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 (AaDO₂), decreased pulmonary diffusing capacity for carbon monoxide (DlCO) and scintigraphic, computed tomography (CT) and ¹⁸F-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
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 (PaO2 53.9 Torr) with an elevated alveolar-arterial oxygen difference (AaDO2) (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 18F-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 AaDO2, 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 AaDO2 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 patients 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 AaDO2 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 18F-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 IVLBC. High levels of LDH and sIL-2R have been observed in most cases of IVLBC (13, 14, 16).

Since 1983, there have been 76 additional cases of IVLBC 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 IVLBC with FDG-PET/CT (Table 2) (10-12, 14, 29, 37, 39, 43, 50). These reports suggested that 18F-FDG PET-CT scanning may facilitate suspicion of IVLBC 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 IVLBC 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 IVLBC by a random TBLB, despite the lack of abnormal FDG accumulation in lung fields (10). They suspected pulmonary IVLBC because of progressive dyspnea and hypoxemia. Conversely, Table 2 also mentions four cases of IVLBC 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.

| Gender                | Total n=76 |
|-----------------------|------------|
| 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) |
| PaO2, median (range), Torr | 58.3 (35-98.3) |
| AaDO2, median (range), Torr | 51.8 (3.6-196.5) |
| %DLCO, 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) |

AaDO2: alveolar-arterial oxygen difference, CT: computed tomography, DLBCL: diffuse large B-cell lymphoma, DLCO: diffusing capacity of the lung for carbon monoxide, FDG: 18F-fluorodeoxyglucose, GGO: ground-glass opacity, IVLBCL: intravascular large B-cell lymphoma, LDH: lactic dehydrogenase, NA: not applicable, PaO2: 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 AaDO2, decreased DLCO 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 18F-FDG PET-CT scan should be performed early to make the diagnosis, even if in the absence of skin lesions or
| Case | Age/ Sex | Dyspnea or dyspnea on exertion | Fever | Cough | LDH (IU/L) | sIL-2R (U/mL) | PaO₂ (Torr) | AaDO₂ (Torr) | %D₂/CO (%) | 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 | No abnormality | No abnormality | Diffuse uptake in both lung fields | Random TBLB | 14 |
| 6 | 71M | + | - | + | 2,670 | 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 | NA | No abnormality | 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 | 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 | 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. AaDO₂: alveolar-arterial oxygen difference, CT: computed tomography, DLBCL: diffuse large B-cell lymphoma, D₂/C0: diffusing capacity of the lung for carbon monoxide, FDG: ¹⁸F-fluorodeoxyglucose, GGO: ground-glass opacity, IVLBCL: intravascular large B-cell lymphoma, LDH: lactic dehydrogenase, NA: not applicable, PaO₂: pressure of arterial oxygen, PET: positron emission tomography, RHS: reversed halo sign, sIL-2R: soluble interleukin-2 receptor, TBLB: transbronchial lung biopsy
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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