Case Report

A Case of Diffuse Large B-Cell Lymphoma Mimicking Primary Effusion Lymphoma-Like Lymphoma

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Keywords

Diffuse large B-cell lymphoma · Pericardial effusion · Pleural effusion · Primary effusion lymphoma-like lymphoma · Diagnosis

Abstract

A 93-year-old female was transferred to the emergency ward of our hospital due to disturbance of consciousness and hypotension. Computed tomography showed bilateral pleural and pericardial effusion without evidence of tumor masses or lymphadenopathy. Cytodiagnosis of pleural effusion revealed proliferation of atypical lymphoid-like cells with pan-B surface markers. We suspected primary effusion lymphoma-like lymphoma; however, the monoclonality of these cells was not confirmed. Cytodiagnosis of bone marrow revealed lymphoma cells with monoclonal B-cell markers. These findings prompted a diagnosis of diffuse large B-cell lymphoma with bone marrow invasion. In the case of pericardial or pleural effusion, clinicians should consider carefully both hematological malignancy and its classification.

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Introduction

Originally described in 1995, primary effusion lymphoma (PEL) is a rare subtype of diffuse large B-cell lymphoma (DLBCL) universally associated with human herpes virus-8 (HHV-8) that involves body cavities and causes serous effusions without detectable masses or lymphadenopathy according to the World Health Organization (WHO) classification of tumors about hematopoietic and lymphoid tissue [1–4]. It occurs mainly in immunocompromised patients infected with human immunodeficiency virus (HIV) and Epstein-Barr virus (EBV) [2, 4, 5]. On the other hand, in Japan, many cases of DLBCL with lymphomatous effusions on serosal surfaces and no detectable mass lesion like PEL have been reported. These cases were not regarded as cases of PEL but as a new entity, “PEL-like lymphoma (PEL-LL)” [6].

Herein, we report a case of an elderly female patient with DLBCL with bilateral pleural effusion and massive pericardial effusion. The type of DLBCL was difficult to determine because clinical features and several findings of examinations resembled PEL or PEL-LL; however, the patient’s hematological findings could not be diagnosed as both.

Case Report

A 93-year-old female was transferred to the emergency ward of our hospital due to disturbance of consciousness and hypotension. Her medical history included gastric tube feeding due to cerebral infarction and disuse syndrome, complicated by hypertension, atrial fibrillation, chronic renal insufficiency, and constipation. She was under treatment with antiplatelet, antihypertensive, and cathartic medications. She had been bedridden for a number of years and had received regular medical and nursing care at home. When the ambulance call to render medical assistance arrived at her home, she had fully recovered her consciousness, her blood pressure was within normal limits, and she did not complain of B symptoms.

In the emergency room, she presented with mild disturbance of consciousness (Japan coma scale 1), irregular pulse rate, and mild pitting edema to bilateral lower legs. She was negative for lymphadenopathy and hepatosplenomegaly. Urinalysis showed asymptomatic bacteriuria, and routine blood tests showed normocytic anemia, hypoalbuminemia, and several chemical data such as C-reactive protein, lactate dehydrogenase, creatinine, blood urea nitrogen, potassium, ferritin, and soluble interleukin-2 receptor were elevated. Electrocardiogram showed atrial fibrillation, and carotid ultrasonography showed moderate arteriosclerosis. Computed tomography of her head, neck, chest, and abdomen showed multiple lacunar infarction, bilateral pleural effusion, pericardial effusion, and bilateral renal atrophy. There was, however, no evidence of tumor mass, lymph node enlargement, or hepatosplenomegaly on computed tomography. Echocardiography showed massive pericardial effusion. Examination ruled out heart failure, infectious disease, and collagen disease. The patient was admitted to our hospital for intensive examination and treatment. Pericardial drainage was not performed because she was not in cardiac tamponade and, in addition to this, there was apprehension about iatrogenic damage to her heart. Pleural effusion was revealed to be exudative and seemed to be the cause of the patient’s dyspnea. Microscopic

observation of pleural effusion showed hemophagocytosis as well as proliferation of atypical lymphoid-like blast cells, which were positive for cluster of differentiation (CD) 19, CD20, and CD25 (Fig. 1a, b). Flow cytometry of the cells in pleural effusion was negative for monoclonality in B-lymphocyte fraction. Additionally, evidence of HIV and/or EBV infection was not detected, and cytogenetic analysis for HHV-8 and lymph node biopsy could not be performed. From the above, we suspected malignant lymphoma such as PEL-LL; however, we were unable to arrive at a conclusive diagnosis. Bone marrow examination revealed the same atypical lymphoid-like cells seen in pleural effusion; however, there was no evidence of neoplastic proliferation tumorous growth (Fig. 2a, b). Cell surface antigen analysis of bone marrow cells revealed strong deviation to gamma-chain side in B-lymphocyte fraction, which we suspected was due to neoplastic proliferation tumorous growth (Fig. 2c). Furthermore, because the CD20-positive cell rate was high (approx. 70%), we suspected that the tumor cells were CD20-positive. Chromosomal abnormality was not confirmed. The above findings prompted a diagnosis of DLBCL with bone marrow invasion rather than PEL-LL.

Considering the patient's age and the side effects of chemotherapy, we administered 8 cycles of chemotherapy with rituximab 375 mg/m² once per week (Fig. 2). Fortunately, her vital signs improved immediately and her symptoms gradually resolved. Furthermore, we confirmed that her pericardial effusion significantly decreased after 4 cycles of chemotherapy and disappeared after 8 cycles. Judged to have been in complete remission, she was discharged from the hospital on day 109 of hospitalization (Fig. 3). At the 28-month follow-up, the patient remained free of recurrence.

Discussion

The most significant lesson learned from our experience with the present case is our initial diagnosis of PEL-LL. Actually, the present case had many clinical features mimicking PEL-LL. She suffered from circulatory failure and had massive pericardial fluid with pleural effusion, in which many atypical lymphoid cells were detected. It was our inability to confirm monoclonal B-cell tumor after more careful examination that prompted us to change our diagnosis to DLBCL.

Here, a fundamental question arises as to whether it is possible to diagnose B-cell lymphoma on first observation. The WHO classification proposes that PEL be universally defined as an immune deficiency-related lymphoma and associated with HHV-8 infection [7]. Therefore, our patient's condition could not have been diagnosed as PEL because she had no immunodeficiency. In addition, PEL-LL was not a definite disease unit in the 2016 revision of the WHO classification of lymphoid neoplasms. This should, therefore, be discussed at greater length [8]. HCV, iatrogenic immunodeficiency, alcoholism, liver cirrhosis, cancer, and advanced age have been reported as possible reasons for PEL-LL. PEL-LL affects elderly patients (median age, 74 years) and patients with volume overload such as those with liver cirrhosis (12%) or congestive heart failure (5.5%); and PEL-LL patients have a greater number of CD20-positive cells (86%) than PEL patients. Additionally, patients with ascites have a higher incidence of HCV infection (39%) than pericardial effusion (7%) or pleural effusion (9%) [2, 6, 9–11]. Cytologically, PEL-LL cells resemble the large atypical cells of DLBCL, and

their neoplastic cells show immunoreactivity for pan-B-cell markers such as CD19, CD20, and CD79a; the lymphoma cells express pan-B-cell antigens in 86.7%, and CD20 is expressed in 71.1% of the cases. On the other hand, the neoplastic cells in PEL usually lack such immunoreactivity [3, 5, 6, 9]. The features of our case are close to previously reported cases of PEL-LL in terms of age, pleural and pericardial effusions, lack of tumor mass, and detected atypical lymphoid blasts in the effusion (Table 1, Table 2). Due to the fact that monoclonal lymphoma cells had not been detected in pleural effusion, pericardial and pleural effusion was thought to be associated with lymphoma, especially PEL-LL, and not DLBCL. In addition, the patient maintained complete remission after rituximab monotherapy without recurrence of pericardial or pleural effusion, and without treatment for heart failure or other condition for an extended period, which is also generally consistent with the clinical course of PEL-LL. Even if the disease had been DLBCL, this case is remarkable because monotherapy with rituximab is a suboptimal and noncurative treatment for DLBCL in elderly patients. However, it is quite difficult to diagnose from nonspecific symptoms and laboratory abnormalities. Considering Tables 1 and 2, the presence of neoplastic change in bone marrow, absence of monoclonal B cell in pleural effusion by flow cytometry, and chromosomal abnormality are inconsistent with the characteristics of PEL-LL. Hence, the diagnosis may be PEL-LL-like DLBCL rather than PEL-LL. Strictly speaking, a diagnosis of DLBCL or intravascular lymphoma can only be made in a broad sense. From this point of view, massive pericardial and pleural effusion including atypical lymphoid cells in the present case are quite interesting.

In conclusion, we experienced an elderly patient with DLBCL mimicking PEL-LL. This case suggests the need for a careful and detailed examination from the first observation when encountering patients with pericardial or pleural effusion and inclusion of hematological malignancy in the differential diagnosis.

Statement of Ethics

The article does not contain data to identify patients. The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors state that they have no conflicts of interest.

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Fig. 1. Images of cytodiagnosis: pleural fluid. **a** Atypical cell is confirmed (green arrow). May-Giemsa staining. ×1, 000. **b** Atypical cell (green arrow) and hemophagocytosis (red arrows) are confirmed. May-Giemsa staining. ×400.

Fig. 2. Histopathological images and cell surface antigen analysis of bone marrow. **a** Histopathological image of the specimen. Atypical cells are confirmed (red arrow). May-Giemsa staining. $\times 1,000$. **b** Histopathological image of the specimen. Hemophagocytosis is confirmed. May-Giemsa staining. $\times 1,000$. **c** Cell surface antigen analysis of bone marrow cells. Analysis reveals strong deviation among cell surface of immunoglobulin light chain in B-lymphocyte fraction. Furthermore, the rate of CD20-positive cells is high, about 70%. CD, cluster of differentiation.

Fig. 3. Clinical course of the patient. After diagnosis of diffuse large B-cell lymphoma, 375 mg/m² rituximab therapy, once per week, was started on day 46 of hospitalization. Afterwards, pleural effusion and the values of LDH and sIL-2R markedly decreased, and the patient was discharged on day 109 of hospitalization. LDH, lactate dehydrogenase; sIL-2R, soluble interleukin-2 receptor.

Table 1. Reported cases of primary effusion lymphoma-like lymphoma including our case

Case	Age, years	Sex	Symptoms	HBV	HCV	HIV	EBV	HHV-8	HTLV-1	Serum LDH, U/L	Serum sIL-2R, U/mL	Pleural effusion	
												detection of atypical lymphoid cells	monoclonality (flow cytometry)
1	99	F	Hypoxemia	ND	–	–	–	–	ND	169	ND	+	+
2	52	F	ND	ND	ND	–	–	ND	ND	ND	ND	+	+
3	90	F	Orthopnea	–	–	–	–	–	–	738	1,370	+	+
4	32	F	Abdominal distension, night sweats	–	+	–	–	–	–	2,344	7,090	+	–
5	74	F	Dyspnea, edema of lower limbs	–	+	–	–	–	ND	574	14,000	+	+
6	88	M	Dyspnea, weakness	–	–	–	–	–	ND	670	ND	+	ND
7	68	M	Dyspnea	ND	–	–	–	–	ND	230	ND	+	+
8	77	M	Dyspnea, edema of lower limbs	+	–	–	+	–	–	ND	ND	+	+
9	79	M	Dyspnea	–	–	–	–	ND	ND	114	ND	+	+
10	65	F	Cough, general fatigue, shortness of breath	–	–	ND	–	–	ND	ND	ND	+	+
11	76	M	Cough, general fatigue, night sweats	ND	–	–	–	–	–	377	525	+	+
12	77	M	Abdominal distension, pitting edema of both lower limbs	–	–	–	–	–	ND	393	ND	+	ND
13	71	F	Abdominal distension	–	–	–	+	–	ND	1,404	1,060	+	+
Our case	93	F	Hypotension, disturbance of consciousness	0	ND	0	ND	ND	ND	286	1,700	+	–

“+” indicates that the data are positive or detected. “–” indicates that the data are negative or undetected. ND, not done or not described; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; EBV, Epstein-Barr virus; HHV, human herpesvirus; HTLV, human T-cell leukemia virus; LDH, lactate dehydrogenase; sIL-2R, soluble interleukin-2 receptor.

Table 2. Reported cases of primary effusion lymphoma-like lymphoma including our case (continued from Table 1)

Case	Bone marrow infiltration	Immunohistochemistry	Chromosomal abnormality	Site involved	Treatment	Outcome	Ref.
1	–	CD5, CD19, CD20, CD25, SmlgM, SmlgD, Ig-λ light chain	+	Pleura, pericardium	Drainage	Alive, 16 months	3
2	–	CD19, CD20, CD22, CD45, DR antigen	+	Pleura, pericardium	Unknown	Unknown	12
3	–	CD20, CD79a, bcl-2	+	Pleura, epicardium, peritoneum	None	Died, 5 months	13
4	–	CD10, CD19, CD20, HLA-DR	+	Pleura, peritoneum	THP-COP, PBSCT	Died, 22 months	14
5	–	CD19, CD20, CD25, CD45, HLA-DR, SmlgG-κ	+	Pleura, pericardium, peritoneum	THP-COP, rituximab	Alive, 26 months	15
6	–	CD20, CD30, CD45, CD79a	ND	Pleura, pericardium	R-CHOP	Alive, 9 months	16
7	–	CD20, CD79a	–	Pleura	Pleural drainage, R-CHOP	Alive, 22 months	17
8	–	CD19, CD20, CD38, CD66, CD71, cCD79a	+	Pleura	Rituximab, cyclophosphamide, vincristine, prednisolone	Alive, 3 months	18
9	–	CD20, CD45, CD79a, bcl-2, bcl-6, MUM1	+	Pleura	Drainage, pleurodesis	Alive, 55 months	19
10	–	CD19, CD20, CD38, CD79a, CD138, MUM-1, PAX-5	–	Pleura	Rituximab, cyclophosphamide, vincristine, prednisolone	Died, 5.5 months	20
11	–	CD19, CD20, CD30, CD79a, Ig-λ light chain	+	Pleura	R-CHOP	Alive, 18 months	21
12	–	CD20, CD45, MUM-1	–	Pleura, peritoneum	R-CHOP	Alive, 15 months	22
13	–	CD10, CD20, CD45, CD79a, bcl-6	+	Pleura, peritoneum	R-CHOP	Died, 16 months	23
Our case	+	CD19, CD20, CD25, Ig-λ light chain	–	Bone marrow (pleura? pericardium?)	Rituximab	Alive, 28 months	

“+” indicates that the data are positive or detected. “–” indicates that the data are negative or undetected. ND, not done or not described; CD, cluster of differentiation; DR, D-related; HLA, human leukocyte antigen; MUM, multiple myeloma oncogene; PAX, paired box; EMA, epithelial membrane antigen; THP-COP, pirarubicin/cyclophosphamide/vincristine/prednisolone; PBSCT, peripheral blood stem cell transplantation; R-CHOP, rituximab-cyclophosphamide/doxorubicin/vincristine/prednisone.