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CASE REPORT

Intravascular large B-cell lymphoma with diffuse FDG uptake in the lung by ^{18}FDG-PET/CT without chest CT findings

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Abstract We report a rare case of intravascular large B-cell lymphoma (IVLBCL) with diffuse fluorodeoxyglucose (FDG) uptake in the lung by ^{18}FDG-positron emission tomography/computed tomography (PET/CT). CT showed nodular shadow, whereas diffuse FDG uptake in PET/CT suggested IVLBCL in the lung. A random skin biopsy provided histological evidence of IVLBCL. The patient responded well to combination chemotherapy. Only two cases of IVLBCL in which diffuse pulmonary FDG uptake was demonstrated have been reported previously. FDG-PET/CT plus random skin biopsy may be useful for the early diagnosis of IVLBCL with pulmonary involvement even without convincing radiological findings in the lung.

Keywords Intravascular large B-cell lymphoma (IVLBCL) · ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}FDG-PET/CT) · Random skin biopsy

Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare extranodal large-cell lymphoma characterized by the presence of tumor cells within the blood vessels [1]. Pfleger and Tappeiner [2] first described this lymphoma as systemic proliferative angioendotheliomatosis in 1959. IVLBCL is listed as a subtype of diffuse large B-cell lymphoma (DLBCL) in the current World Health Organization (WHO) classification [3]. It commonly presents with a variety of symptoms, due to the 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 [4].

Although involvement in the lung is often detected at autopsy, early diagnosis is quite difficult [5]. However, with the application of aggressive chemotherapy in the early stage of the disease, the therapeutic effect resembles that in conventional DLBCLs [6]. Computed tomography (CT) cannot always reveal the presence of the disease in the lung. To our knowledge, there are only two IVLBCL cases reported to date that showed diffuse pulmonary uptake of ^{18}F fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT in the absence of abnormal findings on chest CT [7, 8].

We describe here a man who developed an idiopathic fever and severe hypoxemia, accompanied by IVLBCL. Diffuse pulmonary FDG uptake on a PET scan was helpful in the diagnosis.

Case report

A 66-year-old man presenting with a 2-week history of persistent fever in April 2008 was admitted to a nearby hospital. Although serum levels of the hepatobiliary enzymes and acute inflammatory reactants were elevated, magnetic resonance cholangiopancreatography (MRCP)

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revealed no significant abnormality, the fever resolved spontaneously, and the patient was discharged. However, the patient developed periodic febrile episodes every 3 weeks thereafter, with each episode persisting for about a week. Because there was concurrent evidence of hepatic functional impairment, the patient was readmitted to the same hospital in June 2008. Serological testing revealed a positive test result for antinuclear antibodies (ANA) and elevated serum titers of soluble interleukin (IL)-2 receptor (sIL-2R) (3306 U/mL). However, contrast-enhanced thoracoabdominal CT scans, FDG-PET/CT, and a bone marrow examination revealed no significant abnormality. In July, the patient was readmitted for a liver biopsy, which revealed non-specific reactive lobular hepatitis with fibrosis associated with mild inflammatory cell infiltration. These findings seemed insufficient to explain the recurrent episodes of fever. In September, a CT of the chest showed scattered, faint nodular densities in the apical regions of both lungs (Fig. 1a), while a PET/CT at that time revealed homogeneous, diffuse FDG uptake in both lung fields (Fig. 2), which was inconsistent with the CT findings. Thus, he was admitted to this hospital on October 8 for diagnostic video-assisted thoracic surgery (VATS).

Physical examination on admission revealed that respiratory sounds were clear. No lymphadenopathy or hepatosplenomegaly was found. The full blood count findings revealed slight anemia [red blood cells (RBCs) 4.18×10^{12}/L, hemoglobin 115 g/L] with slightly increased white blood cells (9.02×10^{9}/L: 66.0 % neutrophils, 1.0 % eosinophils, 11.0 % lymphocytes, and 19.0 % monocytes)

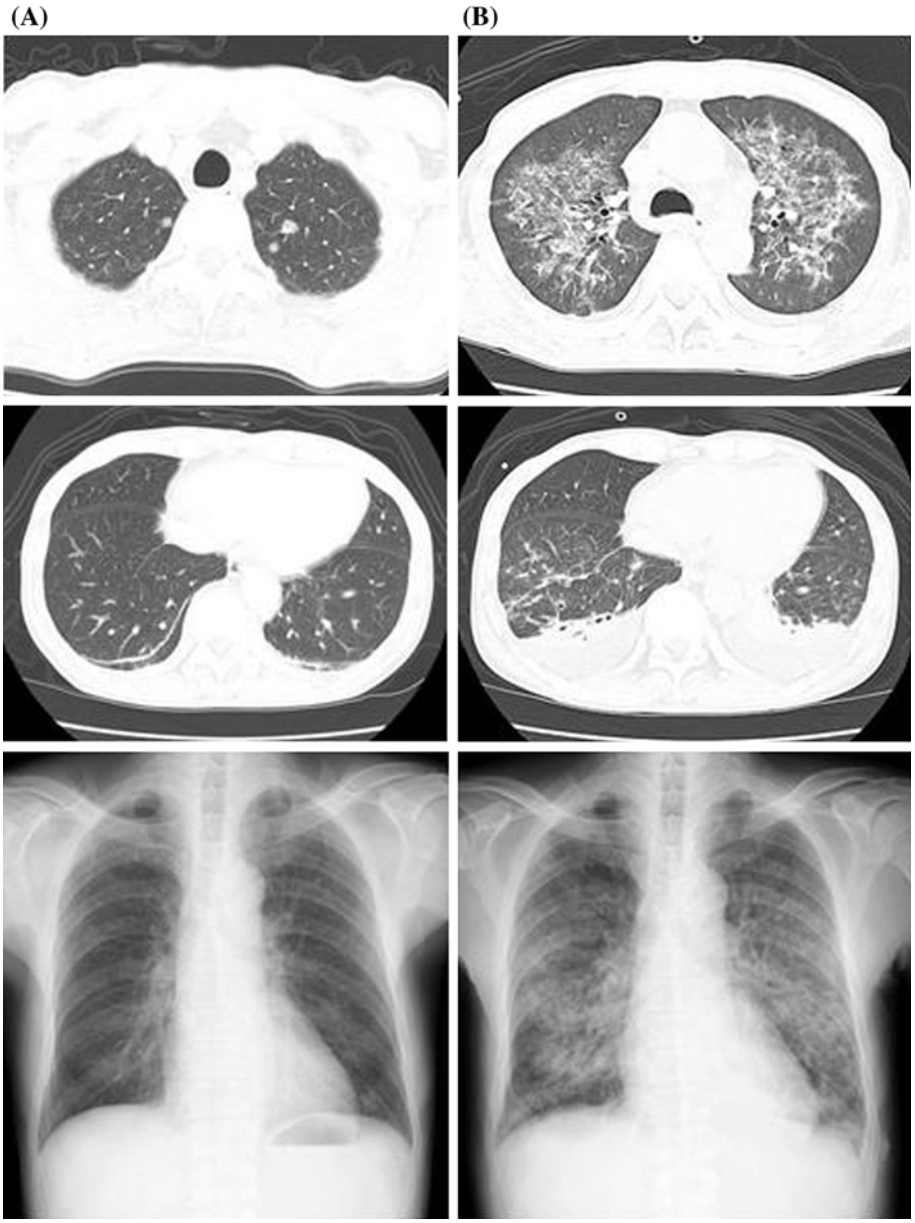

Fig. 1 **a** Chest X-ray and chest CT findings just prior to admission in September 2008 There were several relatively well-defined small nodular infiltrates bilaterally in the apical regions of the lungs on chest CT. However, no significant evidence of active inflammation or tumorous lesion was noted. **b** Chest X-ray findings on the 6th hospital day and chest CT findings on the 9th hospital day. Chest X-ray showed a butterfly shadow and chest CT revealed new emergence of consolidation and ground-glass infiltrates, predominantly in the hilar regions, while the pleural regions tended to be spared. The interlobular septum was generally thickened

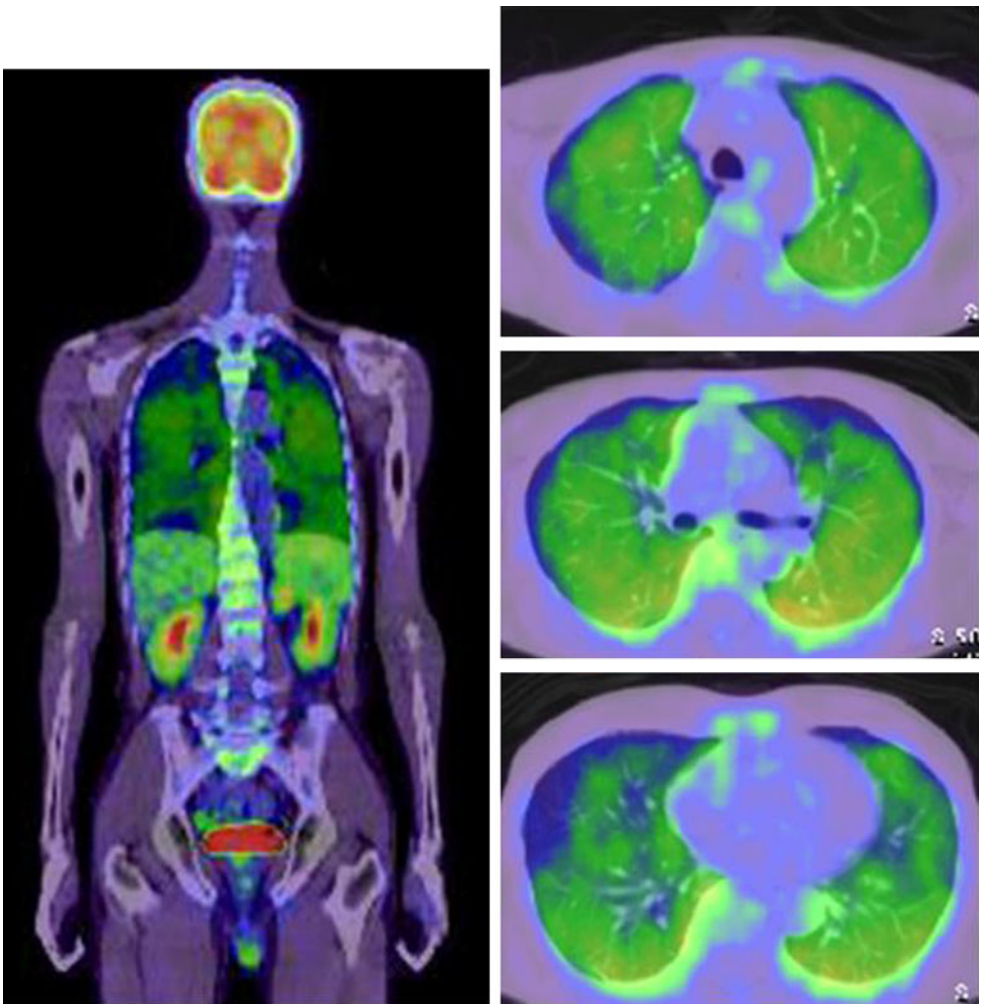

Fig. 2 ^{18}FDG-PET/CT findings just prior to admission in September 2008. Increased diffuse FDG uptake, fairly homogeneous from the basal region to the apical region of the lung, was noted bilaterally. There was no significant increase in lymph node FDG uptake. FDG uptake was also inconspicuous in bone marrow and the spleen

and normal platelets counts (315×10^9/L). Blood chemistry results revealed an elevated lactate dehydrogenase (LDH) level of 431 IU (normal range, 119–229), aspartate aminotransferase (AST) of 37 IU (13-33), C-reactive protein (CRP) of 24.57 mg/dL (<0.30), ferritin of 1230.3 ng/mL (30.0–435.0), and sIL-2R of 3951 U/mL (122–496). All tests performed to explore the possible etiologies of the fever were non-informative: blood cultures, blood films, HIV serology, and tests for Epstein-Barr virus, cytomegalovirus, tuberculosis, and hepatitis B and C. Although the ANA titer was 1:640, autoimmunity markers (antibody to double-stranded DNA, anti-Smith antibody, anti-Scl 70 antibody, anti-RNP antibody, anti-Jo1 antibody, anticardiolipin antibody, and anti-proteinase or antimyeloperoxidase anti-neutrophil cytoplasmic antibody) were all negative.

The patient's general condition was relatively stable following admission. On the 6th hospital day, however, he complained of difficulty in breathing; physical examination at this time revealed a body weight gain of 3 kg, and a chest X-ray showed a butterfly shadow (Fig. 1b). Furthermore, hypoxemia [SpO_2 95 % (nasal 2 L/min)] was noted on pulse oximetry. Abdominal CT revealed no abnormality. Worsening of the respiratory function status due to hypoalbuminemia and heart failure was suspected initially, and the patient was administered intravenous infusions of albumin and a catecholamine, along with diuretics; however, the hypoxemia worsened on the 9th hospital day. Arterial blood gases revealed hypoxemia (50.4 mmHg) and hypercapnia (47.4 mmHg), and the alveolo-arterial difference in oxygen partial pressure ($AaDO_2$) was increased (154.16 mmHg). A repeat chest CT was performed (Fig. 1b), which showed slight extension of the nodular infiltrates in the apical regions of both lungs, with ground-glass densities in adjacent lung regions. In addition, new emergence of consolidation and ground-glass infiltrates

was noted, predominantly in the hilar regions, and the patient was transferred to our department on the 9th hospital day for a medical workup and treatment of the fever of unknown etiology associated with respiratory failure. An initially scheduled VATS was cancelled because the patient's respiratory condition deteriorated. PCP-PCR of the sputum was negative and the serum level of β-D-glucan was normal. While the differential diagnosis included various disorders, such as acute interstitial pneumonia, acute respiratory distress syndrome (ARDS) of unknown cause, and pulmonary alveolar proteinosis was considered, the possibility of IVLBCL was strongly suspected based on the elevated serum LDH and sIL2R, fever of unknown cause, increased serum ferritin, and hypoxemia of unknown cause.

On the 10th hospital day, a random skin biopsy was performed and the pathological analysis showed a small degree of proliferation of large tumor cells in the lumina of the capillary vessels (Fig. 3a). The intravascular tumor cells were positive for CD20 (L26) (Fig. 3b) and negative for CD 10 and 30. Random skin biopsies were taken from five regions, the left forearm, the right and left abdominal regions and both thighs, and there had been no evidence of FDG accumulation in any of these areas on pre-treatment FDG-PET. Based on these results, IVLBCL was diagnosed. After transfer to the department of hematology, combined chemotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) was started immediately after the definitive diagnosis of IVLBCL. His clinical symptoms and laboratory findings improved markedly. Subsequently, he received a total of eight courses of R-CHOP, and complete remission (CR) was achieved. The patient underwent FDG-PET at that time point, with the results demonstrating complete disappearance of the diffuse FDG accumulation in both lungs (Fig. 4). He remains in CR 33 months after treatment.

Discussion

IVLBCL is a rare lymphoma characterized by the presence of large tumor cells within blood vessels [2]. It has been considered that IVLBCL is a highly malignant disease with a poor prognosis [9]. The most common clinical manifestations involve the skin and nervous system; it has been reported that 68 % of IVBCL patients had symptoms present in at least one of these organs. IVBCL is often associated with rapid systemic dissemination and an aggressive clinical course if appropriate therapy is not initiated early. Even in the 1990s or 2000s, it was reported that ante-mortem diagnosis remained at 70–79 % [9]. However, long-term survival has been reported to be possible in patients treated with conventional systemic chemotherapy for B cell lymphoma during the early stage of the disease [10]. Although involvement in the lung is often detected at autopsy (approximately 60 %) [11], early diagnosis is difficult [12]. In addition, predominant or primary presentation in the lung in IVLBCL is rare and only a few cases have been reported to date [5, 9, 13]. Thus, it is necessary to conduct an appropriate biopsy as soon as possible. In our case, the patient was diagnosed with IVLBCL approximately 6 months after the onset of fever and 10 days after admission.

Only two cases of IVLBCL have been reported to date in which diffuse pulmonary FDG uptake was demonstrated on PET images in the absence of abnormal chest CT findings, as in the case described here. In both reported

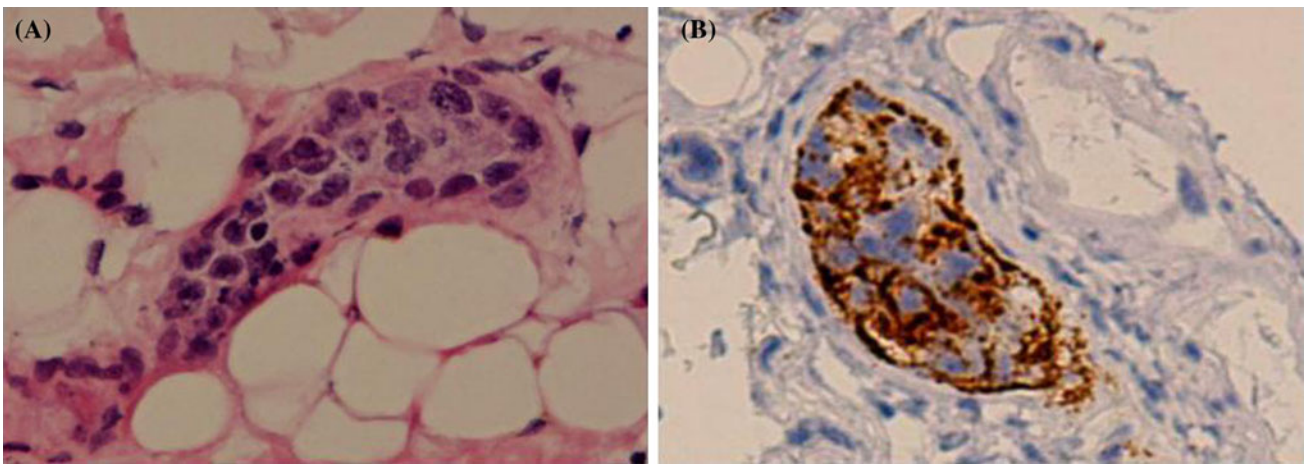

Fig. 3 Histopathological analysis of random skin biopsy specimen. **a** Large lymphoma cells occupied the intravascular space of small vessels (hematoxylin and eosin staining, ×400). **b** Tumor cells were positive for CD20 (CD20 immunostain, ×400)

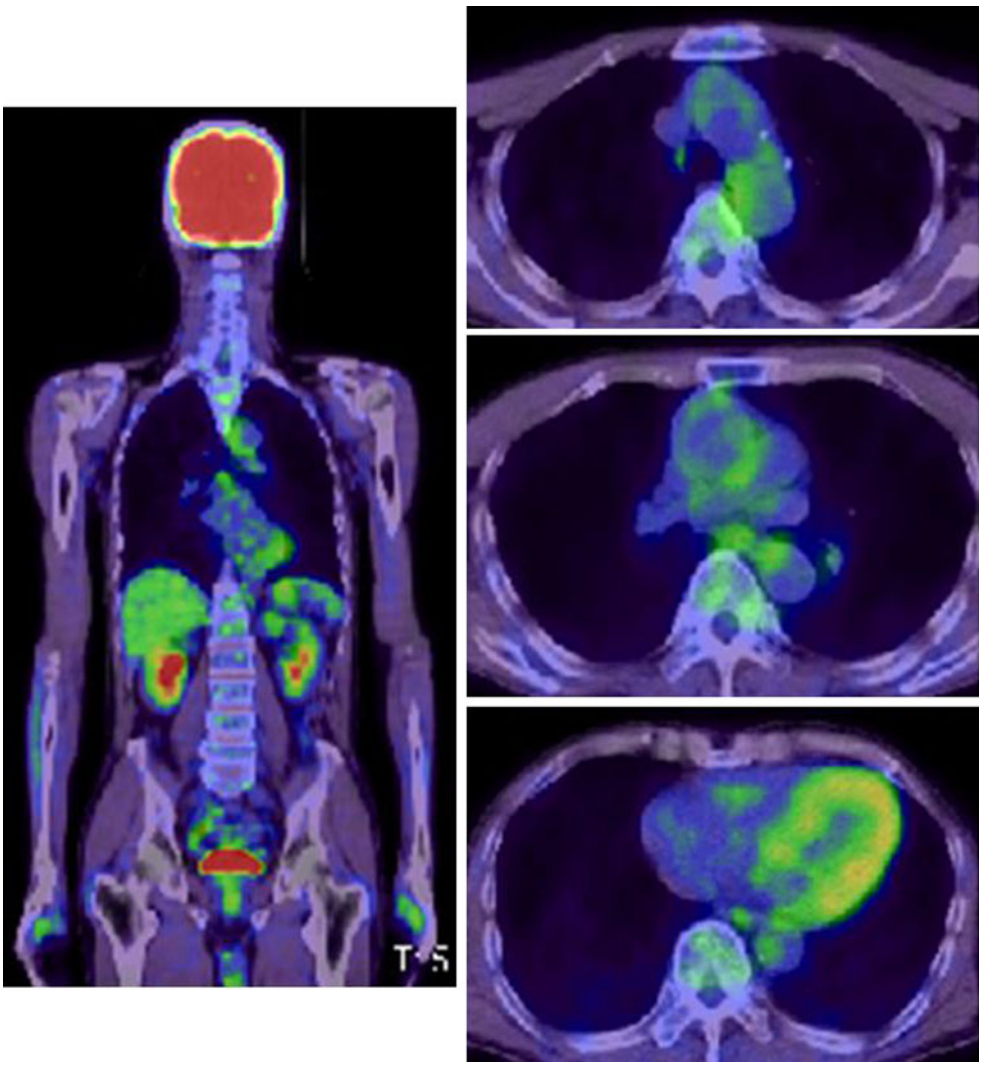

Fig. 4 ^{18}FDG-PET/CT findings after the completion of eight courses of R-CHOP. Diffuse FDG uptake had completely disappeared in both lungs in the FDG-PET/CT findings after the completion of eight courses of R-CHOP

cases, the definitive diagnosis was made by random transbronchial lung biopsy, and a dramatic improvement was obtained with R-CHOP therapy [7, 14]. Our case was another such rare case, where the definitive diagnosis was finally made by a minimally invasive random skin biopsy.

Recently, FDG-PET has been shown to provide high sensitivity for non-Hodgkin's lymphoma (NHL) [8, 11, 15]. Several authors have reported that FDG-PET is useful for the diagnosis of IVLBCL when this type of lymphoma is clinically suspected [8, 16]. In our case, FDG-PET revealed strong FDG uptake in both lung fields. Although lymphoma cell involvement in the lung is frequently found in IVLBCL patients, in most cases, the lack of apparent radiological abnormalities in the lung does not prompt physicians to conduct a lung biopsy for the differential diagnosis. Even if respiratory symptoms do exist, physicians often hesitate to perform TBLB in the absence of convincing radiological findings in the lung field. Indeed, in the reported cases diagnosed as IVLBCL by lung biopsy, they exhibited apparent lung CT abnormalities [17]. On the other hand, in the three cases, including our case, FDG-PET was the only radiological examination that showed lung involvement of lymphoma cells. The data obtained by FDG-PET directed the two reported cases to the optimal biopsy site to obtain definitive histological confirmation. These three cases suggest that FDG-PET can make it easier for physicians to recognize the possibility of IVLBCL with lung involvement even in cases lacking radiological findings. That may encourage physicians to perform lung biopsies or random skin biopsies and may introduce quicker application of chemotherapy. Because it is now considered that systemic chemotherapy for IVLBCL at an early stage may increase survival [18], some improvement in patient outcome may be expected. Shimada et al. [19] described renal biopsy findings

of IVLBCL in two patients proven to be negative for renal FDG accumulation in their comparative study of FDG-PET and biopsy pathological findings in IVLBCL, reporting that FDG-PET is not necessarily useful for exploration in the kidney, unlike in the lung.

Kotakle et al. mentioned that it remains unknown whether FDG-PET can detect IVLBCL even during periods when only subacute pulmonary artery hypertension (PAH) is shown [9]. In our case, however, PET/CT was performed on two separate occasions; PET/CT and chest CT images obtained 4 months before the rapid aggravation of the respiratory condition revealed no abnormality. In contrast, the PET/CT images obtained 2 months later revealed diffuse pulmonary FDG uptake; chest CT at this time still showed only slightly abnormal densities, limited to the apical lung regions, while the patient had no respiratory symptoms at all at that time. One month after the second series of imagings, a repeated CT of the chest revealed the new emergence of diffuse infiltrates in both lungs. On the other hand, there is a reported case in which IVLBCL was strongly suspected, despite the absence of abnormal accumulation of FDG in either lung field on FDG-PET. In that case, the patient presented with acute respiratory failure, and a random transbronchial lung biopsy showed findings indicative of pulmonary IVLBCL; R-CHOP therapy led to CR [20]. Thus, the temporal relationships among the development of respiratory failure symptoms, chest CT abnormalities, and PET/CT abnormalities appear to vary from case to case in patients with IVLBCL. We consider that it may be advisable for random transbronchial lung biopsies and random skin biopsies to be undertaken at an early stage in cases where IVLBCL is included in the differential diagnosis based on the FDG-PET/CT evidence of diffuse pulmonary FDG uptake even in the absence of respiratory symptoms, as in the case presented here. To assess the usefulness of FDG-PET in detecting IVLBCL with lung involvement, a study focusing on these issues is needed in the future.

Recently, the usefulness of random skin biopsy from unaffected skin for the diagnosis of IVLBCL has also been proposed [21]. Given the minimally invasive nature of this technique, it is reasonable to use a skin biopsy in the differential diagnosis of patients with suspected IVLBCL. Although the reliability of a blind skin biopsy has not yet been established, a combination of this low invasive biopsy with conventional biopsy of an affected organ, identified by imaging studies, may further increase the chances of obtaining histological confirmation.

Conclusions

In conclusion, if the possibility of IVLBCL presents in a patient with respiratory symptoms, but without abnormal findings by CT, the use of FDG-PET should be considered. FDG-PET may provide important information for obtaining tissue samples for diagnosis. Early application of FDG-PET may provide early recognition of IVLBCL with lung involvement, which could lead to prompt chemotherapy, contributing to remission and long-term survival.

Conflict of interest None of the authors including Hiroyuki Yamashita, Akitake Suzuki, Yuko Takahashi, Kazuo Kubota, Toshikazu Kano, Akio Mimori have any conflicts of interest associated with this case report.

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