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Diffuse Large B-Cell Lymphoma Arising from the Lesion of Chronic Lobar Atelectasis

Naoko Fujita,[1] Masaru Ando,[1] Akihiko Goto,[1] Masanori Sakata,[2] Masao Ogata,[2] Yuko Usagawa,[1] Hiroki Yoshikawa,[1] Mari Yamasue,[1] Kosaku Komiya,[1] Kenji Umeki,[1] Shin-ichi Nureki[1] and Jun-ichi Kadota[1]

[1]Department of Respiratory Medicine and Infectious Diseases, Oita University Faculty of Medicine, Yufu, Oita, Japan
[2]Department of Medical Oncology and Hematology, Oita University Faculty of Medicine, Yufu, Oita, Japan

Pulmonary lymphoma is rare, accounting for < 1% of primary lung cancers. Most primary pulmonary lymphomas (PPL) are low-grade mucosa-associated lymphoid tissue (MALT)-type, and among PPL, diffuse large B-cell lymphoma (DLBCL) is extremely rare. In contrast, there has been an increase in the incidence of DLBCL among patients with autoimmune disorders and recurrent or chronic bacterial infection. A subset of DLBCL has been reported to develop through transformation of preexisting or concurrent MALT. The respiratory symptoms are non-specific, and the chest X-ray findings demonstrate the presence of interstitial and mixed alveolar infiltrates, nodular lesions, and localized homogeneous consolidations; the diagnosis of pulmonary DLBCL is thus challenging and often leads to a misdiagnosis or delayed diagnosis. We herein report a case of DLBCL which was assumed to have arisen from the lesion of chronic atelectasis that was successfully diagnosed by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). A 74-year-old woman with diffuse bronchiectasis and chronic atelectasis of the left lower lobe suffered from productive cough and high fever. Increased airway filling with mucoid secretion was repeatedly observed within the area of atelectasis with bronchiectasis, and left lower lobe atelectasis developed. Subsequently, the hilar and mediastinal lymph nodes gradually became enlarged, and DLBCL was pathologically confirmed. In the present case, DLBCL was considered to have arisen in the lesion of chronic atelectasis. Physicians should recognize that DLBCL may develop at the site of chronic atelectasis during disease course of diffuse bronchiectasis, and thus DLBCL may be misdiagnosed as superimposed infection of chronic atelectasis.

Keywords: bronchiectasis; chronic atelectasis; diffuse ectasis; diffuse large B-cell lymphoma; endobronchial ultrasound-guided transbronchial needle aspiration
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Introduction

Pulmonary lymphoma is uncommon accounting for < 1% of primary lung cancers (Miller and Allen 1993), and diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin lymphoma (Friedberg and Fisher 2008). Primary pulmonary lymphoma (PPL) is a monoclonal lymphoid proliferation affecting the lungs in patients with no detectable extrathoracic lymphoma and it ranges from relatively indolent mucosa-associated lymphoid tissue (MALT) lymphoma to more aggressive forms of DLBCL. PPL usually originates from MALT, developing into either Hodgkin lymphoma or non-Hodgkin's lymphoma. Non-Hodgkin's B-cell lymphoma is the most frequent of all PPL and the majority of these are MALT lymphoma.

DLBCL directly arising from lung tissue is extremely rare, and accounts for only 0.4% of all lymphomas (Ferraro et al. 2000). However, the incidence of DLBCL may be underestimated, as it can potentially spread rapidly from the lung into mediastinal and extrathoracic lesions. Furthermore, DLBCL associated with chronic inflammation

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Correspondence: Masaru Ando, Department of Respiratory Medicine and Infectious Diseases, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama-machi, Yufu, Oita 879-5593, Japan.
e-mail: mando@oita-u.ac.jp

was reported to occur in elderly people (median 65 to 70 years old) with classical involvement of the pleural cavity, bone, or joint (Chan et al. 2008).

We herein report a case of DLBCL which was considered to have arisen from the lesion of chronic atelectasis. To our knowledge, there are no previous reports of DLBCL associated with chronic atelectasis.

Case Presentation

A 74-year-old woman was admitted to our hospital due to fever, progressive dyspnea and anorexia. The patient has been prescribed clarithromycin (200 mg/day) for diffuse bronchiectasis for several years, but she had repeatedly experienced exacerbations of bronchitis and pneumonia. The clinical course of the patient before admission is summarized in Fig. 1: 26 months earlier, left lower lobe bronchopneumonia (Fig. 1A); 19 months earlier, pneumonia of both lower lobes (Fig. 1B); 13 months earlier, left upper and lower lobe pneumonia (data not shown); and 10 months earlier, left lower lobe pneumonia (data not shown). Treatment for two weeks with intravenous ceftriaxone followed by another two weeks of oral levofloxacin was not effective. The patient was then treated with the intravenous administration of meropenem. Following the treatment with meropenem, her clinical symptoms and laboratory data were improved, although the collapsed infiltration of the left lower lobe was detected (Fig. 1C).

Two months before admission, the patient presented with high fever and exacerbation of productive cough with bloody phlegm. Chest X-ray showed infiltration of the right upper field and left lower lobe. After the administration of oral antibiotics (levofloxacin and azithromycin), the right upper field infiltration was disappeared on conventional computed tomography (CT), whereas the bronchiectatic airway filling by mucoid secretion was increased in the left lower field and prominent hilar and mediastinal lymphadenopathy developed (Fig. 2). However, treatment for five days with intravenous sulbactam/ampicillin was not effective; consequently, the patient was transferred to our hospital.

A physical examination on admission revealed the following findings: body temperature, 36.9°C; blood pressure, 155/85 mmHg; pulse, 104 beats/min. The superficial lymph nodes were not palpable. Chest auscultation revealed the attenuation of respiratory sounds in the left lower lung field. She was a never smoker. Laboratory tests revealed decreased total protein (5.62 g/dl) and albumin (2.50 g/dl), and elevated aspartate aminotransferase (AST; 56.8 IU/l), alanine aminotransferase (ALT; 37.8 IU/l), alkaline phosphatase (ALP; 377 IU/l), lactate dehydrogenase (LDH; 358

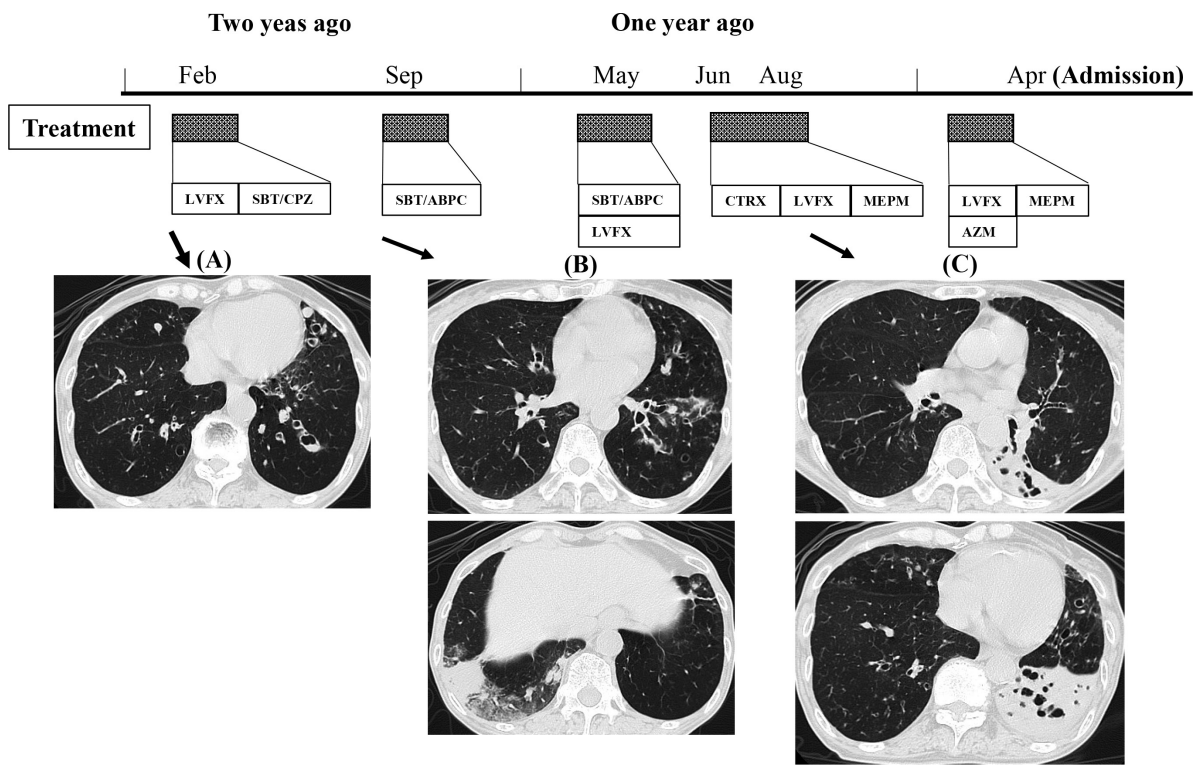

Fig. 1. Clinical course before admission.
A) Conventional computed tomography (CT) demonstrated left lower lobe bronchopneumonia 26 months prior to admission.
B) Conventional CT demonstrated bilateral lower lobe pneumonia 19 months prior to admission.
C) Conventional CT demonstrated the collapsed infiltration of the lower lobe 8 months prior to admission.
LVFX, levofloxacin; SBT/CPZ, sulbactam/cefoperazone; SBT/ABPC, sulbactam/ampicillin; CTRX, ceftriaxone; MEPM, meropenem; AZM, azithromycin.

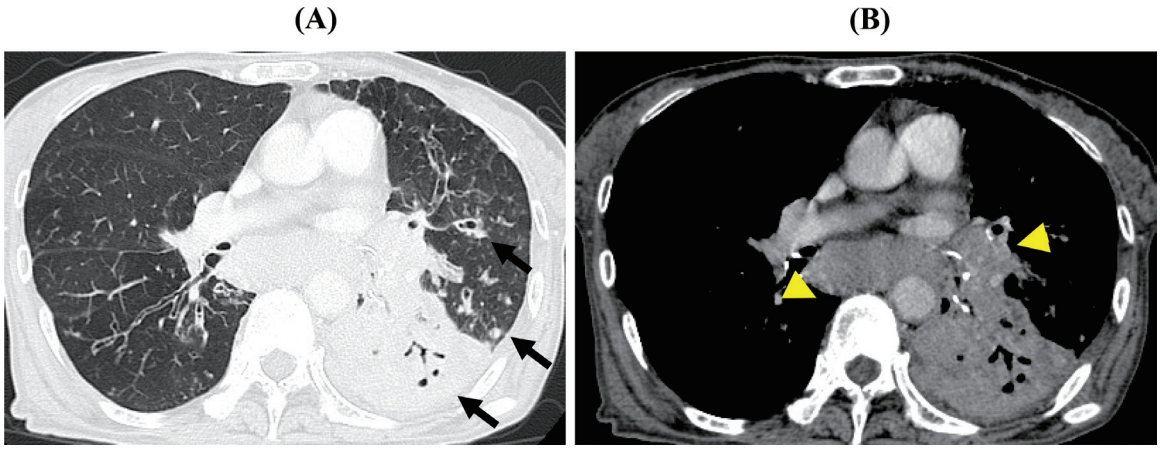

Fig. 2. Conventional CT findings five days prior to admission.
Conventional CT (A, B) demonstrated increased bronchiectatic airway filling by mucoid secretion on the lingular segment and lower lobe of the left lung (arrow) and the enlargement of the hilar and mediastinal lymph nodes (arrowhead).

IU/l), C-reactive protein (CRP; 9.24 mg/dl), and soluble interleukin-2 receptor (sIL-2R; 5,516 U/ml). An echocardiogram revealed a normal ejection fraction. An arterial blood gas analysis revealed the following: pH, 7.45; PaO_2, 104 mmHg; $PaCO_2$, 35 mmHg at a flow rate of 2L/min with a nasal cannula. Except for cytokeratin 19 fragment (CYFRA 21-1; 3.0 ng/ml), the patient's tumor marker levels (carcinoembryonic antigen [CEA], squamous cell carcinoma antigen [SCC], neuron-specific enolase [NSE] and pro-gastrin releasing peptide [pro-GRP]) were almost within the normal range. High-resolution computed tomography (HRCT) showed that the volume of the collapsed parenchyma had increased and that the hilar and mediastinal lymph nodes had increased in size (Fig. 3A). Moreover, both pleural and pericardial fluid was present. Positron emission tomography-CT (PET-CT) showed a number of lesions with the high accumulation of FDG in the left lower lobule, the mediastinal and hilar lymph nodes, the left adrenal gland, and multiple bones (Fig. 3B). Endobronchial ultrasound-guided transbronchial needle biopsy was per-

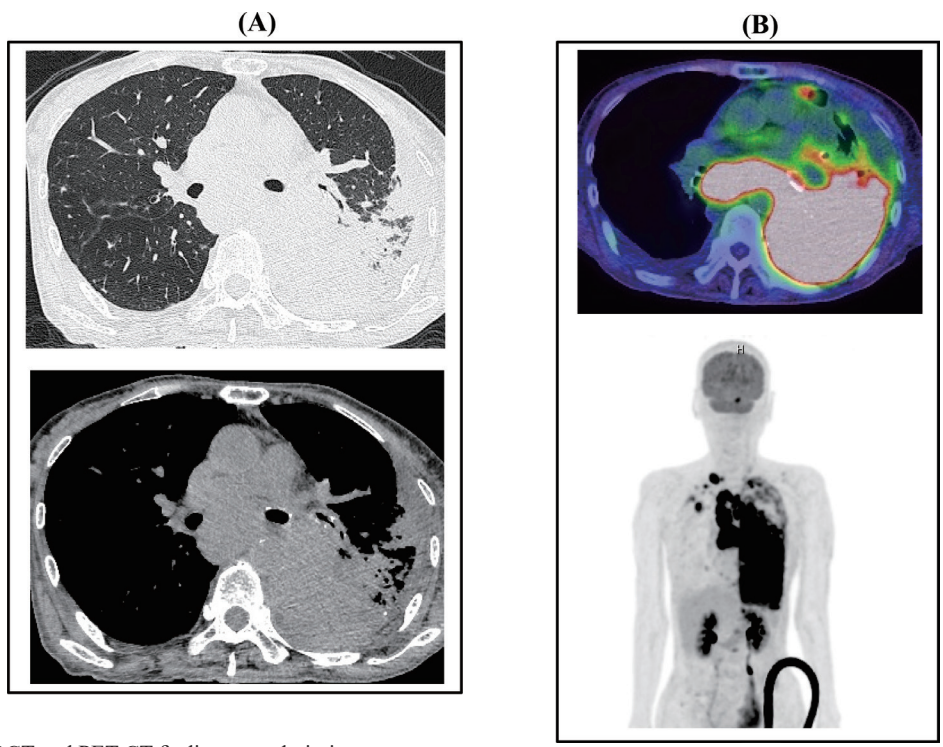

Fig. 3. HRCT and PET-CT findings on admission.
A) High-resolution computed tomography (HRCT) demonstrates the increased volume of atelectasis and the enlargement of the hilar and mediastinal lymph nodes, compared with the CT images obtained before admission (see Fig. 1C).
B) Positron emission tomography-CT (PET-CT) shows a number of sites with the high accumulation of FDG in the left lower lobule, the mediastinal and hilar lymph nodes, the left adrenal gland, and multiple bones.

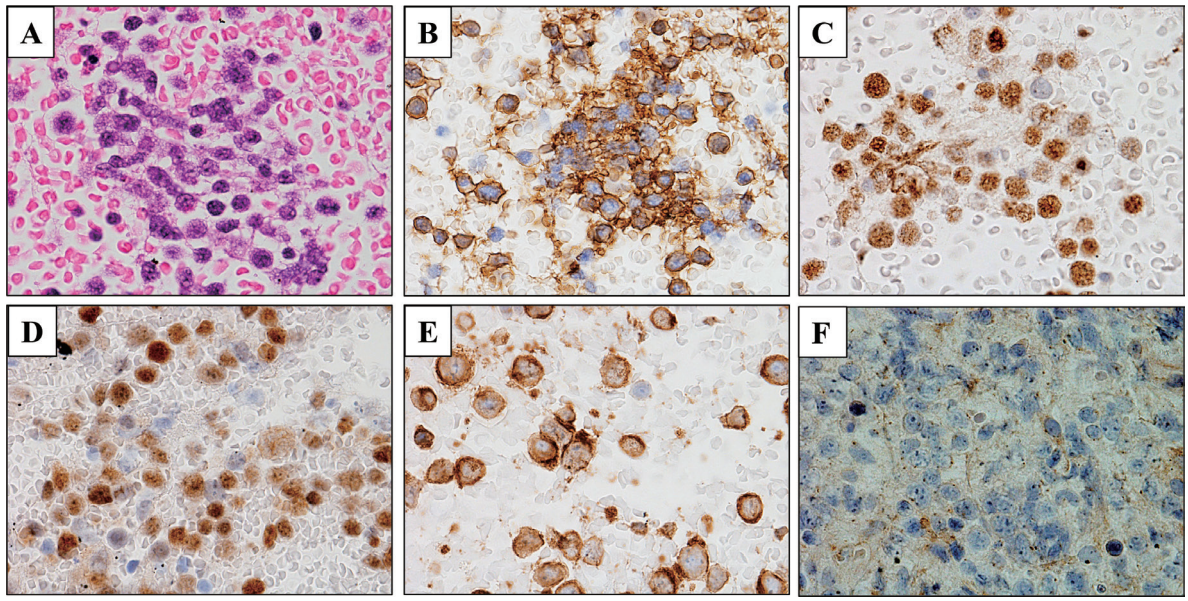

Fig. 4. Histopathology and immunohistochemical findings.
A) Hematoxylin-eosin staining shows the diffuse proliferation of large cells.
B)-E) Immunohistochemistry staining show positive for CD 20, BCL-6, MUM-1 and CD 79a.
F) Immunohistochemistry staining show negative for CD 10 (× 400).

formed for the #4R and #7 mediastinal lymph nodes. Hematoxylin-eosin staining showed diffuse infiltrate of medium-sized to large atypical lymphocytes with small nucleoli, accompanied by moderate vascular and histiocytic reactions (Fig. 4A). An immunohistochemical study revealed that the cells were positive for CD20 (Fig. 4B), B cell lymphoma 6 [BCL-6] (Fig. 4C), multiple myeloma oncogene 1 [MUM-1] (Fig. 4D), CD79a (Fig. 4E), B cell lymphoma/leukemia-2 [BCL-2], c-Myc [CMYC], and Ki-67 [MIB-1], and negative for CD10 (Fig. 4F), CD3, Cyclin D1, CD25, and CD30. Accordingly, DLBCL was pathologically confirmed. EBV-encoded small RNA *in situ* hybridization (EBER-ISH) was negative.

Combination therapy with THP-COP (pirarubicin, cyclophosphamide, vincristine and prednisolone) and rituximab was highly effective, and her symptoms were gradually improved. By six months after the start of chemotherapy, the left lower lobe had reduced in size and returned to the findings of collapsed lung with bronchiectasis (Fig. 5A). By eight months, the slight uptake of FDG was observed in the collapsed lung; the other lesions with the uptake of FDG had disappeared (Fig. 5B).

Discussion

The present patient with diffuse bronchiectasis suffered from persistent productive cough for several years and presented with lobular atelectasis and cavities due to recurrent exacerbation of bronchitis or pneumonia. Two months before admission, the patient presented with high fever, bloody phlegm and an exacerbation of productive cough. Chest radiography showed infiltration in the right upper and left lower fields. After treatment with antibiotics, the right upper field infiltration disappeared, whereas the airway filling by mucoid secretion on the left lower field increased and hilar and mediastinal lymphadenopathy developed (see Fig. 3A). Eventually, DLBCL was pathologically confirmed.

DLBCL is the second most common type of primary pulmonary lymphoma next to extranodal marginal zone lymphoma of mucosa-associated lymph node tissue (MALT). Patients have no overt symptoms during the initial stages; however, as the disease progresses, they are likely to present non-specific symptoms, including dyspnea, cough, chest pain, sputum and other obstructive and infectious symptoms, as well as fever and weight loss (Cadranel et al. 2002). DLBCL has variable imaging manifestations but most commonly appears as single or multiple nodules or masses; cavitation is common, particularly, in larger lesions (Hare et al. 2012; William et al. 2013). The CT findings of the present case are thought to be unique in that multiple cysts in the left lower lobe were surrounded by consolidation of the lung parenchyma, which mimicked pneumonia superimposed on chronic atelectasis.

The accurate diagnosis of pulmonary lymphomas requires tissue sampling through invasive procedures. Open thoracotomy or chest CT-guided percutaneous biopsy is widely used in the diagnosis (Yu et al. 2012; Wang et al. 2013). However, current evidence suggests that endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can be used for the initial evaluation of patients with suspected lymphoma (Kheir et al. 2016). A cytological diagnosis of lymphoma has been thought to be problematic. In non-Hodgkin's lymphoma the presence of necrosis and geographic involvement of lymph nodes may

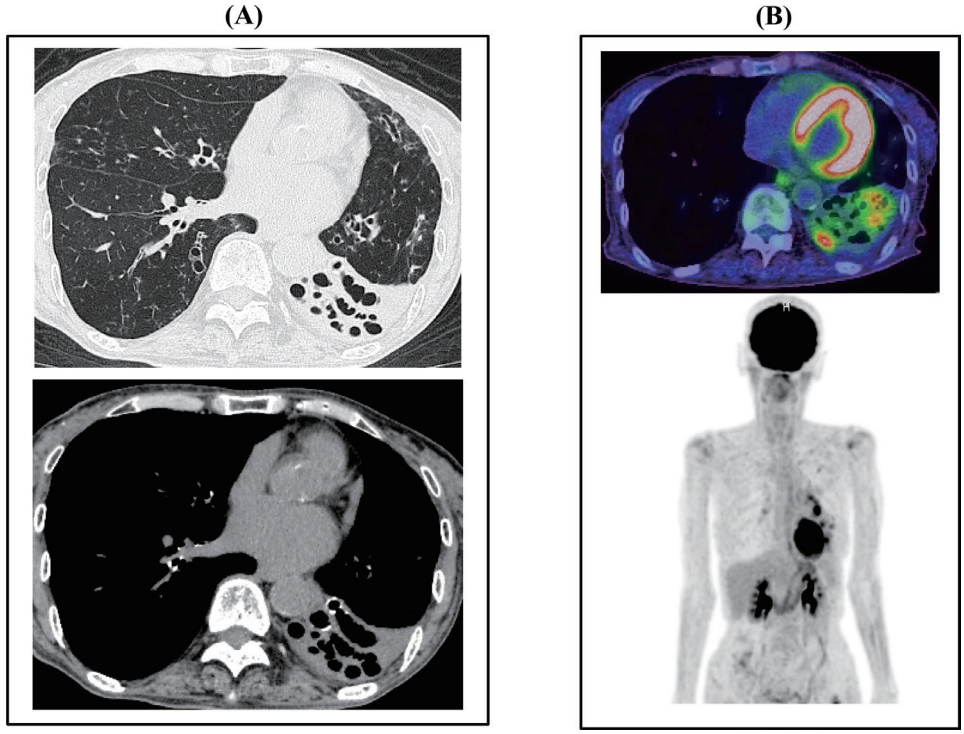

Fig. 5. HRCT and PET-CT findings after 8-month chemotherapy.
A) Expanded atelectasis of the left lower lobe decreased in size, and the airspace of bronchiectasis was resumed.
B) PET-CT shows the slight uptake of FDG in the left lower lobe of the lung. No other lesions with an increased FDG uptake were found.

affect the results of EBUS-TBNA (Yilmaz and Ozturk 2018). Adequate sampling by TBNA may resolve these problems. Ko et al. (2013) showed that EBUS-TBNA provides sufficient samples for definitive primary diagnosis and the classification of malignant lymphoma by providing adequate material for ancillary studies such as immunohistochemical staining, flow cytometry, florescence *in situ* hybridization (FISH), and microbiologic studies. In the present case, these ancillary assays were performed using EBUS-TBNA.

According to the relationship between lobar atelectasis and lymphoma, approximately 50% of patients with endobronchial lymphoma are known to show lung collapse on chest radiography (Eng and Sabanathan 1993). Endobronchial lymphoma is classified into two types, according to the pattern of involvement. Type I includes diffuse submucosal infiltration originating from hematogenous or lymphangitic spread in the presence of systemic lymphoma. Type II includes airway involvement by a localized mass due to direct the spread of lymphoma from the adjacent lymph nodes or arising *de novo* from bronchus-associated lymphoid tissue (BALT) (Rose et al. 1986; Solomonov et al. 2008). The present case did not show airway obstruction or narrowing, or enlargement of the lymph nodes adjacent to the left lower lobe bronchus when lobar atelectasis was initially identified. With chronic atelectasis, secondary infection supervenes and complicates the process, including self-perpetuating chronic inflammatory involvement of bronchi and parenchyma resulting in bronchiectasis and destruction of the lobe (Kala et al. 2008). In the present case, we hypothesize that the history of recurrent exacerbation of bronchitis or pneumonia caused by mucus plugging but not endobronchial lymphoma located on the lobar bronchus was associated with the development of chronic atelectasis.

Cases of DLBCLs associated with severe chronic inflammation have been reported; they are most frequently associated with longstanding pyothorax (Fukayama et al. 1993). However, this phenomenon is also seen with osteomyelitis, assorted metal implants and chronic venous ulcer and almost all cases are EBV-positive (Mori et al. 1996; Copie-Bergman et al. 1997; Cheuk et al. 2005). In contrast, there are a few reports on EBV-negative DLBCL arising from the replacement of a prosthesis or refractory lung abscess (Matsumoto et al. 2015; Sunitsch et al. 2016). Likewise, our case was EBV-negative DLBCL. It is controversial whether DLBCL associated with chronic inflammation is always associated with EBV infection.

In the present case, the pathological diagnosis of abnormal shadows, which occurred in conjunction with the collapse of the left lower lobe was not confirmed. DLBCL superimposed on collapsed lung was not histopathological confirmation. FDG-PET revealed the marked accumulation of FDG in multiple organs, such as the left lower lobe, the mediastinal and hilar lymph nodes, the let adrenal gland, and also in multiple bones. Re-evaluation FDG-PET after

THP-COP and rituximab revealed the slight uptake of FDG in the collapsed lung and the disappearance of other lesions. Therefore, pulmonary DLBCL located coincident with the collapsed lung was suspected. DLBCL can develop in lymph nodes or outside of the lymphatic system in areas like the intestines, skin, bone, or brain and pulmonary lesions is rare. It may be located (in one spot) or generalized (spread throughout the body). Primary pulmonary lymphoma (PPL) is defined as clonal lymphoid proliferation affecting one or both lungs (parenchyma and/or bronchi) in a patient with no detectable extrapulmonary involvement at diagnosis or during the subsequent 3 months (Cadranel et al. 2002), PPL originates frequently from the B cell-lymphoma of MALT of the bronchus that is assumed to be acquired as a result of chronic antigenic stimulation such as smoking, autoimmune diseases, or infection (Zinzani et al. 2003). In the present case, high accumulation of FDG-PET was detected at multiple sites of extrathoracic locations, which did not fulfill the diagnosis of PPL. However, due to its rapid spread into the mediastinum and extrathoracic locations, the quite incidence of primary pulmonary DLBCL may be underestimated (Dirweesh et al. 2017; Zhu et al. 2017).

In the present case, it was presumed that DLBCL initially developed from the lesion of the collapsed lung and had already disseminated to multiple extrathoracic organs by the time when the patient had been referred to our hospital. On the other hand, the pulmonary lesions may represent secondary extranodular disease spread. The designation of stage III and IV lymphomas as primary extranodal non-Hodgkin lymphoma is indeed questionable (Vannata and Zucca 2015).

In conclusion, due to its non-specific presentation, the diagnosis of pulmonary DLBCL is difficult, which often leads to a misdiagnosis or delayed diagnosis. Physicians should recognize that DLBCL may develop at the site of chronic atelectasis during disease course of diffuse bronchiectasis and that it may be misdiagnosed as a superimposed infection in patients with chronic atelectasis.

Conflict of Interest

The authors declare no conflict of interest.

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