Intravascular Large B-cell Lymphoma Presenting Pulmonary Arterial Hypertension as an Initial Manifestation

Takeshi Kotake¹, Satoru Kosugi¹, Takayuki Takimoto¹, Soichi Nakata¹, Junko Shiga¹, Yasuhiro Nagate¹, Tsutomu Nakagawa², Hironori Take¹ and Shuichi Katagiri¹

Abstract

We report a 39-year-old man with intravascular large B-cell lymphoma (IVLBCL) who had been treated as a case with pulmonary arterial hypertension (PAH) for one year. After he became worse, diffuse pulmonary ¹⁸F-fluorodeoxyglucose (FDG) uptake in positron emission tomography (PET) suggested the existence of IVLBCL in the lung showing normal CT images. The diagnosis was confirmed with random transbronchial lung biopsy, and he was then successfully treated. Since IVLBCL presenting PAH has been rare and is difficult to diagnose, early application of FDG-PET may provide early recognition of the disorder, leading to a better outcome.

Key words: intravascular large B-cell lymphoma (IVLBCL), pulmonary arterial hypertension (PAH), ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET)


Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of non-Hodgkin lymphoma (NHL) that is characterized by proliferation of malignant lymphoid cells within the small vessels of various organs (1). It commonly presents with a variety of symptoms due to occlusion of small vessels by tumor cells in different organ systems; such as central nervous system (CNS) manifestations, cutaneous lesions, fever of unknown origin, or hemophagocytic syndrome (2). Although autopsy findings have revealed that pulmonary involvement is not rare in this disorder (3), predominant pulmonary arterial hypertension (PAH) has been only rarely described (4-6).

We describe here a man that was once treated as PAH, and then developed idiopathic fever and severe hypoxemia, accompanied by diffuse infiltration of lymphoma cells to small arterioles especially in lung. Diffuse pulmonary ¹⁸F-fluorodeoxyglucose (FDG) uptake in positron emission tomography (PET) scan was helpful in the diagnostic procedure.

Case Report

A 39-year-old man consulted our hospital because of dyspnea on exertion in February 2008. Doppler echocardiography showed paradoxical interventricular septal movement and moderate tricuspid regurgitation (estimated pressure gradient 41.2 mmHg), that suggested PAH. Neither intracardiac shunt nor valvular disease was identified. Computed tomography (CT) of the lung did not reveal any abnormal findings: There was no occlusion or thrombus of pulmonary arteries. Several autoimmunity markers (i.e., antinuclear antigens antibody, antibody to DNA, anti-RNP antibody, anti-cardiolipin antibody, and lupus anticoagulant) were examined, and all of them showed negative results. Then, a tentative diagnosis of idiopathic PAH was made, and he was treated with warfarin. Though this therapy provided no apparent improvement, his condition remained sta-
Figure 1. CT scan of the chest. A) Although CT scan never revealed any abnormal shadow or infiltration, B) FDG-PET/CT showed diffuse FDG-uptake in bilateral lung fields.

Figure 2. Frontal section view of FDG-PET of the present case. A) Abnormal diffuse accumulation of FDG in bilateral lung fields and spleen, B) disappeared after two cycles of R-CHOP therapy.

ble for almost one year. In February 2009, he suddenly developed fever (>38°C), general fatigue and progressive dyspnea. Because of these symptoms, he was admitted to our hospital in March 2009.

Physical examination on admission revealed a loud pulmonary component of second heart sound. The respiratory sound was clear. No lymphadenopathy nor hepatosplenomegaly was found. The full blood count findings revealed slight anemia (RBC 4.18×10¹²/L, hemoglobin 124 g/L) with normal white blood cells (6.3×10⁹/L: 70% neutrophils, 0.5% eosinophils, 0.5% basophils, 20.0% lymphocytes, and 9% monocytes) and normal platelets counts (232×10⁹/L). Blood chemistry results revealed a markedly elevated LDH level of 2,214 IU (normal range, 100-211), AST of 151 IU (10-37), CRP of 9.4 mg/dL (<0.3) and soluble IL-2 receptor (sIL-2R) of 1,950 U/mL (145-519). Arterial blood gases revealed hypoxemia (61.6 mmHg) and hypocapnia (34.6 mmHg), and alveolo-arterial difference of oxygen partial pressure (AaDO₂) was increased (45.2 mmHg). All tests performed to explore possible etiologies of fever were not contributory: blood cultures, blood films, HIV serology, and tests for mycoplasma, chlamydiae, legionellae, cytomegalovirus, tuberculosis, Epstein-Barr virus, and hepatitis B and C. Autoimmunity markers (anti-nuclear antigens antibody, antibody to double-stranded DNA, anti-Smith antibody, anti-Scl70 antibody, anti-RNP antibody, anti-Jo1 antibody, anti-cardiolipin antibody, and anti-proteinase or antimyeloperoxidase anti-neutrophil cytoplasmic antibody) were also negative.

Chest radiography or CT of whole body showed normal image (Fig. 1A). There was also no abnormal finding with electrocardiography (ECG) or spirography. Doppler echocardiography showed findings indicating PAH as before, and estimated mean pulmonary arterial pressure (mPAP) was 40 mmHg (<25 mmHg).

The extremely high level of LDH and sIL-2R prompted us to think that he might have malignant lymphoma. Bone marrow aspiration and biopsy provided no evidence of the disorder. However, in whole-body scan of FDG-PET, abnormal diffuse accumulation of tracers was noted in bilateral lung fields and spleen (Figs. 1B, 2A). Maximal standardized uptake value (SUV) in the lung fields was 4.0. From this result, random transbronchial lung biopsy (from the right upper and lower lobes) was performed. All biopsied specimens demonstrated obstruction of the small vessels by large neoplastic lymphoid cells (Fig. 3A), which expressed leukocyte common antigen (CD45) and B-cell associated antigen (CD20) (Fig. 3B). These histological findings confirmed the diagnosis of IVLBCL.

He was treated with cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 2 mg/body, prednisolone 60 mg/body, and rituximab 375 mg/m² (R-CHOP). His fever
and dyspnea rapidly improved after the start of chemotherapy. LDH, sIL-2R and mPAP levels normalized after 7 days, 10 days and two weeks, respectively. In addition to these findings, subsequent PET showed disappearance of the diffuse FDG-uptake in the lung and spleen after two cycles of the chemotherapy (Fig. 2B). As of the time of writing, the patient remains alive and continues to be treated with R-CHOP.

**Discussion**

In this report, we have described a rare IVLBCL case presenting PAH as an initial manifestation.

The great majority of reported IVLBCL cases are characterized by nonspecific clinical features, and diagnosis has been difficult and delayed (2, 7). Even in the 1990s or 2000s, it was reported that ante-mortem diagnosis remained as 70%-79% (8, 9). The most common clinical manifestations involve skin and the nervous system, and some authors found that 68% of IVL patients had symptoms present in at least one of these organs (9). Although autopsy findings indicated that lung involvement in IVLBCL is relatively frequent (approximately 60%) (3, 4), predominant or primary presentation in lung has been rare and only a few cases have been reported in the literature to date (4-6, 9-12). Among them, only four cases with PAH have been described, including the present case (4-6). Histopathological analysis revealed diffuse partial or complete obstruction of pulmonary arterioles by large lymphoma cells, and this mechanism like pulmonary tumor thrombotic microangiopathy could cause the PAH. In cases with pulmonary tumor thrombotic microangiopathy, it has been suggested that tumor-microemboli in the small arterioles activate some chemokines and stimulate intimal proliferation (13), leading to the limitation of alveolar to end-capillary O₂ diffusion. This mechanism causing hypoxemia should be analogous to the IVLBCL with PAH. If we examined the diffusing capacity for carbon monoxide, a decreased value might have been observed. In contrast to the majority of IVLBCL cases with lung involvement, in which radiological examinations revealed diffuse interstitial infiltrates or patchy consolidations (10, 14-16), three of the four cases with PAH lacked such lesions that could promote physicians to take account of lung biopsy. Thus, two cases could not be treated with chemotherapy due to lack of evidence of lymphoma, and they were diagnosed at autopsy (4, 6). The present case is the only one that was successfully treated after a histological diagnosis of specimens taken from lung areas, despite the lack of findings of conventional radiographic measures.

FDG-PET was helpful in the diagnostic procedure. Recently, FDG-PET has emerged as a powerful functional imaging tool in the assessment of patients with NHL (17). Several authors have reported that FDG-PET is useful for the diagnosis of IVLBCL when this type of lymphoma is clinically suspected (18-22). Recently, Kitanaka et al reported a case with fever of unknown origin that was diagnosed as IVLBCL with lung involvement by FDG-PET (23). In that case, neither CT nor ⁶⁷gallium scintigraphy could reveal the presence of disease in the lung, but PET revealed diffuse pulmonary FDG-accumulation. That case, as with our case, was successfully treated. These two cases suggest that FDG-PET could make it easier for physicians to recognize the possibility of IVLBCL with lung involvement even in cases lacking any radiologic finding. That may encourage physicians perform lung biopsy, and may introduce prompt application of chemotherapy. Since it is now assumed that systemic chemotherapy for IVLBCL at an early stage may increase survival (24), some improvement in patients’ outcome might be provided.

However, it remains unknown whether the FDG-PET could detect IVLBCL even in the period when our case showed only subacute PAH. If we can recognize IVLBCL in cases with PAH earlier, a better outcome could be provided. Since the accuracy of FDG-PET in identifying IVLBCL has not been established (25), one may argue that it would be difficult to differentiate IVLBCL with PAH at such an early stage from other inflammatory conditions (i.e., interstitial pneumonitis and collagen disease-related lung disease), some of which relate to pulmonary hypertension and can also show positive FDG-PET results with lower SUV (usu-
ally less than 2.5) (26, 27). Recently, some investigators suggested that dual-time point FDG-PET is useful for the differential diagnosis of lung diseases (27). Such new evaluation methods would have some potential to provide earlier recognition of the IVLBCL with PAH. In order to determine the usefulness of FDG-PET in detecting IVLBCL with PAH, a study focusing on these issues is needed in the future.

In summary, the possibility of IVLBCL with primary lung involvement might be considered in some cases diagnosed as ‘idiopathic PAH’. The present case suggested the potential utility of FDG-PET in indicating the appropriate application of lung biopsy. Early application of FDG-PET may provide early recognition of IVLBCL with PAH, which could lead to prompt chemotherapy contributing to a patient’s remission and long-term survival.

Acknowledgement
Histopathological analysis was performed by Dr. Shiro Adachi (Department of Pathology, Toyonaka Municipal Hospital, Toyonaka, Osaka). We would like to thank Dr. Seiki Hamada (Jinsenkai MI Clinic, Toyonaka, Osaka) for his skillful FDG-PET interpretation.

References