Abstract

Intravascular large B-cell lymphoma (IVLBCL) is a rare extranodal lymphoma characterized by the presence of tumor cells within blood vessels, and it is considered to be a subtype of diffuse large B-cell lymphoma. We report a case of IVLBCL presenting as progressive hypoxemia. In this case, a definitive diagnosis could not be achieved by repeated transbronchial lung biopsy, a bone marrow biopsy, and a random skin biopsy, and the ultimate diagnosis was made on the basis of a pulmonary microvascular cytology (PMC) examination. Therefore, PMC is considered to be a useful strategy for the diagnosis of IVLBCL, particularly in this critically ill patient suffering from hypoxemia.

Key words: intravascular large B-cell lymphoma, pulmonary microvascular cytology (PMC), hypoxemia

Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare entity characterized by the exclusive, or predominant, growth of neoplastic cells within the lumina of blood vessels (1). However, antemortem diagnosis is relatively difficult, and although the prognosis is reported to be relatively poor, long-term survival is possible for patients treated with a combination therapy that includes rituximab (2). IVLBCL usually occurs in elderly patients, and the tumor cells affect various organs (3). When hypoxemia, respiratory symptoms, and abnormalities are present on chest radiography, the diagnosis can often be reinforced with a transbronchial lung biopsy (TBLB) (4). However, TBLB does not provide a definitive diagnosis in all cases.

Although our patient could not be definitively diagnosed by repeated TBLBs, bone marrow biopsy, or a random skin biopsy, pulmonary microvascular cytology (PMC) detected tumor cells that were strongly suspicious of large B-cell lymphoma. Because we considered that a diagnosis of IVLBCL did not contradict the findings from the patient’s clinical course and laboratory test results, the patient was treated with early chemotherapy that resulted in improvement. We report this valuable case because PMC may be a useful strategy enabling early diagnosis of IVLBCL in critically ill patients.

Case Report

An 85-year-old man was admitted to our hospital with a fever, and progressive dyspnea on exertion of 3 weeks duration. Examination revealed anemia (hemoglobin 9.2 g/dL), and elevated serum lactate dehydrogenase (LDH) 936 IU/L and soluble IL-2 receptor (sIL2R) 602 U/mL. Peripheral artery oxygen saturation (SpO₂) was 87%, and blood gas analysis showed a partial pressure of oxygen in arterial blood (PaO₂) level of 54.5 Torr, and a partial pressure of
PSL dose on admittance was 5 mg/day. Admittingly, weakness, and he was readmitted to our hospital. His later he developed fever, dyspnea, night sweats, and general weakness, and he was readmitted to our hospital. His immediately and he was discharged. At a follow-up 30 mg/day (0.6 mg/kg/day). The patient’s condition im-

steroid therapy can elicit an anti-tumor effect in malignant lymphoma (5) we began administration of prednisolone (PSL) at 30 mg/day (0.6 mg/kg/day). The patient’s condition improved immediately and he was discharged. At a follow-up examination, it was decided to taper his PSL dose slightly by 5 mg every month, and he was monitored to maintain normal levels of LDH and sIL2R. However, five months later he developed fever, dyspnea, night sweats, and generalized weakness, and he was readmitted to our hospital. His PSL dose on admittance was 5 mg/day.

Vital signs on admission were as follows: temperature 37.8°C, blood pressure 128/75 mmHg, pulse 86 beats/min, and respiratory rate 22 breaths/min with a SpO₂ of 90% on room air. Blood gas analysis showed a PaO₂ of 62.7 Torr and a PaCO₂ of 34.7 Torr with room air. Pulmonary function tests showed %VC of 81.2%, FEV₁% of 84.0%, and DLco of 78.4%, and whole-body CT showed mild ground-glass opacity in the right lower lung (Fig. 1) and mild hepatosplenomegaly. ⁶⁷Ga scintigraphy showed abnormal accumulation in the spleen, but no abnormality in either lung. On initial examination, no abnormalities in his breath sounds were noted. His extremities were slightly edematous, but no eruptions were seen. His white blood count was 5,900/mm³ (65.0% neutrophils, 24.2% lymphocytes, 9.5% monocytes, 0.8% eosinophils, and 0.5% basophils), hemoglobin 8.9 g/dL, thombocytes 11.8×10⁴/µL, serum creatinine 0.85 mg/dL, glutamic-oxaloacetic transaminase 74 IU/L, glutamic-pyruvic transaminase 35 IU/L, alkaline phosphatase 429 IU/L, γ-glutamyl transpeptidase 110 IU/L, and total bilirubin 0.6 mg/dL, thus indicating anemia, thrombocytopenia, and disorders in liver function. Serum LDH was elevated at 829 IU/L, sIL2R at 2,000 U/mL, and C-reactive protein at 4.1 mg/dL, although serum ferritin was not elevated at 168 ng/mL. A peripheral blood smear detected no abnormal cells.

PMC was then performed, whereby a Swan-Ganz catheter was inserted and situated in the right pulmonary artery wedge position, and blood was gently withdrawn from the wedged catheter. Hemodynamic parameters monitored during the procedure included a mean pulmonary capillary wedge pressure of 12 mmHg; pulmonary artery pressure of 38/13(26) mmHg; and cardiac index of 3.5 L/min/m², which indicated mild pulmonary hypertension. Extracted blood samples were heparinized and centrifuged. Because malignant cells tend to accumulate in the buffy coat of centrifuged blood, slides were made from the buffy coat, immediately fixed in 95% alcohol, and stained using the Giemsa method (6). The cytological specimens showed loosely aggregated small clusters of large atypical lymphoid cells (Fig. 2A). Immunochemical analysis showed the tumor cells to be positive for CD20 and CD79a (Fig. 2B, C), which strongly indicated large B-cell lymphoma. In addition, random skin biopsy and bone marrow biopsy were performed, but atypical cells were not seen in those specimens. Furthermore, TBLB was performed four times in the right lower lung, but the specimens collected revealed very few atypical cells that were positive for CD20 and CD79a (Fig. 2D-F). Although the patient could not be definitively diagnosed by TBLB, there was no histological evidence detecting lymphoma cells in the vessels, and there was a complete absence of swollen lymph nodes and masses, it was considered that the results of PMC were compatible with IVLBCL, based on the existence large atypical lymphocytes in the pulmonary microvasculature. In addition, hypoxemia, anemia, thrombocytopenia, and hepatosplenomegaly were present, which are characteristic of Asian variant IVLBCL. Af-
poxemia progressively exacerbated (on hospital day 15, his SpO2 was 92% O2 at 5 L/min), and we started rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone (R-CHOP) chemotherapy. After one cycle of chemotherapy, the patient’s condition and hypoxemia immediately improved and returned to normal, and he was discharged. Throughout the follow-up, he has remained well without any recurrence, and is scheduled to regularly undergo outpatient chemotherapy.

Discussion

We presented a case of IVLBCL in which PMC detected tumor cells strongly suspicious of large B-cell lymphoma. Although a few atypical cells were seen in the lung tissue retrieved by TBLB, this technique did not lead to a definitive diagnosis in our patient. However, because PMC detected lymphoma cells, we considered that a diagnosis of IVLBCL was not contradictory to findings from this patient’s clinical course and laboratory test results.

IVLBCL, also known as angiotropic large-cell lymphoma or malignant angioendotheliomatosis, is a rare systemic disease characterized by the occlusion of arterioles, capillaries, and venules throughout the body by malignant lymphomatous cells (1). Infiltration of the lungs, kidneys, adrenal glands, and prostate is also common, but only 5-9% of patients show peripheral blood involvement (7). Morphological findings show large lymphoid cells infiltrating the vessels and/or sinusoids, which are positive for CD19, CD20, CD79a and HLA-DR, but negative for CD10, CD23, and CD30 (1). Reports of antemortem diagnosis have increased recently, but most cases are diagnosed at autopsy because of the misleading clinical features that mimic dementia, vasculitis, stroke, infection, or other neoplasms. The mean interval between onset of symptoms and death has been reported as three months, emphasizing the importance of early diagnosis (8). 67Ga scintigraphy and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) are reported to be useful for early diagnosis, in combination with successful biopsy, because of the uptake in involved organs (9, 10). However, in our patient with hypoxemia, 67Ga scintigraphy in the lungs showed no remarkable findings. Moreover, random skin biopsy, bone marrow biopsy, and TBLB offered no definitive findings, and we were thus at a loss for a diagnosis. We therefore considered that PET may show an abnormal uptake, because it has been reported that FDG-PET has a significantly higher site sensitivity than 67Ga scintigraphy in lymphoma patients (11).

PMC has been reported useful in the diagnosis of fat embolism and pulmonary tumor embolism (12, 13). In addition, two cases have been reported in which PMC detected tumor cells that led to a diagnosis of IVLBCL (7, 14). Chest CT showed no abnormalities in these two cases, despite the presence of hypoxemia, but inhomogeneous perfusion was revealed on perfusion scans (Table). In 1947, Dexter et al. showed that the oxygen saturation of blood withdrawn from pulmonary artery catheters in the wedge position had characteristics of pulmonary capillary blood. In reality, since the

Figure 2. Photomicrographs of pulmonary microvascular cytology (A-C) and transbronchial lung biopsy specimens (D-F). A: Pulmonary microvascular cytology specimen showing loosely aggregated small clusters of large atypical lymphoid cells (Giemsa stain, ×100). B: Immunochemical analysis showing tumor cells to be positive for CD79a (×100). C: Immunochemical analysis showing tumor cells to be positive for CD20 (×100). D: Transbronchial lung biopsy specimen showing very few atypical cells (arrows) (Hematoxylin and Eosin staining, ×150). E: Immunochemical staining showing atypical cells to be positive for CD79a (×150). F: Immunochemical staining showing atypical cells to be positive for CD20 (×150).
References


Table. Overview of the Literature on IVLBCL with Lymphoma Cells Detected by Pulmonary Microvascular Cytology.

<table>
<thead>
<tr>
<th>Case</th>
<th>Reference</th>
<th>Age/sex</th>
<th>PaO₂</th>
<th>Pulmonary abnormality on chest CT</th>
<th>Perfusion scan</th>
<th>Bone marrow aspiration/biopsy</th>
<th>TBLB</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[7]</td>
<td>58/M</td>
<td>60.0 Torr (room air)</td>
<td>None</td>
<td>Inhomogeneous perfusion</td>
<td>Unremarkable</td>
<td>Atypical cells</td>
<td>Improved</td>
</tr>
<tr>
<td>2</td>
<td>[14]</td>
<td>68/M</td>
<td>64.4 Torr (5L/min O₂)</td>
<td>None</td>
<td>Inhomogeneous perfusion</td>
<td>Atypical cells detected</td>
<td>Unenforced</td>
<td>Improved</td>
</tr>
<tr>
<td>3</td>
<td>[our case]</td>
<td>85/M</td>
<td>62.7 Torr (room air)</td>
<td>Mild ground glass opacity</td>
<td>Normal study</td>
<td>Unremarkable</td>
<td>Atypical cells</td>
<td>Improved</td>
</tr>
</tbody>
</table>

IVLBCL: intravascular large B-cell lymphoma, PaO₂: partial pressure of oxygen, CT: computed tomography, TBLB: transbronchial lung biopsy.