

Primary intravascular large B-cell lymphoma of the lung: a review and case report

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Objective: To investigate the clinicopathological features of primary intravascular large B-cell lymphoma (IVLBCL) of the lung.

Methods: Histopathological and clinical data based on lung biopsy were analyzed and used to diagnose a patient with IVLBCL of the lung.

Results: Fever and respiratory symptoms were the main presentations, lung biopsy revealed lymphoma cells in the lumen of small blood vessels. Tumor cells expressed Bcl-2, the Bcl-6, CD20, Ki67, MUM-1, Pax5, CD, CD30, and vascular endothelial CD34.

Conclusions: Primary pulmonary IVLBCL of the lung is extremely rare, on chest CT it manifests as diffuse ground glass shadow, or nodular consolidations in the lung, lactate dehydrogenase and C-reactive protein was found to increase, fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is an important and significant diagnostic modality in its early diagnosis. Also, bronchial lung biopsy has the advantage of less trauma and high sensitive rate. R-CHOP is the main treatment for lung primary pulmonary IVLBCL of the lung; however, its prognosis is relatively poor.

Keywords: Intravascular lymphoma; large B-cell; lung; case report

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Background

Intravascular large B-cell lymphoma (IVLBCL) of lung is a rare type of extranodal large B-cell lymphoma (LBCL) characterized by the selective growth of lymphoma cells within the lumina of vessels, particularly within capillaries, with sparing of larger arteries and veins. The clinical presentation is highly variable due to occlusion of small vessels or capillaries in different organ systems. This is an aggressive lymphoma with poor prognosis that in part reflects frequent delays in diagnosis due to above variable symptoms. The most common clinical manifestations involve central nervous system (CNS) presentations, cutaneous lesions, fever, or hemophagocytic syndrome. Although autopsy findings have revealed that pulmonary involvement is common in this disease, primary presentation in the lungs is distinctly uncommon and has been rarely described. Here we report a case with its predominant

clinical manifestation as interstitial lung disease, which was finally diagnosed as IVLBCL by biopsy. The clinical features, histopathological characteristics, and differential diagnosis of primary IVLBCL were also discussed in this article. Our patient was diagnosed with the help of the bronchial lung biopsy (TBLB). The clinical features, histopathological characteristics, and differential diagnosis of primary IVLBCL were also discussed in this article.

Case presentation

A 35-year-old, previously healthy woman presented to our hospital, with one-month history of cough, breathlessness and fever for two weeks. At a local hospital, based on the radiological findings, she was tentatively diagnosed with pulmonary infection and treated with various antibiotics and an intermittent use of methylprednisolone (40 mg/d). Her fever remained constant, and her breathlessness was

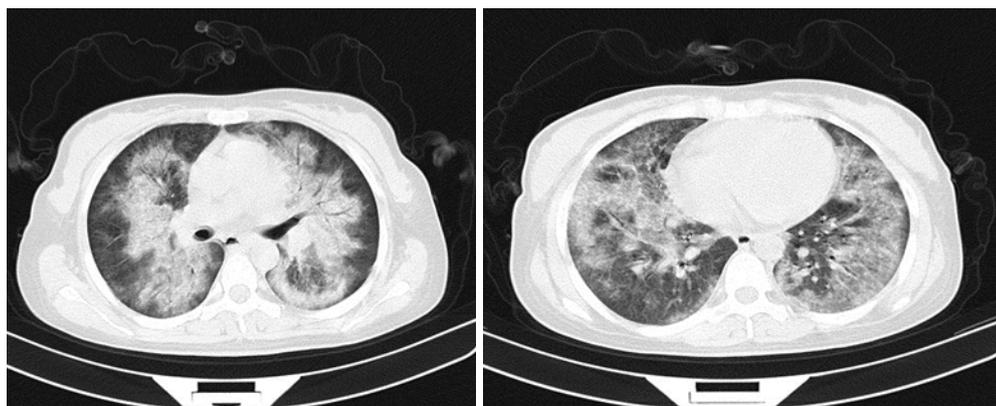


Figure 1 Chest CT-scan showing diffuse bilateral interstitial shadows with small granules and nodules. CT, computed tomography.

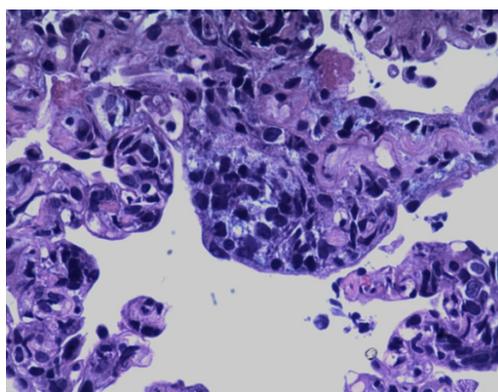


Figure 2 Hematoxylin-eosin staining of pulmonary interstitium intravascular lymphoma, (400 \times).

worsening even after treatment. She was a housekeeper and lived in Beijing for ten years. She denies any dust exposure or illicit drug use. At her initial presentation (day 1), she appeared well, and vital signs showed blood pressure of 106/54 mmHg, temperature 38.6 °C, heart rate 112 beats/min, respiratory rate 23 breaths/min and oxygen saturation 92-95% (FIO₂ = 5 L/min). Physical examination showed emaciation and no inspiratory fine crackles and superficial lymphadenopathy was noted. Serum laboratory examinations showed a mild decrease in leucocyte count (3,600 μ L); hemoglobin (72 g/L) and marked elevation of lactate dehydrogenase (LDH; 1,554 IU/L), C-reactive protein (175 U/L), procalcitonin (0.331 ng/mL), β 2 microglobulin (5.22 mL) and antinuclear antibodies, and antineutrophil cytoplasmic antibodies were negative. Blood gas analysis showed pH 7.406, PaCO₂ 33.5 mmHg, PaO₂ 64.2 mmHg. Chest CT-scan showed diffuse interstitial shadows (*Figure 1*).

Lung function test showed decline in diffusion and a mild restrictive ventilatory disorder.

Echocardiography showed moderate pulmonary hypertension (mean pulmonary artery pressure of 43 mmHg). After admission, prophylactic treatment was given, but her fever persisted intermittently (temperature range, 37-39 °C), with oxygen saturation fluctuations in the 92-95% (nasal 5 L/min). A TBLB was immediately performed. On HE staining, the biopsied specimen showed accumulation of abundant atypical lymphocytes in the capillary vessels (*Figure 2*). Immunohistochemical (IHC) staining showed cells were positive for CD20, Pax5 (*Figure 3A,B*), BCL2, BCL6 and MUM-1 and negative for CD3, CD10, CD2, CD30, CD34 (*Figure 4*), CD5, CD56, CD68, EBER, Syn, TTF-1, Granzyme B, and P63. The mean Ki-67 proliferation rate was 60% (*Figure 5*), indicating the tumour was in an active growing status. Bone marrow biopsy specimen revealed hyperplastic bone marrow, and atypical lymphocytes (9%) were also found (*Figure 6*).

Based on thorough history and investigation, the patient was diagnosed with IVLBCL. She was treated with R-CHOP (rituximab 600 mg, the day before chemotherapy, cyclophosphamide 1.0 g on day 1 + doxorubicin 60 mg on day 1 and day 2 + leucovorin 2 mg on day 1 + prednisone 60 mg from day 1 to day 9, daily) for one cycle.

Due to severe respiratory failure, the patient died from multiple organ failure a week after the diagnosis.

Discussion

Pfleger and Tappeiner first described IVLBCL in 1958. It is characterized by tumor cells located almost entirely in the intravascular, peripheral blood and bone marrow

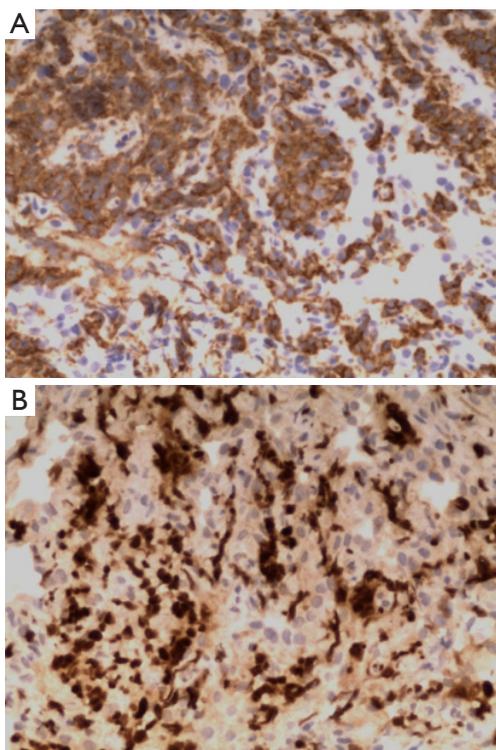


Figure 3 (A) CD20 immunostain of neoplastic intravascular B lymphocytes, (200×); (B) Pax5 immunostain showing the neoplastic lymphocytes, (200×).

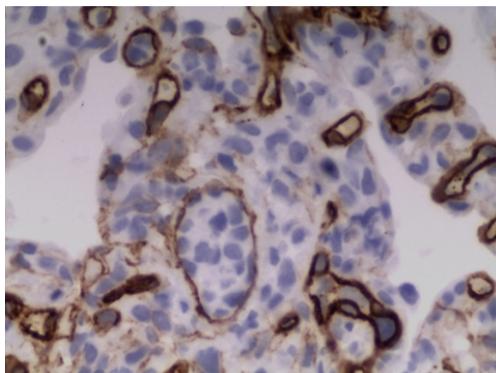


Figure 4 CD34 immunostain showing neoplastic lymphocytes located in the alveolar capillaries, (400×).

which makes it difficult to correctly differentiate from other tumors and it is regarded as a source of endothelial cells of the tumor. With the development of immunohistochemical and monoclonal antibody technology, it has been classified as a special type of lymphoma. In 2008 WHO identified it as a rare type of non-Hodgkins lymphoma (NHL). The

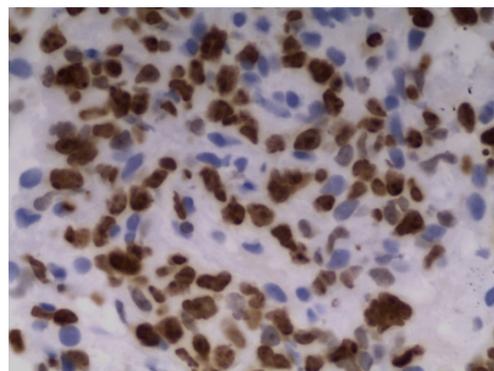


Figure 5 KI-67 immunostain highlighting the proliferation of intravascular lymphoma cells, (200×).

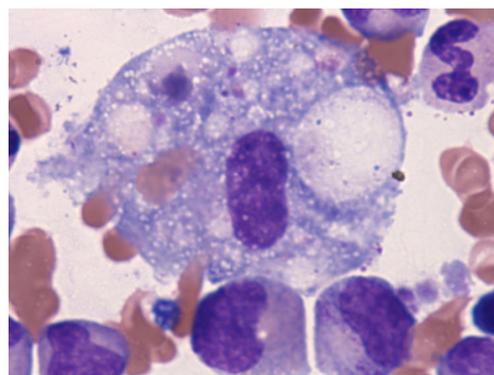


Figure 6 Bone marrow smear shows hemophagocytic syndrome (red cells are engulfed).

main characteristics of this type of lymphoma are diffuse, occlusive proliferation, especially in the capillaries, small arteries and veins (1). There's also the involvement of different organs and tissues including the CNS, skin, lung, kidney, but rarely affects the liver, spleen and lymph nodes. The pathogenesis of IVLBCL is unclear, however the splitting and translocation of chromosome maybe related with the pathogenesis of this disease (2).

The clinical manifestations of IVLBCL were nonspecific. Fever, weight loss and sweating (3) were the most common presentations. The main clinical findings were cough, sputum, hypoxaemia and dyspnea when lung was involved. Some patients also presented with hypercalcemia, pulmonary embolism, pulmonary hypertension or hemophagocytic syndrome as initial symptoms (3-5). In this case, pulmonary arterial hypertension was the main presentation with bone marrow hemophagocyte found on

histological examination.

An increased serum LDH, CRP and β 2-microglobulin interleukin-2R (IL-2R) were found in most cases, and close relation between increased LDH levels and the differentiation of tumor cells was observed, accompanied with anemia, decreased platelets and white blood cell count (6,7). The abnormal lung function usually seen in such cases was limitation of ventilation and diffusion dysfunction (8).

Thoracic computed tomography (CT) findings of the lung involvement of IVLBCL patients were diverse, including ground glass opacity (GGO), multiple centrilobular nodules, interlobular septal thickening, interstitial shadows and thickening of bronchovascular bundles, suggesting lymphatic and or haematological spread (8). Recently, FDG-PET has emerged as a powerful functional imaging tool in the assessment of patients with this type of NHL. Several authors have reported FDG-PET is useful in the diagnosis of IVLBCL when this type of lymphoma is clinically suspected. FDG-PET is a powerful tool for the early diagnosis of IVLBCL with pulmonary involvement, when there is a suspected possibility of the presence of this disease in a patient with respiratory symptoms without abnormal findings by CT (9).

The diagnosis is often delayed due to varied clinical presentations and limited understanding of the entity. Histopathology remains the gold standard for diagnosis, showing the classic appearance of large malignant lymphocytes filling small vascular lumina particularly in cases involving the lung; TBLB was a useful method in our diagnosis. If it cannot be confirmed with TBLB, it is necessary to perform an open lung biopsy or a thoracoscopy (10).

Treatment recommendations are extrapolated from results of trials of more common subtypes of lymphoma. Most cases of IVL are associated with poor prognosis and should be treated systemically with an anthracycline-based regimen. Anthracycline-based chemotherapy has been associated with a 60% response rate and a 3-year overall survival rate of more than 30%. CHOP (cyclophosphamide, doxorubicin, vincristin, prednisone) and CHOP-like regimens are also considered to be effective. The treatment of cases with lung involvement is similar to that of diffuse LBCL. Takahashi *et al.* (11) found that the effect of rituximab combined with CHOP was better than just the single CHOP regimen, through analysis of the effect on 1,221 cases involving the various organs in patients with LBCL.

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