INTERNAL MEDICINE

□ CASE REPORT □

Pulmonary Intravascular Large B-cell Lymphoma (IVLBCL) Disguised as an Asthma Exacerbation in a Patient with Asthma

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Abstract

A 62-year-old man with asthma presented with a 1-month history of wheezing and exertional dyspnea. Although the wheezing symptoms disappeared after systemic corticosteroid therapy, the exertional dyspnea and hypoxemia did not improve. A diagnosis of intravascular large B-cell lymphoma (IVLBCL) with pulmonary involvement was suspected because of the increased serum lactic dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R) level, increased alveolar-arterial oxygen difference ($AaDO_2$), decreased pulmonary diffusing capacity for carbon monoxide (D_{LCO}) and scintigraphic, computed tomography (CT) and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT findings. The patient was diagnosed as having IVLBCL with pulmonary involvement based on a pathological analysis of a random skin biopsy and a transbronchial lung biopsy. IVLBCL should be considered in patients with symptoms of asthma that are refractory to corticosteroid treatment.

Key words: intravascular large B-cell lymphoma, asthma, positron emission tomography, transbronchial lung biopsy

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Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare extranodal subtype of non-Hodgkin's diffuse large B-cell lymphoma (DLBCL) that is characterized by the selective growth of malignant lymphocytes within the lumen of small- to medium-sized blood vessels, particularly capillaries (1). In the current World Health Organization classification of hematopoietic tumors, IVLBCL is listed as a subtype of DLBCL (2). The intravascular proliferation of malignant lymphocytes in extranodal organs, such as the skin, central nervous system, bone marrow, liver, and spleen, is most commonly observed in IVLBCL (3). However, autopsy findings have revealed that intravascular lymphoma often involves the lungs (4-6). Pulmonary involvement is rare at the initial presentation, and its diagnosis is often difficult due to the lack of specific symptoms and pathognomonic findings. IVLBCL in the lung is suspected with dyspnea and abnormal chest findings on chest X-ray and/or computed tomography (CT). It is usually diagnosed pathologically by a random skin biopsy and transbronchial lung biopsy (TBLB) (7-14).

We herein report a case of a male patient with asthma who developed exertional dyspnea, which was disguised as an exacerbation of asthma, accompanied by IVLBCL. He

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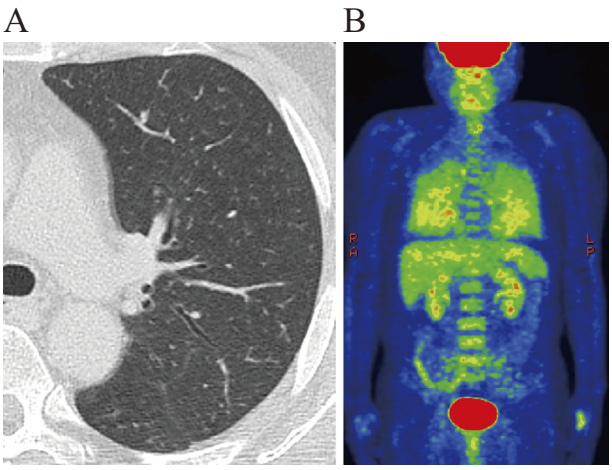

Figure 1. Chest CT (A) and ^{18}F-FDG PET-CT (B) scans at the initial presentation, showing diffuse multiple small nodules in the lung fields and an increased diffuse FDG uptake in both middle-lower lung fields. FDG: fluorodeoxyglucose, PET: positron emission tomography

did not exhibit abnormal chest X-ray findings, and the diagnosis was ultimately proven by a random skin biopsy and TBLB. Furthermore, the diffuse pulmonary ^{18}F-Fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET)-CT was helpful in our suspicion of the diagnosis and in assessing the response to chemotherapy.

Case Report

A 62-year-old man who had been treated for severe persistent asthma for 10 years at a local hospital presented to our hospital with a 1-month history of wheezing and exertional dyspnea. At his local hospital, he had been treated with high-dose inhaled corticosteroid, an inhaled long-acting beta2-agonist, leukotriene receptor antagonist, xanthine and intermittent systemic corticosteroids at least once a month for half a year. At our hospital, his wheezing disappeared after the administration of oral corticosteroid, but his exertional dyspnea did not improve. He was admitted to our hospital for the investigation of dyspnea and pulse oximeter desaturation.

A physical examination was normal despite hypoxemia. Chest sounds were normal, and expiratory wheezing was no longer heard after bronchodilator administration. There were no skin lesions, lymphadenopathy or neurological findings. Laboratory findings showed elevated serum lactic dehydrogenase (LDH) (1,482 IU/L), aspartate aminotransferase (AST) (39 IU/L) and C-reactive protein (CRP) (1.6 mg/dL) levels. An arterial blood gas analysis at rest while breathing room air showed hypoxemia (PaO_2 53.9 Torr) with an elevated alveolar-arterial oxygen difference ($AaDO_2$) (60.9 Torr). The serum tumor markers were within normal limits, except for an elevated soluble interleukin-2 receptor level (sIL-2R) (1,570 U/mL). Although chest X-ray showed no abnormal findings, chest CT showed diffuse multiple small nodules in the lung fields, no mass and no lymphadenopathy in the thorax or the abdominal cavity (Fig. 1A). Respiratory function testing showed a decline in the pulmonary diffusing capacity for carbon monoxide (DLCO). Pulmonary blood flow scintigraphy showed decreased accumulation in both middle-lower lung fields. A diffuse pulmonary ^{18}F-FDG PET-CT scan showed an increased diffuse FDG uptake in both middle-lower lung fields (Fig. 1B). The existence of malignant lymphoma, such as IVLBCL, without clinical findings was suspected because of the hypoxemia, the high levels of LDH and sIL-2R, the increased $AaDO_2$, the decreased DLCO and the scintigraphic, CT and PET-CT findings. A random skin biopsy and TBLB were performed, and the pathological findings revealed atypical lymphoid cells located within the intravascular space of the capillary vessels and pulmonary artery. In immunohistochemical staining, these atypical lymphoid cells were positive for CD20 and CD79a, which are B-cell markers (Fig. 2), and demonstrated a high proliferation index, as revealed by MIB-1 (Ki-67) (data not shown). Based on these results, the patient was diagnosed as having IVLBCL with pulmonary involvement.

After transfer to the Department of Hematology, the patient was treated with prednisolone and vincristine to reduce the pulmonary tumor burden due to his worsening respiratory condition. After one week, his respiratory condition improved. Following prednisolone and vincristine administration, he was treated with R-CHOP chemotherapy, consisting of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisolone. He achieved complete remission after eight cycles of R-CHOP chemotherapy with no severe adverse events, and the LDH and sIL-2R levels, the $AaDO_2$ and chest CT and FDG-PET findings subsequently revealed no signs of lymphoma involvement (Fig. 3).

Discussion

To our knowledge, this is the first report of a case of IVLBCL with pulmonary involvement disguised as exacerbation of asthma in a patient with asthma. It may be associated with the typical symptoms of patients with asthma that are difficult to diagnose correctly. A diverse array of diseases, including ischemic heart disease, pulmonary thrombosis and pulmonary lymphoma, generally involve exertional dyspnea and/or wheezing. Furthermore, asthmatic patents often exhibit exertional dyspnea without wheezing. This patient was initially treated for exacerbation of asthma due to the exertional dyspnea with wheezing, suggesting that the exacerbation of asthma might have initially coexisted with IVLBCL. Furthermore, it has been reported that corticosteroid treatment before the diagnosis of lymphoma might be used to reduce tumor size and might cause a delay in the definitive diagnosis (15). Therefore, the repeated intermittent treatments with oral corticosteroids as rescue medication for asthma exacerbations in this patient might have complicated and delayed the ultimate diagnosis. However, the increased serum LDH and sIL-2R levels, the increased $AaDO_2$ levels, the decreased DLCO and the scintigraphic and CT findings

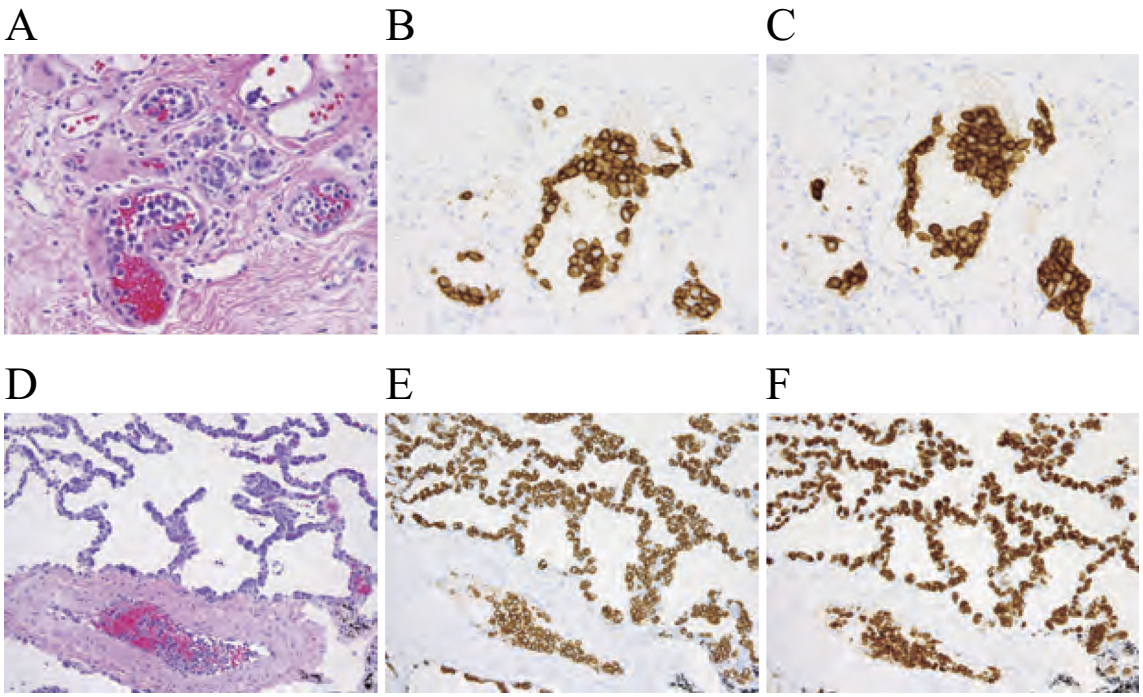

Figure 2. **A histopathological analysis of random skin (A, B and C) and transbronchial lung (D, E and F) biopsy specimens. Atypical lymphoid cells were seen in the intravascular space of capillary vessels and pulmonary artery (Hematoxylin and Eosin staining, ×400) (A and D). These cells were positive for CD20 (B and E) and CD79a (C and F) (CD20 and CD79a immunostaining, ×400).**

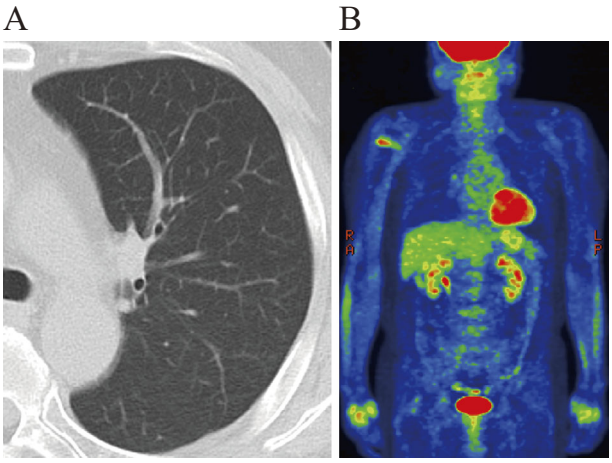

Figure 3. **Chest CT (A) and ^{18}F-FDG PET-CT (B) scans after the completion of eight courses of R-CHOP. Diffuse multiple small nodules and the diffuse FDG uptake disappeared completely in the lung fields on CT and FDG-PET/CT findings, respectively. FDG: fluorodeoxyglucose, PET: positron emission tomography**

that showed diffuse multiple small nodules in the present case led to the suspicion of IVLBCL. High levels of LDH and sIL-2R have been observed in most cases of IVLBCL (13, 14, 16).

Since 1983, there have been 76 additional cases of IVLBCL with pulmonary involvement reported in the medical literature, including 16 articles in Japanese and the present case (Table 1) (5, 6, 9-14, 16-51). The male-to-female ratio was 44:32, and the median age was 61.5 years (range 35 to 85 years). The median LDH and sIL-2R levels were 1,357 IU/L (range 352 to 5,085 IU/L) and 2,279 U/mL (range 602 to 24,500 U/mL), respectively. Seventy cases (92%) had symptoms of a fever (n=56, 73.7%), cough (n=21, 27.6%) or dyspnea (n=52, 68.4%). Chest CT was performed in 57 cases (75%). Eleven of those 57 cases (19.3%) showed no abnormalities on chest CT. Ground glass opacity (GGO) and diffuse multiple small nodules were present in 34 (59.6%) and 10 (17.5%) of the 57 cases, respectively. The present case showed increased serum LDH and sIL-2R levels and diffuse multiple small nodules on chest CT.

Furthermore, there were 13 previous case reports of pulmonary IVLBCL with FDG-PET/CT (Table 2) (10-12, 14, 29, 37, 39, 43, 50). These reports suggested that ^{18}F-FDG PET-CT scanning may facilitate suspicion of IVLBCL with pulmonary involvement, even in the absence of radiological findings (11, 12, 14, 42). In the present case, the PET-CT findings were pivotal in the suspected diagnosis of IVLBCL with pulmonary involvement and in assessing the response to treatment. Furthermore, in Case 14 in Table 2, Nakazato et al. successfully obtained an early diagnosis of pulmonary IVLBCL by a random TBLB, despite the lack of abnormal FDG accumulation in lung fields (10). They suspected pulmonary IVLBCL because of progressive dyspnea and hypoxemia. Conversely, Table 2 also mentions four cases of IVLBCL with a diffuse FDG uptake in the lung that were diagnosed by a skin or renal biopsy without a lung biopsy (11, 12, 37, 39). In this case, pathological findings

Table 1. Seventy-six Cases of Pulmonary IVLBCL.

	Total n=76
Gender	
Male, n (%)	44 (57.9)
Female, n (%)	32 (42.1)
Age, median (range), years	61.5 (35-85)
Fever, n (%)	56 (73.7)
Cough, n (%)	21 (27.6)
Dyspnea or dyspnea on exertion, n (%)	52 (68.4)
Hypoxemia	35 (46.7)
LDH, median (range), IU/L	1,357 (352-5,085)
sIL-2R, median (range), U/mL	2,279 (602-24,500)
PaO_2, median (range), Torr	58.3 (35-98.3)
$AaDO_2$, median (range), Torr	51.8 (3.6-196.5)
$\%D_{LCO}$, median (range), %	46.7 (20-87.3)
Cases with chest CT, n (%)	57 (75)
Chest CT findings	
No abnormality, n (% of cases with chest CT)	11 (19.3)
GGO, n (% of cases with chest CT)	34 (59.6)
Diffuse multiple small nodules, n (% of cases with chest CT)	10 (17.5)
Cases with diagnosis during life, n (%)	60 (78.9)
Diagnosis	
Ante-mortem diagnosis, n (%)	60 (78.9)
Post-mortem diagnosis, n (%)	16 (21.1)
Pathological confirmation	
Autopsy, n (%)	16 (21.1)
Surgical lung biopsy, n (%)	14 (56.7)
Random TBLB, n (%)	10 (16.7)
CT-guided percutaneous lung biopsy, n (%)	1 (1.3)
Pulmonary microvascular cytology	1 (1.3)
Random skin biopsy	9 (11.8)
Percutaneous renal biopsy	1 (1.3)
Cases with chemotherapy, n (% of cases with ante-mortem diagnosis)	50 (83.3)
CHOP therapy, n (% of cases with chemotherapy)	15 (30)
R-CHOP therapy, n (% of cases with chemotherapy)	30 (60)

$AaDO_2$: alveolar-arterial oxygen difference, CT: computed tomography, DLBCL: diffuse large B-cell lymphoma, D_{LCO}: diffusing capacity of the lung for carbon monoxide, FDG: ^{18}F-fluorodeoxyglucose, GGO: ground-glass opacity, IVLBCL: intravascular large B-cell lymphoma, LDH: lactic dehydrogenase, NA: not applicable, PaO_2: pressure of arterial oxygen, PET: positron emission tomography, RHS: reversed halo sign, sIL-2R: soluble interleukin-2 receptor, TBLB: transbronchial lung biopsy

from a random skin biopsy and TBLB led to a diagnosis and prompt chemotherapy. Of the 76 cases in Table 1, an ante-mortem diagnosis was made in 60 patients (78.9%) who underwent a lung and/or skin biopsy. Among these 60 cases, 50 (83.3%) received systemic chemotherapy, i.e. CHOP or R-CHOP therapy. The chemotherapy improved the clinical outcomes for IVLBCL in 41 of the 50 cases (82%). These previous reports have suggested that a random skin biopsy and TBLB, which were useful in diagnosing the present case while the patient was still alive, should be considered early on, even when skin lesions or abnormal pulmonary findings are not apparent, in order to rapidly initiate the administration of chemotherapy (7-14). These previous reports have also suggested that it is necessary to diagnose pulmonary IVLBCL comprehensively based on the clinical symptoms, image analyses and pathological findings. Ultimately, systemic chemotherapy for IVLBCL at an early stage may improve the long-term survival (9, 12, 14, 16, 38, 46, 51).

In conclusion, we encountered an asthmatic patient having IVLBCL with pulmonary involvement disguised as an asthma exacerbation. The exertional dyspnea, hypoxemia, increased serum LDH and sIL-2R, increased $AaDO_2$, decreased D_{LCO} and scintigraphic, CT and PET-CT findings led to the correct diagnosis. IVLBCL should be considered in such cases of exertional dyspnea and/or hypoxemia, even when wheezing symptoms disappear after systemic corticosteroid therapy. Furthermore, a random skin biopsy, TBLB and ^{18}F-FDG PET-CT scan should be performed early to make the diagnosis, even if in the absence of skin lesions or

Table 2. Thirteen Previous Case Reports of Pulmonary IVLBCL with FDG-PET/CT.

Case	Age/ Sex	Dyspnea or dyspnea on exertion	Fever	Cough	LDH (IU/L)	sIL-2R (U/mL)	PaO_2 (Torr)	$AaDO_2$ (Torr)	$\%D_{LCO}$ (%)	Chest X-ray findings	Chest CT findings	FDG-PET/CT findings in the lung field	Pathological confirmation	Reference
IVLBCL with diffuse FDG uptake in the lung diagnosed by lung biopsy or autopsy														
1	57F	-	+	-	1,315	NA	NA	NA	NA	No abnormality	Interstitial infiltrates in right lung field	Diffuse uptake in right upper-middle lung fields	Postmortem examination	29
2	50F	+	+	NA	3,386	6,499	66.9	44.9	NA	No abnormality	No abnormality	Diffuse uptake in both lung fields	Random TBLB	14
3	39M	+	+	NA	2,214	1,950	61.6	45.2	NA	No abnormality	No abnormality	Diffuse uptake in both lung fields	Random TBLB	14
4	61M	+	+	NA	698	4,130	74.1	41.3	41	No abnormality	No abnormality	Diffuse uptake in both middle-lower lung fields	Random TBLB	14
5	71F	+	+	NA	NA	NA	NA	NA	NA	NA	No abnormality	Diffuse uptake in both lung fields	Random TBLB	14
6	71M	+	-	+	2,670	NA	NA	NA	NA	NA	GGO in both lung fields	Diffuse uptake in both lung fields	Surgical lung biopsy	43
7	71M	+	+	+	+	NA	+	NA	NA	NA	GGO in both lung fields	Diffuse uptake in both lung fields	Surgical lung biopsy	14
8	59M	-	-	+	712	NA	NA	NA	NA	Patchy high-attenuation opacities in the upper lung field	Patchy GGO and RHS in both upper lung fields and a small nodule in right upper lobe	Uptake in both lung fields	Surgical lung biopsy	50
9*	62M	+	-	-	1,482	1,570	53.9	60.9	46.9	No abnormality	Diffuse multiple small nodules in both lung fields	Diffuse uptake in both middle-lower lung fields	Random skin biopsy and TBLB	
IVLBCL with diffuse FDG uptake in the lung diagnosed by skin or renal biopsy														
10	39F	-	+	NA	1,051	24,500	NA	NA	NA	No abnormality	No abnormality	Diffuse uptake in both lung fields, predominantly in upper fields	Random skin biopsy	37
11	41F	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	Diffuse uptake in both lung fields	Percutaneous renal biopsy	39
12	66M	+	+	NA	431	3,951	50.4	154.2	NA	NA	GGO and diffuse multiple small nodules in both lung fields	Diffuse uptake in both lung fields	Random skin biopsy	11
13	53F	NA	+	NA	849	2,380	NA	NA	NA	NA	No abnormality	Diffuse uptake in both lung fields	Random skin biopsy	12
PET-negative pulmonary IVLBCL diagnosed by lung biopsy														
14	84M	+	NA	NA	1,120	2,238	53.3	53.1	NA	No abnormality	No abnormality	No abnormal uptake in both lung fields	Random TBLB	10

*Current case. $AaDO_2$: alveolar-arterial oxygen difference, CT: computed tomography, DLBCL: diffuse large B-cell lymphoma, D_{LCO}: diffusing capacity of the lung for carbon monoxide, FDG: ^{18}F-fluorodeoxyglucose, GGO: ground-glass opacity, IVLBCL: intravascular large B-cell lymphoma, LDH: lactic dehydrogenase, NA: not applicable, PaO_2: pressure of arterial oxygen, PET: positron emission tomography, RHS: reversed halo sign, sIL-2R: soluble interleukin-2 receptor, TBLB: transbronchial lung biopsy

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abnormal pulmonary findings, possibly leading to prompt chemotherapy, contributing to remission and improving the long-term survival.

The authors state that they have no Conflict of Interest (COI).

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