

## Case Report

# Intravascular large B-cell lymphoma confirmed by lung biopsy

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**Abstract:** Intravascular lymphoma is a very rare form of large B-cell non-Hodgkin's lymphoma which is characterized by selective growth of lymphoma cells within the lumina of small blood vessels. We report a 64-year-old woman visited hospital because of persistent cough, intermittent high fever as high as 38.7 °C and occasional shortness of breath. Her chest CT showed left upper lobe pneumonia and tuberculosis skin test (PPD test) was positive. She was suspected with tuberculosis and treated with anti-tuberculosis drugs. However, her symptoms and general condition deteriorated, and she visited our hospital. She had no abnormal findings on physical examination, but had abnormal laboratory findings, including decreased hemoglobin, elevated LDH and C-reactive protein. Arterial blood gas analysis showed moderate hypoxaemia. A chest radiograph showed pneumonia in whole lung and CT showed diffused ground glass opacities in both lung fields. Lung biopsy confirmed a diagnosis of intravascular large B-cell lymphoma. Primary pulmonary manifestation is very rare. The diagnosis is based on the histopathology and immunohistochemistry.

**Keywords:** Intravascular large B-cell lymphoma, lung biopsy, immunohistochemistry

## Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of large cell lymphoma which is characterized by the proliferation of lymphoid cells within the lumina of small blood vessels, particularly within capillaries [1]. When lymphoma cells proliferate within the lumina of the small vessels clinical symptoms occur. The most common clinical symptoms involve central nervous system (CNS) manifestations, fever of unknown origin, cutaneous lesions, or hemophagocytic syndrome [2-4]. Although autopsy findings have demonstrated that pulmonary involvement is common in this disease, primary manifestation in the lung has been only rarely described [5]. An IVLBCL patient had diffused ground glass opacities on CT, though hypoxia and dyspnea was present, and the diagnosis was made by lung biopsy.

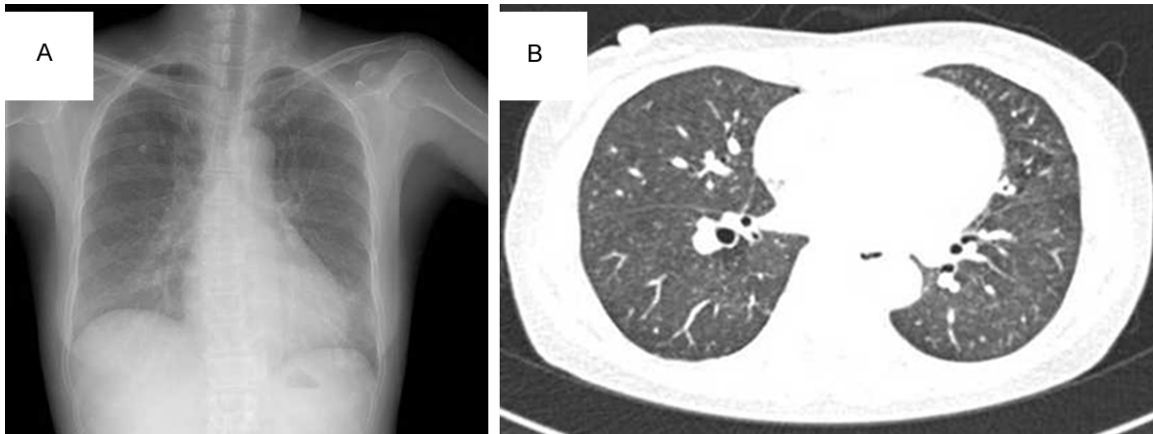
## Case presentation

A 64-year-old woman who had been complaining of persistent cough, intermittent high fever

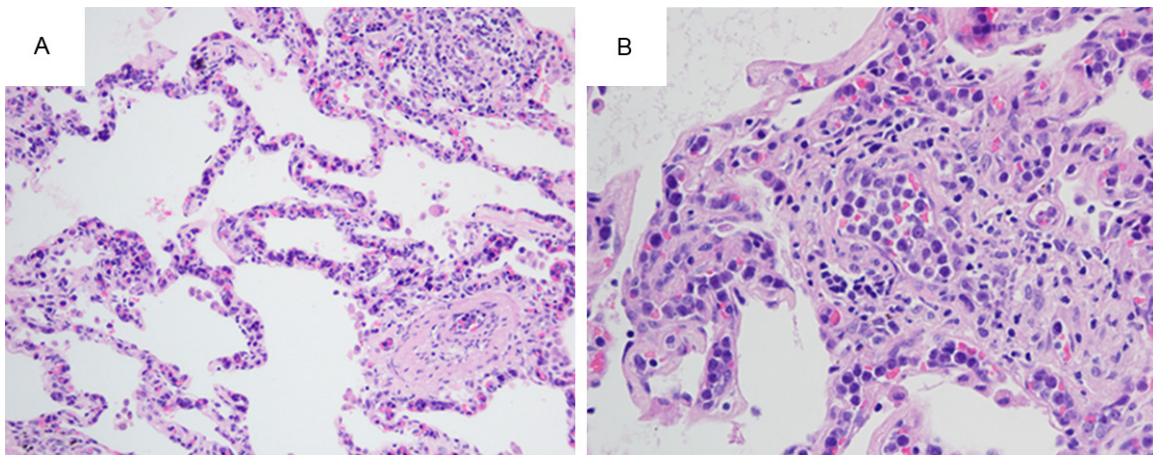
as high as 38.7°C and occasional shortness of breath for 6 months was admitted to a community hospital. Her chest CT showed left upper lobe pneumonia and tuberculosis skin test (PPD test) was positive. A concomitant bacterial or tuberculosis was suspected, and administration of quinolones, isoniazid, rifampicin and ethambutol for 3 months.

However, her symptoms and general condition deteriorated, and she was admitted to our hospital. On admission, hypoxia (SpO<sub>2</sub>, 88% on 2 L/min oxygen) and dyspnea were present. She had no prior history of lung disease, and no exposure to dust or occupational hazards. Chest auscultation was normal, and there were no lymphadenopathy, skin lesions or neurological signs. The full blood count findings showed slight anemia (red blood cells (RBCs) 3.2×10<sup>12</sup>/L, hemoglobin 87 g/L) with slightly decreased white blood cells (3.23×10<sup>9</sup>/L: 62.6% neutrophils, 1.0% eosinophils, 23.5% lymphocytes, and 12.4% monocytes) and normal platelets counts (212×10<sup>9</sup>/L). Serum biochemistry

## Intravascular large B-cell lymphoma and lung biopsy



**Figure 1.** Chest X-ray and computed tomography of the patient. A. Chest X-ray at the time of admission showed pneumonia in whole lung; B. CT showed diffused ground glass opacities in both lung fields.



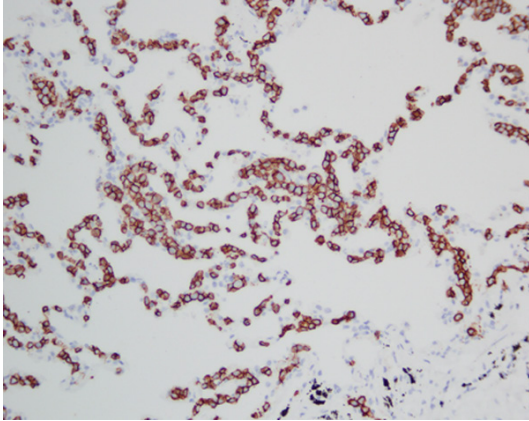
**Figure 2.** A. Lung biopsy demonstrated the invasion of lymphoma cells to the pulmonary interstitium on hematoxylin-eosin staining (200 $\times$ ); B. Lung biopsy demonstrated the invasion of lymphoma cells to the pulmonary interstitium on hematoxylin-eosin staining (400 $\times$ ), the alveolar septae was widen and filled with lymphoma cells showed in high magnification.

showed a raised levels of lactate dehydrogenase (LDH): 554 U/L (normal range: 135-215 U/L) and hypoalbuminemia: 30.9 g/L (normal range: 35-55 g/L). The C-reactive protein level was 2.85 mg/dL (normal range: 0-0.20 mg/dL). The rest of the biochemical findings were normal. Chest X-ray showed pneumonia in whole lung (**Figure 1A**). CT showed diffused ground glass opacities in both lung fields (**Figure 1B**).

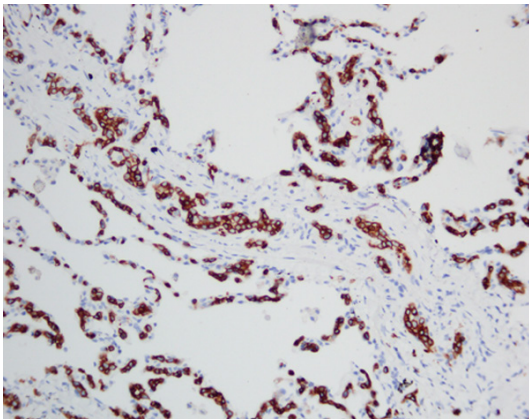
Infection, rheumatic diseases, lung cancer and lymphoproliferative diseases were suspected as the primary disease causing the persistent cough, intermittent high fever and shortness of breath. However, microbiological examinations, such as sputum, blood culture and urine were negative. Antinuclear antibodies, rheumatoid

factor and C-and P-antineutrophil cytoplasmic antibodies (ANCA) were all negative. We suspected IVLBCL because of her persistent cough, shortness of breath and evidence of hypoxia (pH 7.461, PaO<sub>2</sub> 52.6 mmHg, PaCO<sub>2</sub> 28.7 mmHg on 2 L/min oxygen). Histological confirmation was very important for the diagnosis of IVLBCL. To obtain a diagnosis, lung biopsy (from the left upper lobes) was performed.

Tissue sections were fixed in 10% formalin and hematoxylin and eosin (H&E) stains. The lymphoma cells were mainly lodged in the lumina of capillaries, small pulmonary arterioles, venules, but not outside the vessels (**Figure 2A, 2B**). The neoplastic cells showed irregular shaped with prominent nucleoli and moderate

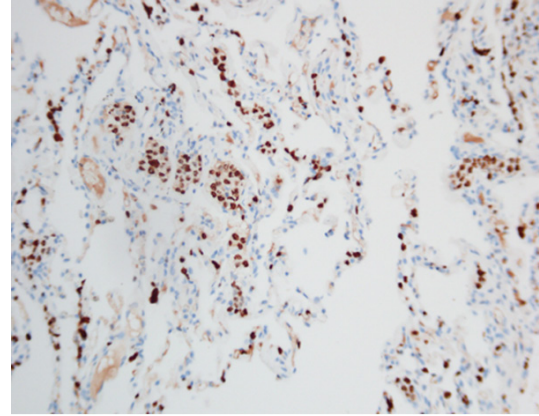


**Figure 3.** Immunohistochemical staining demonstrated that intravascular B lymphocytes were positive for CD20 (200×).



**Figure 4.** Immunohistochemical staining demonstrated that intravascular B lymphocytes were positive for CD79a (200×).

amount of cytoplasm. Immunohistochemical studies were conducted in selected formalin-fixed, paraffin-embedded blocks of case. The tumor cells were highlighted by staining for common leukocyte antigen, B-cell marker CD20 (**Figure 3**) and CD79a (**Figure 4**). The tumor cells showed no immunoreactivity for CD21, ALK, CD15, CD4. Proliferative marker, Ki67 showed distinctive nuclear reaction involving 80% neoplastic cells (**Figure 5**). IVLBCL was the final diagnosis. The patient have had chemotherapy treatment (CTX, ADM, VCR, prednisone and mabthera) in another hospital after the IVLBCL diagnosis was made. The life quality of the patient improved significantly after two courses of chemotherapy. Six minutes walk test showed the patient can walk 400 m after 6 minutes. The lung function test showed normal



**Figure 5.** Ki-67 immunostain showed the proliferation of intravascular lymphoma cells (200×).

lung ventilation and moderately decreased diffusing capacity for carbon monoxide (DLCO).

#### Discussion

IVLBCL is a very rare extranodal large-cell lymphoma characterized by intravascular proliferation of neoplastic lymphoid cells with a propensity for systemic dissemination [1, 5-7]. This disease was first reported by Tappeiner and Pflieger in 1959 [2]. The most frequent presenting symptoms are fever and general fatigue, neurological symptoms and skin eruptions. Other common clinical manifestations are very different and involve dyspnea, oedema and gastrointestinal symptoms [8]. IVLBCL patients usually show skin involvement and symptoms of central nervous system in Western countries [3, 4]. By contrast, IVLBCL patients in Asian countries often show hepatosplenomegaly, thrombocytopenia and fever, but very rarely with CNS and skin involvement [9, 10]. Primary presentation in lung has been very rare and only a few cases have been reported [3, 11-13]. In this case, the patient did not demonstrate any neurological symptoms, and only show dyspnea and shortness of breath. The laboratory findings were almost normal, except the chest CT showed diffused ground glass opacities in both lung fields. Then she was diagnosed with tuberculosis and treated with quinolones, isoniazid, rifampicin and ethambutol, but the treatment was not effective. Even if respiratory symptoms exist, many physicians often hesitate to perform transbronchial or surgical lung biopsy in the absence of apparent radiological findings in the lung field. For the purpose of



## Intravascular large B-cell lymphoma and lung biopsy

diagnosis, surgical lung biopsy was performed in our hospital. The biopsied specimens showed obstruction of the small vessels by large neoplastic lymphoid cells, which were positive for the B-lymphoid marker CD20. The histological findings confirmed the diagnosis of IVLBCL.

Although the lung is a special site used to make the diagnosis of IVLBCL, biopsy has demonstrated that changes in the lungs in about 60% of cases [4, 5]. Currently, TBLB is a well-established diagnostic technique used by almost all bronchoscopists and the flexible bronchoscope is used almost exclusively. The utility of the TBLB is the possibility of diagnosing specifically the patients with IVLBCL and avoiding a surgical lung biopsy. Recently, some cases in which abnormal findings were absent or less were finally diagnosed as having IVLBCL via TBLB [14, 15]. These data strongly demonstrated that random TBLB is very necessary for diagnosis of IVLBCL. In our case, we did not perform TBLB, because the tiny specimens obtained by TBLB may not be sufficient to diagnose IVLBCL and surgical lung biopsy is considered the best way to obtain enough tissue for pathological study.

Recently, FDG-PET has emerged as a powerful functional imaging tool in diagnosing the patients with non-Hodgkin lymphoma (NHL) [16]. Some physicians have reported that FDG-PET is very helpful for the diagnosis of IVLBCL, when this disease is clinically suspected [17-20]. Hiroyuki Yamashita et al. reported a case with fever of unknown origin that was diagnosed as IVLBCL with lung involvement by FDG-PET [21]. This case suggests that FDG-PET can make it easier for physicians to recognize the possibility of IVLBCL with lung involvement even in cases lacking radiological findings. That may encourage physicians to perform transbronchial or surgical lung biopsy and introduce quicker application of chemotherapy. In our case, we could not perform FDG-PET early because of the patient's very poor general status and her unwillingness to be transported to another branch of our hospital. FDG-PET should be performed earlier to make the diagnosis of hypoxia cases, in which IVLBCL is strongly suspected.

Lung biopsy plays a very important role in the diagnosis of IVLBCL. The tumor cells are lodged in the lumina of small pulmonary arterioles, venules, capillaries. Three variants of lympho-

ma cell are most commonly seen: centroblastic, immunoblastic, and anaplastic. Most are centroblastic, having the appearance of medium-to-large-sized lymphocytes with scanty cytoplasm. Oval or round nuclei containing fine chromatin are prominently visible, having two to four nucleoli within each nucleus. Sometimes the tumor may be monomorphic, composed almost entirely of centroblasts. However, most are polymorphic, with a mixture of centroblastic and immunoblastic cells. Immunohistochemistry also provides great help for the correct diagnosis. Most IVLBCL cells express B-cell antigen such as CD19, CD20, CD22, CD79a, CD5, CD10, or BCL6 is expressed in some IVLBCL cells, with about 20% frequency. Ki-67 is a nuclear antigen expressed by cycling cells. The percentage of Ki-67 expressing cells reflects the proportion of the IVLBCL cells that are actively cycling [22]. Cytogenetic abnormalities involving 14q32, 8p21, 19q13, and chromosome 18 have been found in IVLBCL patients in Asian countries.

The IVLBCL is fatal in the past, but more and more reports demonstrate that systemic chemotherapy at an early stage may improve long-term survival in some patients. CHOP or CHOP-like therapy has been commonly used. R-CHOP which is a combination of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone can improve the prognosis of IVLBCL.

In summary, the possibility of IVLBCL with primary lung involvement might be considered in some cases diagnosed as interstitial pneumonia or tuberculosis. Lung biopsy is the best way to diagnose IVLBCL. Early application of CHOP or R-CHOP chemotherapy can improve patient's long-term survival.

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### Disclosure of conflict of interest

None.

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## Intravascular large B-cell lymphoma and lung biopsy

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## Intravascular large B-cell lymphoma and lung biopsy

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