Successful Treatment of Intravascular Large B-cell Lymphoma Diagnosed by Bone Marrow Biopsy and FDG-PET Scan

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Abstract

Early diagnosis of intravascular large B-cell lymphoma (IVLBCL) is difficult, but is critical for longer survival for the patients. We report a case of IVLBCL that was diagnosed with the help of FDG-PET. A 76-year-old woman was referred to us for the evaluation of her elevated serum LDH. She presented with general malaise and high fever. There were no skin lesions or neurological involvement. FDG-PET imaging showed increased uptake of FDG in the vertebra, bilateral femurs, sternum, and iliac bones. A diagnosis of IVLBCL was made by bone marrow biopsy. She was successfully treated with rituximab and modified CHOP therapy.

Key words: lymphoma, intravascular, FDG-PET, FUO

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Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare systemic disease characterized by massive proliferation of large tumor cells in the small arteries, veins, and capillaries. IVLBCL has been listed as a subtype of diffuse large B-cell lymphoma (DLBCL) in the WHO classification (1). Because of the lack of lymphadenopathy or mass formation, and due to its rapid and fatal clinical course, early diagnosis of the disease is extremely difficult. Here, we report a case of IVLBCL presenting with elevated serum LDH and fever of unknown origin (FUO). The disease was diagnosed early enough to start aggressive chemotherapy with the help of an FDG-PET study.

Case Report

A 76-year-old woman presented to a clinic because of general malaise, anorexia, and heartburn in February 2007. She was referred to us two weeks later for evaluation of her elevated level of serum LDH. She had no remarkable past medical history except for bilateral hearing disturbance of unknown cause since her late sixties. On physical examination, superficial lymph nodes, liver or spleen, were not palpated. There were no skin lesions. Her consciousness was alert. No neurological deficit was observed except for the hearing disturbance. Body temperature was 36.5°C. Blood

Figure 1. Bone marrow smear (May-Giemsa staining). Large bizarre cells with cytoplasmic vacuoles were observed.
pressure was 142/88 mmHg. Pulse was 66 and rhythm was irregular.

Her white blood cell count was 6,600/μl, 70% neutrophils, 17.5% lymphocytes, 4.5% monocytes, and 8% atypical lymphocytes. The hemoglobin concentration was 12.1 g/dl and the platelet count was 83,000/μl. Serum biochemistry tests were as follows; total protein 7.0 g/dl (reference range, 6.7-8.3), albumin 3.2 g/dl (3.8-5.3), total bilirubin 0.9 g/dl (0.2-1.1), AST 167 IU/l (10-40), ALT 47 IU/l (5-45), and LDH 1,414 IU/l (115-245). C-reactive protein was 7.29 mg/dl (≤0.30).

Chest and abdominal CT scan studies disclosed no tumor lesions. Bone marrow aspiration was performed and a small number of large bizarre cells with cytoplasmic vacuoles were found (Fig. 1). Hemophagocytosis was not observed. She was admitted to our hospital a month after the first presentation because a diagnosis of carcinomatosis of the bone marrow was suspected. At the time of admission, she had persistent daily fever (up to 39.5°C), which she had not mentioned previously. Her white blood cell count was 2,300/μl, the hemoglobin concentration was 7.0 g/dl, the platelet count was 39,000/μl, and the serum ferritin was 440 ng/ml (reference range, 5-152). Upper and lower gastrointestinal endoscopic examination disclosed no cancerous or lymphomatous lesions. An FDG - PET study with simultaneous whole body CT scan was performed. As shown in Fig. 2, the study showed an increased uptake of FDG in the vertebra, bilateral femurs, sternum, and iliac bones. The uptake in the spleen was also moderately elevated. Soluble IL-2 re-

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**Figure 2.** FDG-PET scan. Increased uptake of FDG in the vertebra, bilateral femurs, sternum, and iliac bones was observed. The uptake in the spleen was also moderately elevated.

**Figure 3.** Bone marrow biopsy. Large lymphoid cells were infiltrated in the bone marrow (A). The cells were positive for CD20 (B). The cells were positive for MUM1 (C). Endothelial cells were stained with anti-Factor VIII antibody, confirmed that lymphoid cells were aggregated in the intra-vascular spaces (D).
ceptor was reported to be extremely high at 10,332 U/ml (reference range, 135-483). Bone marrow biopsy was performed as a diagnosis of intravascular lymphoma was suspected at that time. As shown in Fig. 3, widespread sinusoidal intravascular infiltration by large atypical lymphoid cells was demonstrated. Immunohistochemical analyses showed that the cells were positive for CD20, CD79a (data not shown), MUM1, and Bcl-2 (data not shown). A small number of the tumor cells were faintly positive for CD5 (data not shown). With staining of endothelium with anti-CD34 (data not shown) and anti-factor VIII antibody, the cells were revealed to be proliferated within the blood vessels. Thus, a diagnosis of IVLBCL was made. Chromosomal analysis of the bone marrow cells showed 81-86, XX, -X, -X, add(1)(p11), add(1)(p11), add(3)(p21), i(6)(p10), i(7)(q10), add(14)(q32)x2, add(19)(q13), +mar, inc (A). 46, XX, inv(12)(p11q15) (B). Multiplex FISH (fluorescence in situ hybridization) analysis disclosed the existence of t(3;14) (p21;q32) (Fig. 5).

Administration of dexamethasone (20 mg/day) for four consecutive days completely resolved the fever before the diagnosis was confirmed. The patient was treated with eight cycles of rituximab (375 mg/m²) weekly and 6 cycles of THP-COP (pirarubicin 30 mg/m² on day 1, cyclophosphamide 500 mg/m² on day 1, vincristine 1.0 mg/m² on day 1, and prednisolone 30 mg/body on day 1-5 every three to four weeks) (2). Though grade IV neutropenia, anemia, and thrombocytopenia developed after the first cycle of THP-COP, she recovered uneventfully with lenograstim, and transfusion of red blood cells and platelets. After the second cycles of the therapy, no severe adverse reactions developed. Complete remission was confirmed by the bone marrow bi-
Figure 5. Multiplex FISH (fluorescence in situ hybridization) analysis.

Discussion

Murase et al documented that Japanese IVLBCL cases were associated with hemophagocytic syndrome and bone marrow involvement at presentation, but rarely with neurological complications or skin lesions. They proposed the term ‘an Asian variant of intravascular lymphomatosis’ (AIVL) because of the relatively high prevalence in Asian countries (3, 4). The present case had high fever, cytopenia, and the bone marrow involvement, but lacked neurological complication and a skin lesion. Therefore, the present case might be categorized as AIVL. However, this case did not fulfill the diagnostic criteria of AIVL due to the lack of hemophagocytosis in the bone marrow. Hemophagocytic syndrome might have been observed in the present case if the start of the chemotherapy had been delayed.

Shimazaki et al reported that 8p21 and 19q13 might be a characteristic chromosome abnormality in their seven cases with DLBCL with hemophagocytic syndrome (5). Murase et al reported that the same abnormalities were found in three cases of their AIVL patients (4). Though a complex chromosomal anomaly was observed, 8p21 and 19q13 were not involved in the present case (Fig. 4). Multiplex FISH analysis disclosed the existence of t(3;14)(p21;q32), suggesting that unknown gene located in the 3p21 might be juxtapose to the immunoglobuline heavy chain gene enhancer (Fig. 5). Another abnormal clone having 46, XX, inv(12)(p11q15) also existed in the marrow, and it disappeared after the chemotherapy. This clone is also suggested to be derived from the lymphoma cells. However, the significance of this chromosomal abnormality remains to be elucidated.

DiGiuseppe et al reported that 4 out of 10 intravascular lymphomatosis patients treated with combination chemotherapy were alive with CR at the study point and two have achieved long-term survival (48 and 45 months, respectively) (6). However, standard therapy for DLBCL with the use of CHOP has been disappointing for IVLBCL, with response rates just over 50%, and 3-year event-free survival of only 27% in one report (7). Superior results with chemotherapy regimens that included rituximab have been suggested (8). The present patient responded well to modified-CHOP therapy with rituximab. She has been in CR for more than eight months since the completion of treatment. When the diagnosis of IVLBCL is made early enough to start aggressive chemotherapy, the disease can be potentially curative. Early diagnosis of the disease is critical for longer survival of the patient.

Numerous cases of IVLBCL have been diagnosed at autopsy due to misleading clinical features mimicking dementia, vasculitis, stroke, infection, or other neoplasm. Our case presented with elevated LDH, cytopenia, and fever. The most common clinical sign in the reported patients is FUO (9). Use of FDG-PET scanning is reported to have a sensitivity of 84% and a specificity of 86% for localizing the source of FUO (10). In the present patient, the FDG-PET scan demonstrated diffuse uptake of tracer in the vertebra, bilateral femurs, sternum, and iliac bones. Hoshino et al reported the first case in which FDG-PET imaging of IVLBCL was described in 2004 (11). The pattern of FDG uptake in their case was similar to that of our case. In another report, FDG-PET was useful to diagnose a case of IVLBCL involving the lung, which presented with FUO (12). As far as we are concerned, there are no other reports of IVLBCL describing the FDG-PET imaging pattern. This
case may provide important information concerning the imaging study of IVL/BCL. Because the disease is potentially curative when aggressive chemotherapy is performed early in the disease process, introduction of FDG-PET might be considered in cases with FUO.

References