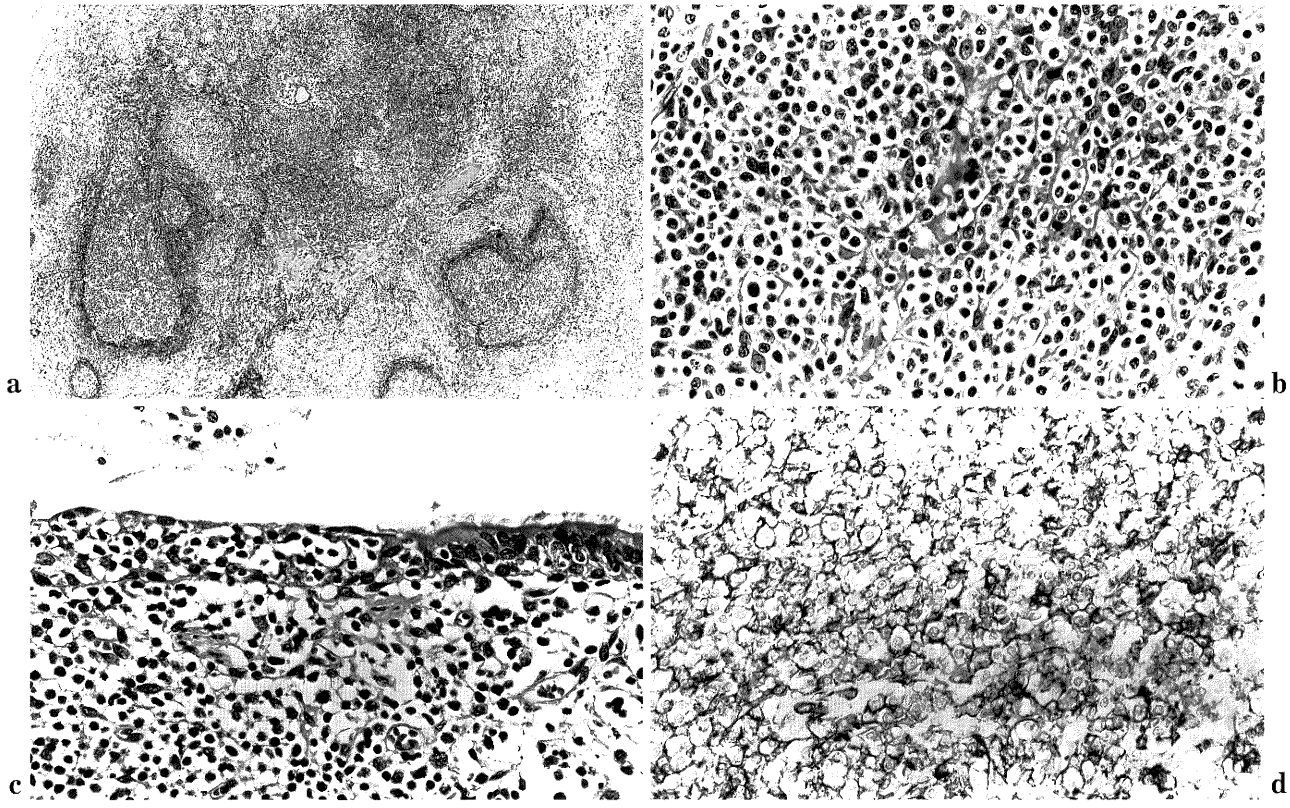

Fig. 5. Histology of the resected lung tumor. **a.** Neoplastic lymphoid cells infiltrate to the para-follicular area with some hyaline sclerosis (H.E. ×24). **b.** The lesion consists of monocytoid cells and centrocyte-like cells (H. E. ×240). **c.** Lympho-epithelial lesion. The neoplastic cells infiltrate into the bronchial epithelium (H.E. ×240). **d.** Neoplastic lymphoid cells are stained with a B-cell marker (L26, DAKO, Denmark), (immunoperoxidase-labelled streptoavidin biotin (LSAB) method (DAKO, USA). ×240)

stinal lymphnode. Brain CT, abdominal CT, gastroscope, and bone marrow examination did not reveal lymphoma invasion. Systemic Ga-scintigram after operation could not detect any uptake of Ga. From the above findings, the diagnosis was primary malignant lymphoma of the lung (clinical stage I-EA: Ann Arbor classification). There was no histological evidence of BOOP in the resected lung.

The patient had no sicca symptoms, and complications of Sjögren's syndrome was neglected by Schirmer's test, sialogram, and lip biopsy. There was no sign nor symptom of other autoimmune diseases.

DISCUSSION

Primary malignant lymphomas of the lung comprise less than 0.5% of all primary malignant tumors in the lung,[1] as the lung is an unusual site for lymphomas. Freeman et al., who compiled 1467 cases of extranodal lymphomas, noted only 53 tumors (3.6%) originating in lower respiratory tract.[2] Li et al. investigated 62 cases of primary malignant lymphoma of the lung[3]: fifty-eight cases were B-cell lymphomas, of which 43 cases were low-grade B-cell lymphoma of the bronchus-associated lymphoid tissue.

Histological findings in our case are coincident with malignant lymphoma of mucosa-associated lymphoid tissue (MALT) advocated by Isaacson et al., in 1983.[4] Histopathology of this tumor can be summarized as follows.[5] Reactive follicles are consistently present and surrounded by neoplastic lymphoid cell infiltrate which consists of small to medium-sized lymphoid cells whose central feature is an irregular nuclear contour (centrocyte-like cell). The centrocyte-like cells selectively invade epithelial structures to form characteristic lympho-epithelial lesions and show plasma cell differentiation in a portion of cases. The most significant clinical feature of MALT lymphomas is their clinical indolence. These lymphomas often remain localized but, when they do disseminate, prefer to involve other sites with mucosa-associated

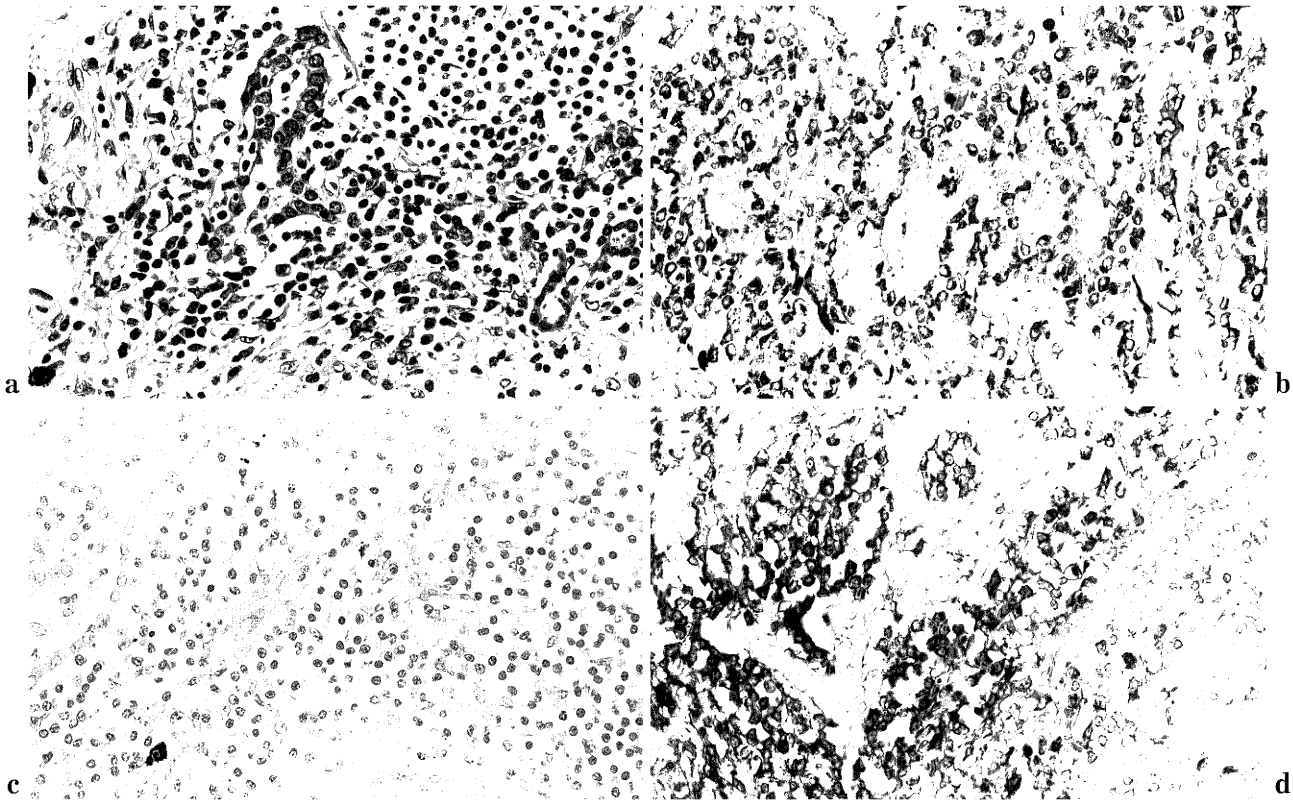

Fig. 6. a. Plasma cells are predominantly distributed beneath the bronchus (H.E. ×240). The plasma cells have monoclonal immunoglobulin, IgMλ. (**b.** IgM (RI/69, DAKO, Denmark). **c.** κ-light chains (A8B5, DAKO, Denmark), **d.** λ-light chains (N10/2, DAKO, Denmark), immunoperoxidase LSAB method ×240).

lymphoid tissue. Many patients have a history of autoimmune disease, such as Sjögren's syndrome or Hashimoto's thyroiditis, or of helicobacter gastritis. In the case of Sjögren's syndrome, it is speculated that B-cells infiltrating the salivary gland undergo cell division as a result of stimulation by activated T-cells, and have an increased opportunity for bcl-2 translocation to result in lymphoma.[6]

At present, there are only two case reports of malignant lymphoma in BOOP that were diagnosed histologically. Both cases are malignant lymphomas that originated in the lymphnode. One case[7] is T-cell lymphoma of cervical lymphnode in which BOOP was diagnosed by open lung biopsy, but its detailed course is unknown. The other case[8] is non-Hodgkin's lymphoma of the cervical lymphnode which developed during steroid therapy, 4 years after BOOP was diagnosed by transbronchial biopsy. In the latter case, the pathogenesis of lymphoma is speculated to be due to the immunosuppressive role of corticosteroids or oncogenic viral infection. There is a case report of a primary T-cell lymphoma of the lung presenting with bilateral, patchy infiltrates,[9] but to out knowledge, no case of primary lymphoma of the lung which developed in BOOP has been described previously in the literature.

Our case showed no history of autoimmune diseases, and did not receive steroid therapy. BAL fluid cell findings in patients with BOOP suggest a hyperimmune reaction in the lung, which is summarized as lymphocytosis with a decreased ratio of $CD4^+/CD8^+$, and an increase in both neutrophils and eosinophils.[10] The appearance of plasma cells in the BAL fluid of eosinophilic pneumonia suggests the presence of T cell-derived cytokines responsible for the differentiation of B cell into plasma cells in the lung.[11] Costabel et al. described the presence of plasma cells as another feature of BAL in BOOP.[12] From the above reported findings, T cells are a major constituent, but B cells are functionally activated in the BAL fluid of BOOP. In our case, a wandering lung shadow was resolved 4 years earlier, but activation of B cells is believed to have been continuous and induced B-cell lymphoma of the lung.

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