Primary pulmonary intravascular large B-cell lymphoma misdiagnosed as pneumonia: Four case reports and a literature review

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Abstract. Primary pulmonary intravascular large B-cell lymphoma (IVLBCL) is a rare, malignant extranodal lymphoma. It is difficult to diagnose clinically as it requires a combination of clinical and computed tomography (CT) evaluations, as well as laboratory and pathological examinations. In the present study, 4 cases of primary pulmonary IVLBCL were reviewed. The patients' ages ranged from 60 to 69 years old. Of the 4 patients, 3 developed progressive dyspnea on exertion and intermittent fever. Other symptoms included coughing, chest tightness and weight loss. Laboratory data indicated that all patients had anemia, thrombocytopenia, hypoxemia, a markedly high serum lactate dehydrogenase level, elevated erythrocyte sedimentation rate and increased C-reactive protein. CT demonstrated increased attenuation in bilateral lung parenchyma, especially in the upper lobes, with multiple ground-glass opacities associated with small nodules in these patients. Initially, all 4 patients were misdiagnosed with pneumonia. However, none of them responded to anti-inflammatory treatments. The pathologies of all patients were confirmed using lung biopsy. Only 1 patient received regular combination chemotherapy. Based on the observations of the present study, a standard regimen for lymphoma treatment may result in a notable clinical response.

Introduction

Intravascular large B-cell lymphoma (IVLBCL) is an aggressive type of extranodal malignant lymphoma with selective proliferation of neoplastic lymphoid cells within the vascular lumina (1). It is divided into 'Eastern' and 'Western' variants, with the former often being associated with bone marrow involvement and hemophagocytic syndrome, and the latter showing central nervous system and skin involvement (2-4).

Pulmonary involvement of IVLBCL is relatively frequent at ~60% (5), and the majority of these cases are secondary lymphomas originating from systemic diseases. However, initial or predominant pulmonary presentations are rarely reported (5). With vascular occlusion of the lungs, patients may show some non-specific clinical presentations, such as hypoxemia, shortness of breath or fever, which may also occur in a number of other lung diseases, such as infection, infarction and diffuse interstitial pneumonia. Thus, primary pulmonary IVLBCL is highly misdiagnosed in clinical practice, and is often confirmed at autopsy or by lung biopsy (6). The present study summarized 4 cases of primary pulmonary IVLBCL and reviewed the previous literature in this area. The patients of the present study were diagnosed based on clinical and computed tomographic (CT) evaluations, as well as the laboratory and pathological examinations at Nanjing Drum Tower Hospital (Nanjing, China). These cases presented at this hospital between March 2010 and March 2017.

Case report

Case 1. A 69-year-old female patient was referred to Nanjing Drum Tower Hospital in March 2010 with a 2-month history of coughing with white sputum without cause and progressive dyspnea on exertion. In addition, the patient experienced fever (37.3-39.8˚C) for a duration of 1 week. A physical examination revealed cyanosis of the lips, edema of the lower limbs, clear consciousness, no skin rashes, nodules or hemorrhagic spots and no hepatosplenomegaly. After admission, CT examination was performed. The CT images demonstrated increased attenuation in bilateral lung parenchyma with multiple ground-glass opacities (GGOs) and part progression to consolidation (Fig. 1A), especially on the superior lobes. Interlobular septal thickening and partial thickening of bronchovascular bundles as well as 'tram track-like' changes were observed (Fig. 1A), along

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with no lymph node enlargement within the mediastinum or hilus (Fig. 1B). During hospitalization, treatment for infection using imipenem/cilastatin sodium (0.5 g/8 h) with intermittent use of acetaminophen tablets (0.5 g) for fever reduction was administered, but no notable effect was revealed. Finally, pulmonary IVLBCL was diagnosed using transbronchial lung biopsy (TBLB). Abnormal lymphoid cells distributed within the blood vessels were observed under a light microscope, and the diagnosis of pulmonary IVLBCL was further confirmed through immunohistochemical staining. The patient rejected chemotherapy treatment and died due to respiratory failure shortly (20 days) after diagnosis.

Case 2. A 68-year-old male with a past medical history of diabetes for ~20 years presented at Nanjing Drum Tower Hospital in May 2012 with a 2-month history of coughing with scantly white sputum, chest tightness, dyspnea on exertion and a recurrent low-grade fever. The patient experienced weight loss (~3 kg) during these 2 months. The patient underwent chest CT. Initial CT imaging evaluation indicated a ground pattern in a mosaic distribution and small centrilobular nodules (Fig. 2A). The patient received anti-inflammatory treatment. However, the symptoms did not significantly improve. Bone marrow aspiration followed by biopsy indicated that the patient had pancytopenia, and a fluorescent *in situ* hybridization study detected clonal rearrangements of Igκ-VJ and Igκ-V/in, without immunoglobulin heavy locus/BCL2, BCL6 and c-MYC fragmentations or TP53 deletion. TBLB was performed, which demonstrated only a small number of atypical cells. Primary pulmonary IVLBCL was eventually confirmed using open lung biopsy. An incision was made in the fourth intercostal space along the anterior axillary line of the left side of the chest, and lung tissues were respectively excised from the lingual and dorsal segments of the left upper lobe and the dorsal segment of the left lower lobe. The patient started receiving rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) treatment but experienced an allergic reaction after being injected with rituximab (600 mg). Rituximab was removed from the treatment plan, and after improvement with anti-allergy treatment, the patient received 6 cycles of CHOP [1.2 g cyclophosphamide, intravenously (iv) day l; 90 mg doxorubicin, iv day l; 4 mg vincristine, iv day l; 50 mg prednisolone, orally twice per day, days 1-5] treatment, with each cycle lasting for 3 weeks. At completion of the sixth cycle, the disease was in complete remission. As visualized using a CT scan, the bilateral lungs were clear (Fig. 2B).

A seventh cycle of chemotherapy began with CHOP (same drug dosage as aforementioned) within 3 months of the completion of the sixth cycle as the patient was admitted to hospital with a fever, cough and chest discomfort. At 2 weeks after discharge after the seventh cycle, an additional three cycles of CHOP (same drug dosage as aforementioned) were provided at 1-week intervals. An additional three cycles of ifosfamide (8 g, iv day 2), carboplatin (500 mg, iv day 2) and etoposide (0.16 g, iv days 1-3) were administered only 1 month after the latest completion of chemotherapy for the recurrence of cough, sputum and fever. The patient's clinical symptoms improved markedly after the treatment. However, the patient was hospitalized again 1 year later due to fever and infection secondary to myelosuppression. Eventually, the treatment failed, and the patient passed away.

Case 3. A 65-year-old male patient was admitted to Nanjing Drum Tower Hospital in March 2017 with a 3-month history of progressive dyspnea and cough. The patient had no prior history of lung disease, chest pain, intermittent fever or night sweating. No focal findings were noted on physical examination, especially of the skin and central nervous system, and lymph nodes were not palpable. A CT examination revealed diffuse ground-glass attenuation and thickened interlobular septa in the upper lungs (Fig. 3A and B). No abnormal soft tissue mass was observed in the mediastinum, bilateral hilus and axilla. Whole-body positron emission tomography-computed tomography (PET-CT) scan revealed only mild ^{18}F-fluorodeoxyglucose (FDG) uptake in both lungs. The patient was mistakenly diagnosed with pneumonia and received wide-spectrum antibiotics treatment (2 g cefazoxime sodium, twice per day) for half a month. The patient's symptoms continued, and the treatment had no effect. The patient was discharged from hospital after diagnosis of IVLBCL using TBLB and did not return for follow-up treatment and examination.

Case 4. A 60-year-old female patient presented at Nanjing Drum Tower Hospital in August 2015 with a 1-month history of progressive dyspnea and a 20-day history of intermittent high fever, with a maximum temperature of ~39˚C. The patient had no history of lung disease and was a non-smoker. No cyanosis, clubbing, neurological abnormalities, nor cutaneous lesions were observed on physical examination. A high revolution chest CT (HRCT) examination was performed, and the images revealed pulmonary nodules with part-solid diffused GGOs in the lungs without pleural involvement (Fig. 4A and B). Additional examinations of whole-body CT examination yielded normal findings. The patient was diagnosed with interstitial pneumonia and the infection was treated with moxifloxacin hydrochloride (0.4 g/day) and sodium chloride injection solution for 7 days, and intermittent use of indomethacin (0.05 g) for antipyretic treatment, but the symptoms did not notably improve. Since there were no specific clinical or imaging findings and anti-inflammatory therapy failed, the patient underwent TBLB examination (of the superior lobe of the right lung). Light microscopy revealed a diffuse intravascular proliferation of atypical B cells and, combined with immunohistochemistry, IVLBCL was diagnosed. After a short period of glucocorticoids (40 mg methylprednisolone sodium succinate per day) treatment, the dyspnea initially improved, and the treatment appeared to be working. Unfortunately, the patient eventually discharged and gave up treatment due to a severe and uncontrollable lung infection.

Laboratory results. Laboratory data demonstrated that the patients had anemia (n=4, 100%), thrombocytopenia (n=4, 100%), pancytopenia (n=3, 75%) and hypoxemia (n=4, 100%). Laboratory findings were notable for marked high serum lactate dehydrogenase (LDH) levels, elevated erythrocyte sedimentation rates (ESRs) and increased C-reactive protein (CRP) levels (Table I).

Histopathological results. All patients underwent TBLB, and partial tissue biopsies of different segments of the lung lobes were performed. Only 1 patient underwent open lung biopsy.

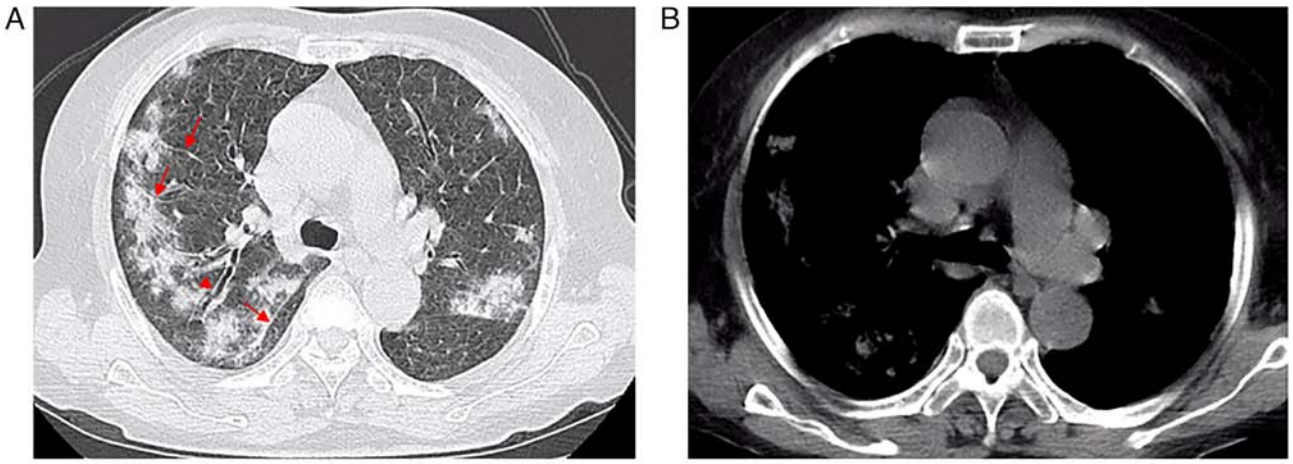

Figure 1. Case 1. Axial computed tomography slices of the chest images showed (A) increased attenuation in bilateral lung parenchyma, characterized by areas of ground-glass opacities and consolidation, and interlobular septal thickening partial (arrows) as well as 'tram track' appearance (arrowhead), and (B) no lymph node enlargement within mediastinum or hilus.

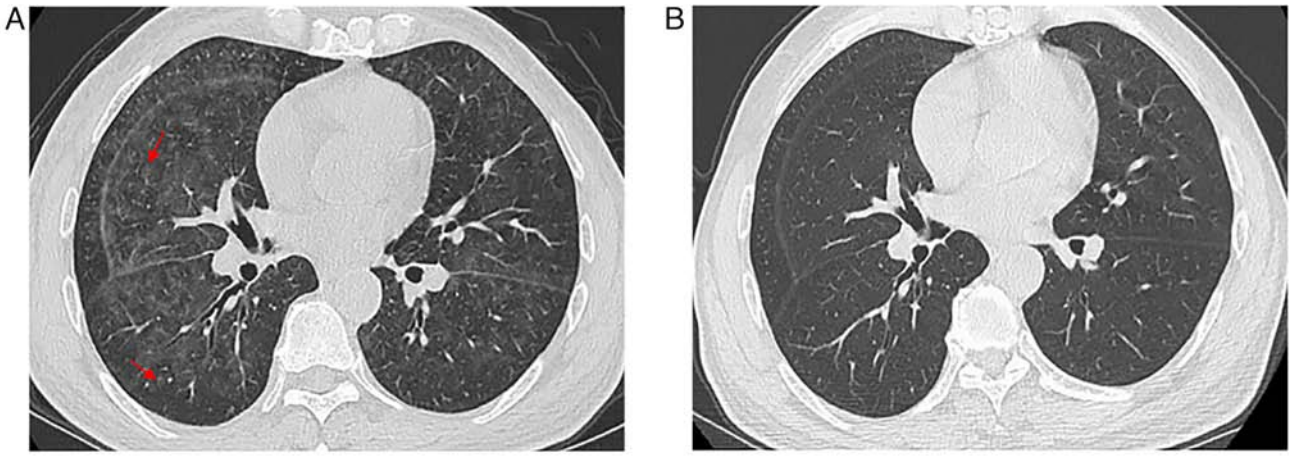

Figure 2. Case 2. (A) The image of lung window setting showed ground pattern in a mosaic distribution and small nodules (arrows) with centrilobular. (B) After 6 cycles of treatment, no abnormal shadows were seen in CT scan image

The pathological analysis showed mild expansion of the capillary lumen within alveolar and peribronchial interstitial tissue by a proliferation of large tumor cells. The intravascular tumor cells had multiple (1-3) nucleoli, little cytoplasm, high nucleus to cytoplasm ratios and irregular nuclear contours. Mitoses, including atypical forms, were observed.

Immunohistochemical results. The tissues were incubated in 10% neutral formalin fixative for overnight fixation at room temperature for 12 h. After slicing the sample to a thickness of 4 μm and performing deparaffinization and hydration pretreatments, 3% hydrogen peroxide was added to cover the part to be stained with peroxidase blocking agent, and the sample was incubated at room temperature for 30 min. Mouse primary antibody was added to the sample and incubated overnight at 4˚C. Rabbit secondary antibody, with a horseradish peroxidase conjugate, was added to the sample and incubated at room temperature for 30 min. DAB (Ultraview Universal DAB Kit; Roche Tissue Diagnostics) was used for 10 sec of chromogenic staining, followed by staining with hematoxylin for 4-8 min at room temperature. Finally, the location and intensity of the markers were observed under an optical microscope. The primary antibodies selected include: CD20 (cat. no. ZM-0039), CD79a (cat. no. ZA-0293), CD31 (cat. no. ZM-0044), CD3 (cat. no. ZM-0417), CD10 (cat. no. ZM-0283), CD5 (cat. no. ZM-0280), Bcl-6 (cat. no. ZM-0011), and Mum-1 (cat. no. ZM-0401), all purchased from OriGene Technologies, Inc.

H&E and immunohistochemistry staining revealed tumor cells that were positive for CD20 (n=4, 100%) and CD79a (n=3, 75%), which identified all four tumors as a lymphoma of B cell lineage (Fig. 5A-C). In addition, the tumor cells of all 4 cases were negative for the T cell markers, CD3 and cytokeratin (n=4, 100%). CD31 was positive in the small vessel endothelium of case 2 (Fig. 5D). Only 1 case was considered to have a germinal center B cell (GCB) phenotype, as the cells were positive for CD10, BCL6 and multiple myeloma oncogene 1 (Mum-1) (Table II).

Discussion

In 1959, Pfleger and Tappeiner first reported a type of malignant lymphoma, known as 'malignant

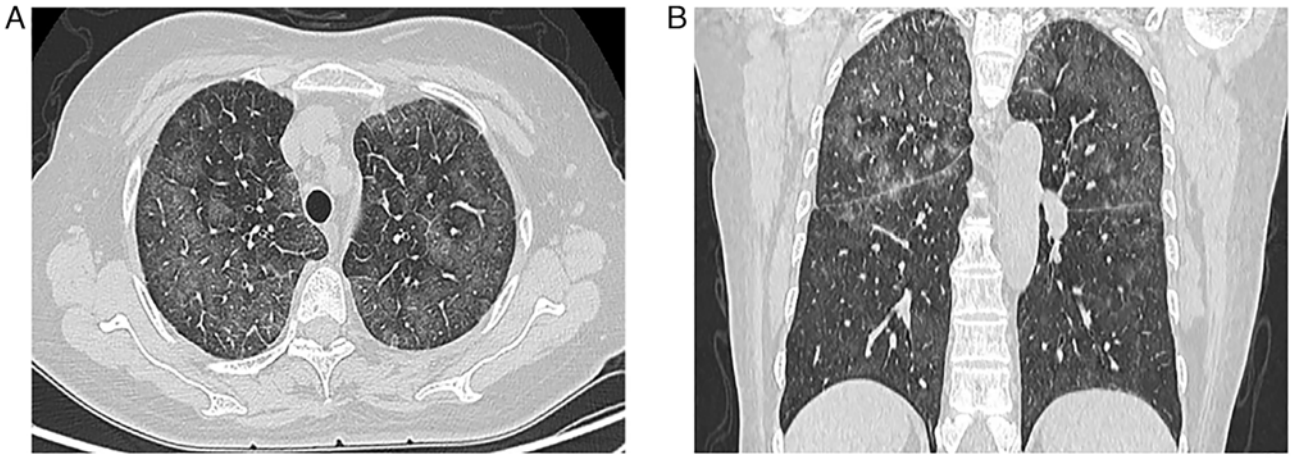

Figure 3. Case 3. (A) Axial computed tomography slice of the chest showed diffused ground-glass attenuation. (B) Coronal images demonstrate predominant distribution in the upper lobes of bilateral lungs.

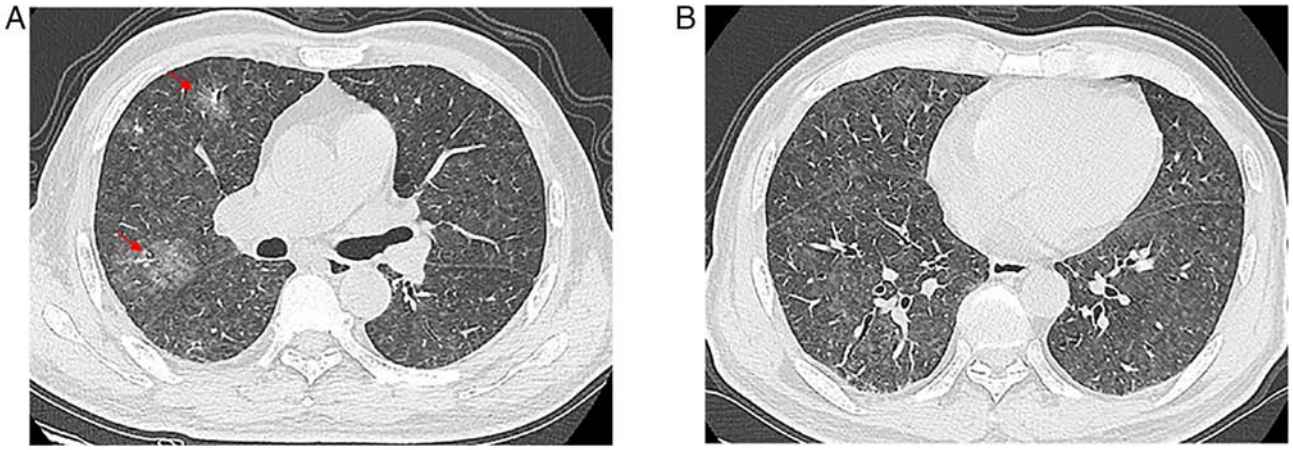

Figure 4. Case 4. (A and B) Axial computed tomography slices of the chest images revealed pulmonary nodules with part-solid diffused ground-glass opacities (arrows).

angioendotheliomatosis' (1,2,7). Malignant angioendotheliomatosis is an uncommon subcategory of extranodal large B-cell lymphoma derived from blood vessels and features the presence of large tumor cells (4,8,9). A study recommended differentiating the classification of 'classical IVLBCL' and 'IVLBCL associated with hemophagocytic syndrome' due to the crossover of clinical manifestations, without being limited to regional differences in Europe and Asia (4). 'Classical IVLBCL' is characterized by cutaneous and/or neurological involvement. The features of 'IVLBCL associated with hemophagocytic syndrome' are hemophagocytic syndrome, bone marrow involvement, fever, hepatosplenomegaly, and/or thrombocytopenia (4).

Pulmonary IVLBCL without evidence of extrapulmonary involvement is uncommonly reported and is difficult to diagnose antemortem (10,11). It predominantly occurs in the 6th decade of life and is likely to get worse if not treated with an adequate remedy. The clinical manifestations of pulmonary IVLBCL are non-specific, and share numerous clinical features with pulmonary tumor embolism, which are often experienced in both diseases, including dyspnea, fever, cough, night sweats, tachypnea and hypoxemia (3,5,6,12-14). The immortal proliferation cells (abnormally proliferating B lymphocytes) play a central role in the development of pulmonary tumor embolism, and the presence of pulmonary hypertension and cor pulmonale are almost irreversibly associated with blood clots that occur in the lung (12). Pulmonary function testing typically measures reduced diffusion capacity for carbon monoxide compared with normal baselines (13). In addition, serum LDH, ESR and CRP levels are often elevated by different degrees in IVLBCL (1,4,11). All these results may indicate that a patient is suffering from a type of lymph-proliferative disease.

Compared with other pulmonary lymphoma, IVLBCL generally does not involve lymphadenopathy or a localizing solid mass, as the lymphomatous cells mainly involve the pulmonary arteries and capillary beds (14). Results of CT assessments are diverse and can be inconspicuous or show GGO and interstitial infiltration (11,12,14). In the cases of the present study, patchy areas of GGO existed on patient presentation and this accentuated the bilateral lung attenuation resulting from pulmonary vascular obstruction. In case 1, the chest HRCT revealed bilateral disease that was pneumonia-like, which progressed partly to consolidation.

Table I. Overview of the 4 cases of primary pulmonary intravascular large B-cell lymphoma.

Case no.	Age, years	Sex	Hb, g/l	Plt, x10^9/l	SaO_2, %	LDH, IU/l	CRP, mg/l	ESR, mm/h	Treatment and outcome
1	69	Female	87	107	91	2,250	88	97	None; deceased shortly (20 days) after diagnosis
2	68	Male	102	96	93	1,449	13	106	R-CHOP, CHOP, ICE; Deceased 17 months after diagnosis
3	65	Male	110	111	92	886	27	92	N/A (outside consultation)
4	60	Female	90	102	94	1,542	80	80	N/A (outside consultation)

Hb, hemoglobin; Plt, platelet; SaO_2, oxygen saturation; LDH, lactate dehydrogenase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; R-CHOP, rituximab, CHOP; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; ICE, ifosfamide, carboplatin and etoposide; N/A, not available.

Table II. Immunohistochemical analysis for the 4 cases of primary pulmonary intravascular large B-cell lymphoma.

	Antibodies							
Case no.	CD20	CD3	CD10	CD79a	Mum-1	Ki-67, % positive	BCL6	CK
1	Positive	Negative	Negative	Positive	Negative	40	Negative	Negative
2	Positive	Negative	Negative	Positive	Positive	70	Negative	Negative
3	Positive	Negative	Positive	Positive	Positive	50	Positive	Negative
4	Positive	Negative	Negative	Negative	Positive	20	Negative	Negative

Mum-1, multiple myeloma oncogene 1; CK, cytokeratin.

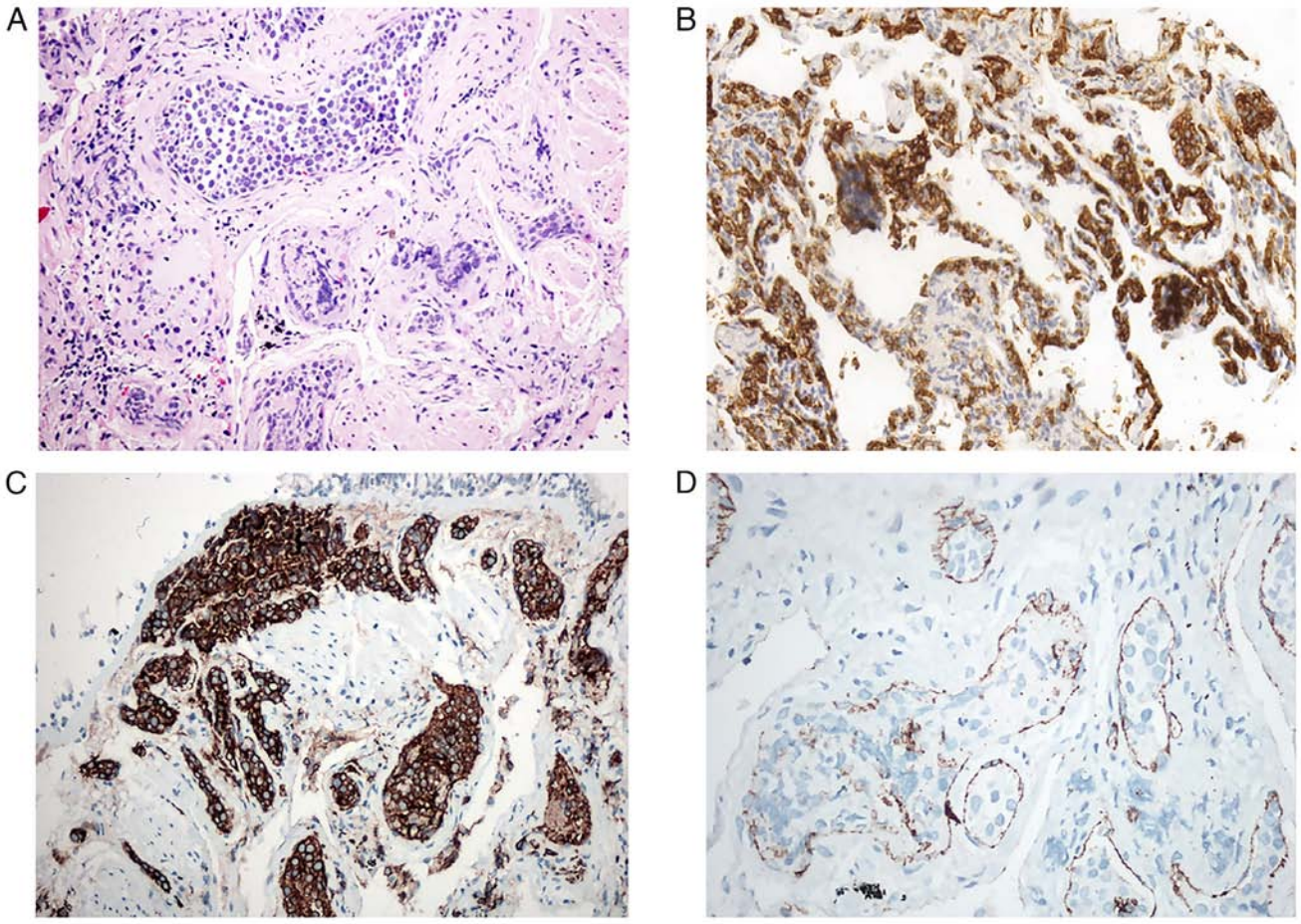

Figure 5. The morphology and immunohistochemical study showed that (A) the predominant growth of neoplastic cells was within the small blood vessels (H&E staining) and the intravascular cells were immunoreactive to (B) CD20, (C) CD79 and (D) CD31, which are immunophenotypic features of B cell lymphoma. Magnification, x40.

Due to local interlobular septal thickening along with the thickening of bronchovascular bundles, new GGO indicated lymphatic and hematological spread. The other 3 cases showed bilateral GGOs, micronodules and thickened interlobular septa in the lungs without pleural involvement, which suggested that the disease may spread along lymphatic structures. In case 2, the pulmonary shadows completely disappeared after a short-term chemotherapy schedule, which supported the diagnosis of IVLBCL. The etiology of GGO (heterogeneous and partially consolidated) in all four patients remains unclear. Malignant cells may invade the alveolar space, resulting in consolidation (increased density) on CT imaging. Increased diffuse density in bilateral lungs with GGOs and thickening of interstitial septum needs to be distinguished from non-neoplastic lesions, such as interstitial diseases and mechanical pneumonia, which may also present as progressive dyspnea with cough and other manifestations of obstructive ventilation. TBLB and bronchoalveolar lavage fluid can be used to aid diagnosis. Undoubtably, IVLBCL needs to be differentiated from venous thromboembolism and other intravascular malignancies of the lung, including lymphomatoid granulomatosis, angiocentric lymphoma and pulmonary involvement by acute and chronic lymphocytic leukemias (3). At this point of the patient examination, the clinical manifestations and CT characteristics may be non-specific, and immunohistochemistry will provide great help for the correct diagnosis.

PET-CT is used in the early diagnosis of isolated pulmonary IVLBCL (11,15) as it can differentiate IVLBCL from other lung diseases, such as idiopathic pulmonary fibrosis and pneumonia. PET-CT scans typically show a high metabolic activity of tumor cells in IVLBCL, which is similar to that observed for diffuse large B-cell lymphoma (DLBCL), as IVLBCL falls under the category of DLBCL (16). At present, PET has a high ability to differentiate lymph nodes, especially invasive lymph node lesions, and almost all the lymph nodes and extranodal organs can be found through a single examination. PET has been widely used in the diagnosis, staging and restaging, efficacy evaluation and prognosis prediction of lymphoma. However, only 1 case in the present study presented pulmonary mild ^{18}F-FDG uptake on PET, which was atypical.

Histological findings, such as pulmonary veins, peribronchial arterioles and accumulation of malignant lymphocytes, are key for the definitive diagnosis of primary pulmonary IVLBCL (3,13). Moreover, small vessels filled with large B cells are also confirmed using H&E staining. B cell markers (CD19, CD20, CD79a and PAX5) are usually expressed while T cell markers (CD3 and CD4) are typically negative on immunohistochemical examination (3,9). CD31 mainly marks

endothelial tissue and can be used to identify benign and malignant vasogenic tumors. Meanwhile, CD31 is not expressed in non-vasogenic tumors, so it has high specificity and sensitivity for studying vasogenic tumors (17). Pathologically, IVLBCL and DLBCL have similar cytology and sometimes the same immunophenotypes. Nonetheless, combined with CT findings, DLBCL often presents as a localized solid mass and is easy to identify. In the present study, 1 patient was positive for CD31, indicating endovascular origin of the tumor. CD10 or BCL6 are hallmarks for the determination for GCB and non-GCB (3,10). Based on the Hans algorithm, cases of $CD10^+$ VLBCL are categorized as GCB-type (1,10,18), thus, the large B cells in case 3 were $CD10^+$/Bcl-6^+/Mum-1^+, which is classified as a GCB-type in immunophenotypical analysis. Moreover, GCB phenotypes with patterns such as $CD10^+$/$BCL6^+$/Mum-1^+, $CD10^+$/$BCL6^-$/Mum-1^+, $CD10^+$/BCL-6^-/Mum-1^-, $CD10^+$/$BCL6^+$/Mum-1^- and $CD10^-$/BCL-6^+/Mum-1^-, are considered to indicate an improved prognosis compared with that of a non-GCB phenotype (18,19). In total, ~20% of cases of IVLBCL have been classified as GCB-type (1), which corresponds with the results of the present study.

In the case of malignant tumor, a high Ki-67 proliferation index (PI) in neoplastic cells is closely associated with poor prognosis. At present, the majority of researchers agree that a 20% cut-off PI for Ki-67 in lymphoma is clinically meaningful (20). The Ki-67 PI was ≥20% (20-70%) in the present study. In addition, in the present study, the patient of case 2 underwent genetic testing, which demonstrated no specific chromosomal alterations and no clonal rearrangement of the variable region of the immunoglobulin heavy chain gene, but a genetic recombination of Igκ-VJ and Igκ-V/in was detected, indicating abnormal lymphocyte proliferation (9). Structural abnormalities of chromosomes 1 (1p), 6 and 18 (trisomy 18) have also been previously reported (3).

With an improved clinical awareness and the development of immunohistochemical technology, it is possible to confirm the diagnosis of this rare disease during the lifetime of the patient. The present study performed a diagnosis of 4 living patient cases of primary pulmonary IVLBCL using lung tissue biopsies (3 cases by TBLB and 1 case by open lung biopsy). IVLBCL is a diffuse lung disease and, even though TBLB is already highly diagnostic, due to the limited availability of lung tissue samples from minimally invasive procedures leading to a failed accurate diagnosis, a surgical lung biopsy may ultimately be performed. Furthermore, we hypothesize that it will be possible for IVLBCL to be cured in the future. Treatment applied in combination with chemotherapy for intermediate and high-grade lymphomas has achieved success in the field of long-term disease-free survival (3,10). In addition, combined systemic chemotherapy, similar to that for diffuse large B-cell lymphoma, may help treat IVLBCL with long-term disease-free survival as a clinical outcome (13).

In conclusion, the present study demonstrated that primary pulmonary IVLBCL should be considered in differential diagnoses, especially when GGOs are associated with small nodules and thickened interlobular septa in the upper lung. Other general clinical manifestations include fever, night sweats and weight loss, high elevations in serum LDH, ESR and CRP in laboratory examination and no response to anti-inflammatory treatments. A histopathological examination of lung biopsy samples is needed to confirm the definitive diagnosis and therapeutic procedures. The present study also demonstrated the potential diagnostic effectiveness of TBLB in early diagnosis and the relative non-invasiveness of the technique, compared with open chest surgery. Taken together, a standard regimen for lymphoma treatment may result in an overall improved clinical response.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable requests.

Authors' contributions

MZ and YC contributed to manuscript writing and editing, and data collection; HF analyzed and interpreted the patient data; JS performed the pathological examinations; BZ contributed significantly to the concept and design of the study; XM contributed to conceptualization and supervision and was responsible for revision of the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript. MZ, YC and XM confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Since this study was a retrospective study, we applied to exempt patients from informed consent, and it was supervised and approved by the Ethics Committee of Nanjing Drum Tower Hospital (Nanjing, China; approval no. 2022-009-01).

Patient consent for publication

Since this study was a retrospective study, we applied to exempt patients from informed consent for publication, and it was approved by the Ethics Committee of Nanjing Drum Tower Hospital (Nanjing, China; approval no. 2022-009-01).

Competing interests

The authors declare that they have no competing interests.

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