Primary Effusion Lymphoma-like Lymphoma in a Patient with Neurofibromatosis Type 1

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(Received May 23, 2016; Accepted June 11, 2016)

To date, there are only 15 case reports of lymphoma in patients with neurofibromatosis type 1 (NF1), a common autosomal dominant tumor predisposition syndrome. Here, we present the first report of a primary effusion lymphoma (PEL)-like lymphoma (PEL-L), which is a human herpes virus 8/Kaposi sarcoma herpes virus-unrelated PEL, in a 73-year-old woman with NF1. The woman presented with pleural effusion following surgery for a small intestinal gastrointestinal stromal tumor and a malignant peripheral nerve sheath tumor. We prepared cellblocks to accurately differentiate between PEL, PEL-L, and pyothorax-associated lymphoma, for establishing a starting point for treatment and for prolonging survival. Attention should be paid to malignant neoplasms in NF1 patients. Diffuse large B-cell lymphoma may not be a rare complication in these patients, although how NF1 promotes its development remains to be determined. PEL-L should be suspected when body cavity effusion is observed in elderly patients. If feasible, it should be treated via rituximab-containing chemotherapy, which according to the literature, results in longer survival times than does drainage or regimens consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone.

Key words: primary effusion lymphoma-like lymphoma, human herpes virus-8/Kaposi sarcoma herpes virus, neurofibromatosis type 1, gastrointestinal stromal tumor, malignant peripheral nerve sheath tumor

INTRODUCTION

Neurofibromatosis type 1 (NF1) is one of the most common autosomal dominant conditions affecting the nervous system. The estimated incidence of NF1 is 1 in 3000−4000 individuals [1], and its primary cause is a set of mutations in the region of chromosome 17q11.2 encoding the tumor suppressor protein neurofibromin. Malignant tumors are the most common cause of death in NF1 patients. The lifetime risk of developing malignant peripheral nerve sheath tumors (MPNSTs), which arise via transformation of benign neurofibromas, is 10% in these patients. Other tumors observed in adults with NF1 include gastrointestinal stromal tumors (GISTs) and pheochromocytomas. Moreover, a UK population-based study [2] found that NF1 patients had a 3.3-fold higher risk of diffuse non-Hodgkin's lymphoma than did patients without NF1. However, to date, there are only 15 case reports of lymphoma in adults with NF1 [3−10].

Primary effusion lymphoma (PEL) is a very rare type of extra-nodal non-Hodgkin's lymphoma that resides in the body cavity but has no tumor mass. It usually occurs in immunocompromised hosts with acquired immunodeficiency syndrome and organ transplant recipients. Although almost all PELs are associated with human herpes virus-8 (HHV-8)/Kaposi sarcoma herpes virus (KSHV), some, termed PEL-like lymphomas (PEL-Ls), are HHV-8/KSHV-unrelated. PEL-L mainly occurs in elderly patients negative for human immunodeficiency virus (HIV) [11]. Its cytomorphologic characteristics are similar to those of PEL, whereas its immunophenotype, demographics, treatment response, and clinical outcome are different [12−16]. Most PEL cases in Japan are HIV- and HHV-8/KSHV-negative (i.e., are PEL-L cases). It is impossible to diagnose PEL-L without first suspecting it and obtaining fluid samples from the body cavity for pathological analysis.

Here, we present the first reported case of PEL-L in a patient with NF1 presenting with pleural effusion following surgery for a small intestinal GIST and an MPNST. We also review the literature pertaining to PEL-L, summarizing its characteristics and the impact of rituximab on PEL-Ls with a B-cell phenotype, as well as on diffuse large B-cell lymphomas (DLBCLs), in adult patients with NF1.

CASE REPORT

A 73-year-old Japanese woman presented at our hospital with a 5-day history of dry cough and dyspnea. She had a 40-year-history of NF1 and a 5-year history of hypertension. Two months before admission, she was diagnosed with and successfully underwent surgery for a small intestinal GIST at our hospital, and shortly before admission, she received surgery for an MPNST on her back, again at our hospital, after which she was discharged. There was no relevant family or personal history.

On physical examination, her vital signs were as follows: blood pressure, 137/99 mmHg; pulse rate, 132 beats/min; respiratory rate, 19 breaths/min; body tem-

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Table 1 Laboratory data on admission.

Complete blood count		**Blood chemistry**			
WBC	7500/μL	TP	7.0g/dL	BS	104mg/dL
Hb	10.8g/dL	Alb	3.7g/dL	Na	139mEq/L
Ht	33.6%	AST	20U/L	K	3.6 mEq/L
MCV	80.4fl	ALT	7U/L	Cl	109 mEq/L
Plt	40.1 x10^4/μL	LDH	672U/L	T. Bil	1.0mg/dL
Coagulation		BUN	12mg/dL	CRP	1.93mg/dL
APTT	34 sec	Cr	0.49mg/dL	sIL-2R	1140U/mL
PT-INR	1.14	UA	3.7mg/dL	sβ2-MG	1.75mg/L
		Serology			
		HIV-I/II	Ab	negative	
		HCV	Ab	negative	
		HBs	Ag	negative	
		HBs	Ab	positive	
		HBc	Ab	positive	
		HBV-DNA		< 3.7 log copies/mL	

Abbreviations: TP, total protein; sIL-2R, soluble interleukin-2 receptor; serum beta-2 microglobulin, sβ2-MG

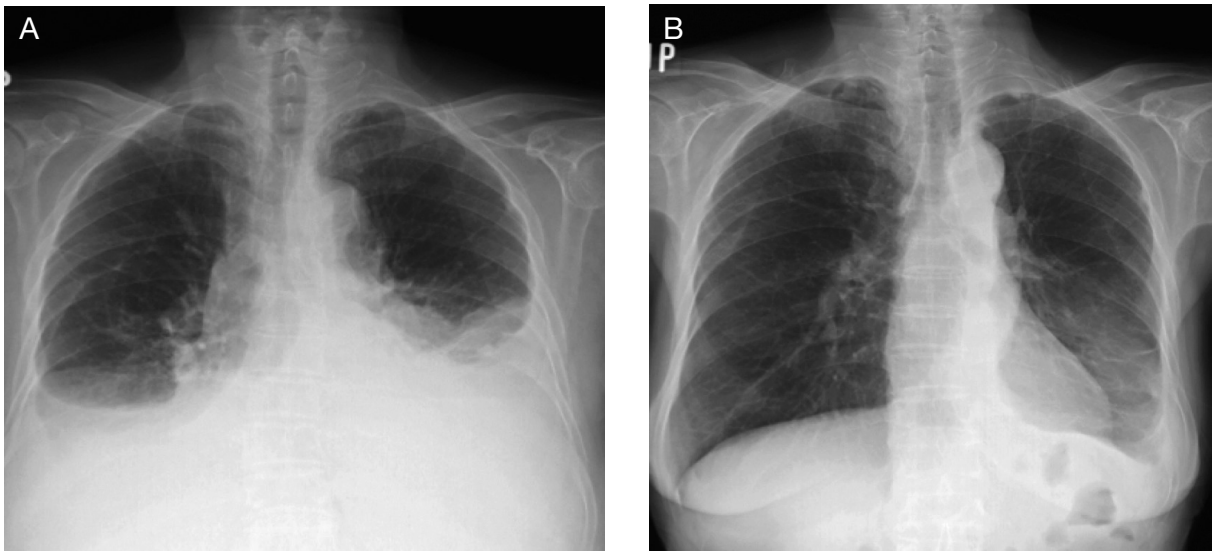

Fig. 1 A: A chest radiograph on admission shows bilateral pleural effusion. B: One month after eight courses of rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy, the cost-phrenic angles on the chest radiograph have become sharp.

perature 37.2°C; and SpO2, 93% at 3 L/min with nasal cannula oxygenation. Abnormal physical findings included a reduced in the intensity of breath sounds on the left side, cutaneous neurofibromas in one of the thighs, and café-au-lait macules on the trunk. Laboratory tests on admission revealed normocytic anemia and elevated levels of lactate dehydrogenase, C-reactive protein, and soluble interleukin-2 receptor (Table 1). The results of serological tests for HIV, human T-lymphotropic virus type I, and hepatitis C virus (HCV) were negative. A chest radiograph revealed bilateral pleural effusion without cardiomegaly or pulmonary congestion (Fig. 1A). A thoracoabdominal computed tomography scan did not reveal any abnormalities such as infiltration, thrombosis, mass, lymphadenopathy, ascites, or pericardial effusion, excepting pleural effusion.

Thoracentesis was performed in the emergency room on admission to determine the etiology of the pleural effusion. The characteristics of the effusion are presented in Table 2. The effusion was diagnosed as a class V exudate from large atypical cells with an irregular shape of nucleus (Fig. 2A). Cellblocks were prepared for further pathological analyses including immunohistochemistry and in situ hybridization. The level of adenosine deaminase (ADA) exceeded 250 IU/L. Flow cytometry revealed λ-predominant B-cell monoclonality (Table 2). Immunohistochemistry showed that the pleural effusion contained atypical cells positive for CD20 (Fig. 2B), but negative for HHV-8/KSHV (Fig. 2C), Epstein-Barr virus encoded RNA (Fig. 2D), CD3, CD5, CD10, and CD38. We diagnosed DLBCL, which was classified as the non-germinal center type because of positivity for Bcl-2, Bcl-6,

Table 2 Laboratory results of pleural effusion.

Pleural effusion				
Color:	red			
Cells:	11450/μL	Glucose	4	mg/dL
Neutrophils	1%	TP	7.4	mg/dL
Lymphocytes	3%	LDH	3273	U/L
Histiocytes	1%	ADA	316.8	U/L
Atypical lymphocytes	95%			
Flow cytometry:	CD19+20+22+λ+			
Tuberculosis PCR:	negative			
Acid-fast bacillus culture	negative			
Chromosomal analysis				
86−88 <4n>, XX, -X×2, add (1) (q21), del (1) (p22), del (1) (q32), +del (1) (p13), add (3) (q21), del (3) (p13), -4, -5, del (6) (q21)×2, -7×2, add (7) (q36), -8, -9, -10, -13, -14, add (14) (q32), i (15) (q10), -17, -18, -19, +21, -22, +3−7mar [20/20]				

Abbreviations: polymerase chain reaction, PCR; adenosine deaminase, ADA

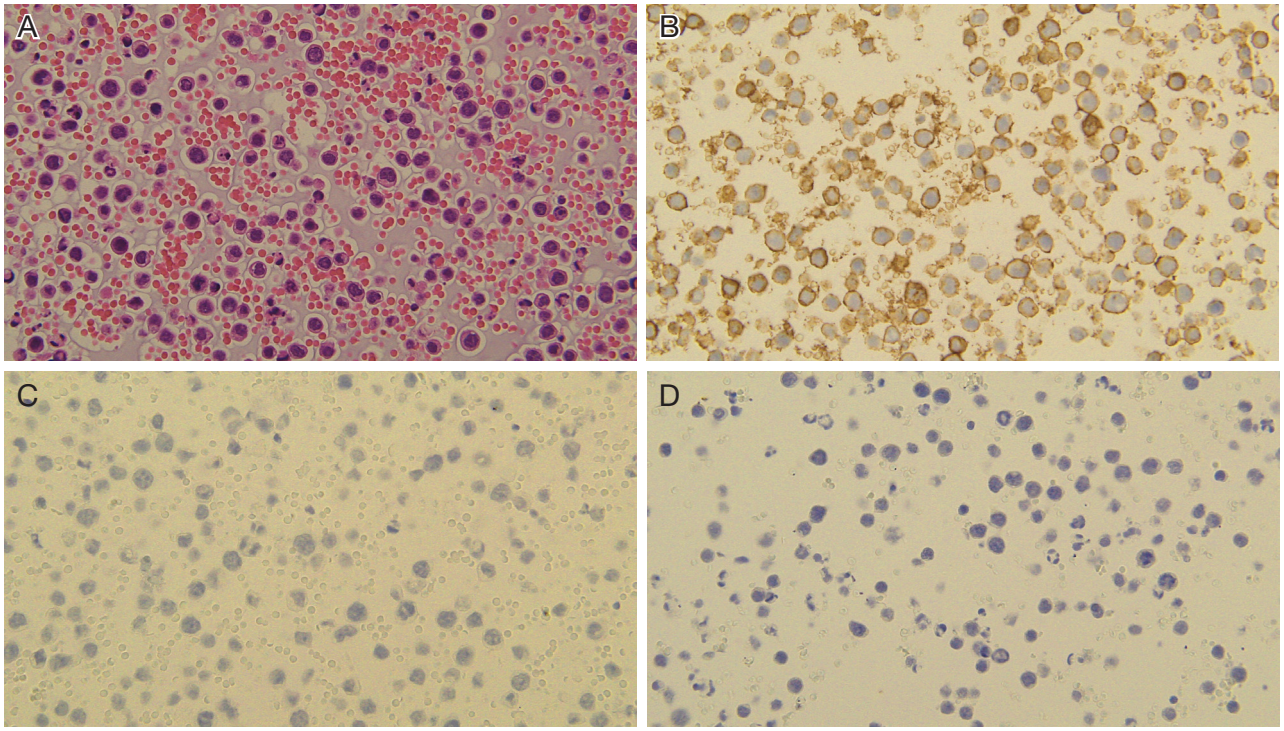

Fig. 2 A−D: Pathological findings of pleural effusion in cellblocks. A: There were many large cells with irregular nuclei. Hematoxylin and eosin (H & E) staining (original magnification ×400). B: Immunohistochemistry of a cellblock specimen shows large cells expressing CD20 (original magnification ×400). C: The lymphoma cells were negative for human herpes virus-8/Kaposi sarcoma herpes virus as determined via immunohistochemistry (original magnification ×400). D: The lymphoma cells were also negative for Epstein-Barr virus encoded RNA as determined via immunohistochemistry (original magnification ×400).

and MUM-1.

Chromosomal analysis of the cells in the pleural effusion revealed complex abnormalities such as a 14q32 translocation. Fluorescent in situ hybridization detected Bcl-6 split signals but not c-MYC split signals. Ultimately, the patient was diagnosed with HIV-negative PEL-L. She received eight courses of rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy and has been in complete remission for more than 26 months after diagnosis. The recent chest radiograph revealed disappearance of bilateral pleural effusion (Fig. 1B).

DISCUSSION

This is the first case report of the successful treatment of PEL-L via R-CHOP chemotherapy in an adult patient with NF1. The clinical course in this case is notable in two important respects (see below). Malignant tumors commonly occur in NF1 patients, and the patient in the present case had had a small intestinal GIST followed by an MPNST and developed PEL-L soon after. So it was not easy to recognize why

Table 3 Characteristics of the adult DLBCL patients with NF1 including our case (n = 9) [7–10].

Median age	59	(28-77)
Gender (male/female)	5/4	
Nodal/extra-nodal	6/3	(PCNSL; 2, PEL-L; 1)
Family history of NF1	50%	(4 out of 8 fully researched cases)
Family history of lymphoma	0%	(0 out of 4 fully researched cases)
Outcome (dead/alive)	2/7	
・CHOP-like regimen	1/6	
・High-dose methotrexate	1/1	(PCNSL; 2)

Abbreviation: primary central nervous system lymphoma, PCNSL; Cyclophosphamide, Doxorubicin, Vincristine and Predonisone, CHOP

this case had pleural effusion in perioperative periods. In addition, imaging study only found body cavity effusion without tumor formation. Cellblocks are useful for performing precise pathological analyses that differentiate between PEL, PEL-L, and pyothorax-associated lymphoma (PAL). Distinguishing between these conditions provides a starting point for urgent and specific treatments and for prolonging survival [17–18].

First, lymphoma in adult patients with NF1 has been rarely reported although a UK population-based study found that NF1 patients had a 3.3-fold higher risk of diffuse non-Hodgkin's lymphoma than did patients without NF1 [2–10]. Nodal DLBCL is the most common type of lymphoma in NF1 patients, occurring in 9 of the 15 (54%) reported cases. To our knowledge, no cases of NF1-associated PEL-L have been reported. Half of the adult DLBCL patients with NF1 have a family history of NF1, but not of lymphoma. Use of CHOP-like regimens for treatment of DLBCL in NF1 patients has a reasonable clinical outcome; 6 of the 7 (86%) such patients receiving these regimens are still alive (Table 3). In a British population-based record-linkage study, patients with NF1 had a 4.0, 1394, 304, 37.9, 14.5, 6.7, and 3.3 higher risk of all cancers, MPNSTs, pheochromocytomas, brain tumors, small intestinal GISTs, chronic myeloid leukemia, and diffuse non-Hodgkin's lymphoma than did patients without NF1 [2]. We need to pay attention to a variety of malignant tumors, including lymphomas, in NF1 patients, although the mechanism whereby NF1 promotes DLBCL remains to be determined [1, 3–10]. There are several speculations of pathophysiology about lymphomagenesis in NF1 patients. One hypothesis is Notch signaling pathway. Lee *et al.* [19] revealed that gain-of-function mutations and copy number increases of Notch2 in DLBCL. In this study, DLBCL was all categorized non-germinal center type because lymphoma cells are negative for CD10, and positive for Bcl-6 and MUM-1. Our case was compatible to this phenotype. Furthermore, Ortega *et al.* [20] recently showed a microRNA-mediated regulatory loop modulated NOTCH and MYC oncogenic signals also in DLBCL. Other pathogenesis is NF1 inactivation cooperated with N-Ras activating Erk-1 and Erk-2 [21].

Second, PEL-L is a rare type of DLBCL. Unless lymphoma is suspected, PEL-L will not be diagnosed. In our case, the initial analysis of the pleural effusion showed an exudate with predominant lymphocytes and an extremely high ADA level (greater than 250 U/L), which raised the possibility of lymphoma [22]. We then prepared cellblocks for further evaluation. Unlike PEL, PEL-L affects elderly patients (median age, 74 years) and patients with volume overload such as those with liver cirrhosis (11/91, 12%) or congestive heart failure (5/91, 5.5%), and has more CD20-positive cells (78/91, 86%) than does PEL. PEL-L patients with ascites have a higher incidence of hepatitis C virus (HCV) infection (11/28, 39%) than of pericardial effusion (1/7, 7%) or pleural effusion (3/35, 9%). They also have a higher incidence of Epstein-Barr virus (EBV) positivity (7/21, 33%) than of pericardial effusion (2/16, 13%) or pleural effusion (5/36, 14%). HCV-positive patients with PEL-L have a short survival time (5 months), and EBV positivity does not predict survival time (Table 4).

Our case is compatible with previous cases of PEL-L in terms of patient age, a diffuse large B-cell phenotype, IgH rearrangement, and pleural effusion without tumor mass. According to our literature review, the median survival time of PEL-L patients is 8 months. Median survival time is much shorter in untreated patients (4 months) than in patients undergoing drainage (16 months) or receiving rituximab-containing chemotherapy (21 months) (Table 4). Therefore, PEL-L should be treated via rituximab-containing chemotherapy (Table 5), which has been shown to result in a complete response rate of 82%, even in patient cohorts with a median age of 73 [7, 15–16, 23–34]. If the patient cannot tolerate chemotherapy, drainage is a reasonable option [23, 35–38]. Our literature review was based on case reports, and publication bias and non-stringent information owing to short follow-up times should therefore be kept in mind.

In conclusion, attention should be paid to malignant neoplasms in NF1 patients. DLBCL may not be a rare complication in such patients, and PEL-L should be considered when body cavity effusion is observed in elderly patients. Cellblocks are useful for differentiating between PEL, PEL-L, and PAL. Lastly, PEL-L should be treated via rituximab-containing chemotherapy if feasible.

Table 4 Review of characteristics of HIV-negative HHV8/KSHV-unrelated PEL-L [7, 15–18, 23–27, 33, 35–44].

	Review of the literature (n = 91)		our case
Median age	74 (27–101)		73
Gender (male /female)	50/41		female
Viral status			
・**EBV**	10/63	(16%)	negative
・**HCV**	11/56	(20%)	negative
Site of effusion			Pleura
・Pleura	56/85	(66%)	
・Pericardium	21/85	(25%)	
・Peritoneum	36/85	(42%)	
Immunophenotype			
・CD20	78/91	(86%)	positive
・Bcl-2	22/50	(44%)	positive
・Bcl-6	13/46	(28%)	positive
・MUM-1	20/43	(47%)	positive
・c-MYC*	18/44	(41%)	negative
Survival time ** (months)	8		26
・No treatment	4	(n = 26, median age: 83)	
・Drainage ***	16	(n = 13, median age: 72)	
・CTx	8	(n = 31, median age: 65)	
・R-including CTx	21	(n = 20, median age: 73)	

*c-MYC includes c-MYC translocation/expression or 8q24 translocation.
**Survival time denotes the number of months between the diagnosis and the last follow-up.
***Drainage: aspiration; 2, tube drainage; 9 and pleurodesis; 2,
Abbreviations: Chemotherapy, CTx; Rituximab, R

Table 5 Characteristics of PEL-L treated via rituximab-containing regimen (n = 20).

Age	gender	regimen	response	Follow-up (months)	reference
65	F	R-CHOP	PD	5.5	[15]
71	M	R-CHOP	NA	4	[16]
83	F	R-CHOP	CR	96	[16]
71	F	R-CHOP	CR	144	[16]
68	M	R-CHOP	CR	22	[23]
66	M	R-THP-COP	NA	9	[24]
70	M	R+ETP	CR	12	[25]
76	M	R-CHOP	CR	18	[26]
89	F	R+ETP	PR → R	13	[27]
74	F	R-THP-COP	CR	26	[28]
90	M	R-THP-COP	PR	38	[29]
87	F	Rituximab	CR	32	[29]
88	M	R-CHOP	CR	11	[30]
82	M	R-CHOP	CR	21	[31]
73	M	R-CHOP	CR	9	[31]
74	M	R-CHOP	NA	7	[32]
70	M	R-CHOP	CR	30	[33]
78	M	R-THP-COP	CR	30	[34]
71	F	R-CHOP	CR → CNS relapse	9	[43]
73	F	R-CHOP	CR	26	our case

Abbreviations: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Predonisone, R-CHOP; same as R-CHOP other than Doxorubicin replaced by THP-adriamycin, R-THP-COP; Etoposide, ETP; complete response, CR; partial response, PR; progressive disease, PD, NA: not applicable, F: female, M: male

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