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Case Report

Indolent primary effusion lymphoma-like lymphoma in the pericardium: A case report and review of the literature

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ABSTRACT

We report a rare case of a 75-year-old man with a history of mild-to-moderate pericardial effusion that was detected on echocardiography performed in October 2011 when the patient was 69 years old. Follow-up echocardiography was performed every 6 months thereafter, showing that the pericardial effusion gradually subsided. However, in April 2017 he started experiencing several episodes of dyspnea, which prompted him to visit our hospital's outpatient department on June 22, 2017. Echocardiography revealed a large amount of pericardial effusion; thus, he was immediately hospitalized. After undergoing pericardiocentesis and drainage, 1740-ml of bloody pericardial fluid was collected. Serum antibody tests for human immunodeficiency virus, hepatitis C virus, and human herpes virus 8 were negative, whereas that for Epstein–Barr virus (EBV) was positive, indicating a prior infection. Cytopathological examination, immunocytochemical staining, lymphocyte surface marker analysis, and cytogenetic assessment were performed. EBV-encoded small ribonucleic acid in situ hybridization was negative. He was diagnosed with primary effusion lymphoma (PEL)-like lymphoma (LL) and was treated with 8 doses of rituximab 375 mg/m^2 over a 2-month period. He has remained in complete response for the past 12 months. Our case shows the possibility of long-term existence of indolent PEL-LL in patients with mild-to-moderate pericardial effusion.

<**Learning objective:** Primary effusion lymphoma (PEL)-like lymphoma (LL) is a rare disease with a poorly understood pathophysiology. Some patients are able to achieve a complete response after drainage of the effusion without chemotherapy. We experienced a case of PEL-LL, which was only diagnosed after 6 years of continually observing the pericardial effusion. Cardiologists should consider PEL-LL as a differential diagnosis in patients with unexplained pericardial effusion.>

Introduction

Primary effusion lymphoma (PEL) infected with human immunodeficiency virus (HIV) and Kaposi's sarcoma-associated herpes virus (KSHV) [similar to human herpes virus 8 (HHV-8)] and consisting of malignant cells existing only in the body's fluid cavities, such as the pericardial, pleural, and peritoneal cavities and the scrotum, without a primary tumor mass formation and lymph node enlargement was defined by the World Health Organization classification system of hematologic neoplasms in 2001 [1]. PEL is rarely encountered in cardiovascular departments and is not widely recognized by cardiologists. In addition, PEL-like lymphoma (PEL-LL), which presents with a large B-cell neoplasm similar to that of PEL, but not infected with HIV and HHV-8, is also a rare disease. The diagnosis of PEL and PEL-LL is difficult, especially in patients presenting only with pericardial effusion without pleural effusion or ascites, and requires

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pericardiocentesis and cytopathological analysis of the pericardial fluid. We report a case of PEL-LL diagnosed via cytopathology after 6 years of continually observing the pericardial effusion, which suggests that indolent PEL-LL may exist in the pericardial effusion for a long period of time.

Case report

We report a case of a 75-year-old male patient who was suspected of having ischemic heart disease, left ventricular hypertrophy, and first-degree atrioventricular block after a medical check-up in August 2011, when the patient was 69 years old. In October 2011, he visited our department for cardiovascular treatment and underwent echocardiography. Transthoracic echocardiography showed mild-to-moderate pericardial effusion without right atrial wall or right ventricular wall collapse (Fig. 1A). Furthermore, left atrial enlargement, thickening of the interventricular septum and left ventricular posterior wall, and impaired left ventricular diastolic function were apparent. However, left ventricular end-diastolic diameter and biventricular systolic function were normal. Neither significant pulmonary hypertension nor valvular disease was observed. He had no history of infection during the past few months. Whole-body computed tomography (CT) did not show any abnormal findings other than mild-to-moderate pericardial effusion. A follow-up echocardiography was performed every 6 months thereafter to evaluate the patient's condition. The pericardial effusion gradually subsided (Fig. 1B and C). During the observation period, at the age of 74 years, he underwent left knee joint replacement surgery for osteoarthritis but received no medications for his condition. Since April 2017, he had experienced shortness of breath and leg edema. Consequently, he sought a consultation at our hospital's outpatient department on June 22, 2017. Echocardiography revealed a large amount of pericardial effusion with right atrial wall and right ventricular wall collapse, despite ejection fraction being normal (Fig. 1D), which prompted his immediate admission. CT showed marked pericardial effusion and mild bilateral pleural effusion, which quickly disappeared following drainage of the pericardial effusion. Thus, the pleural effusion was considered to be secondary to cardiac function deterioration caused by the massive pericardial effusion. Moreover, superficial body lymph nodes were not observed during the physical examination, and no tumors or lymph node enlargement were detected on CT. After undergoing pericardiocentesis and drainage for 3 days, a total of 1740-ml of bloody pericardial fluid was collected. The blood laboratory data related to the pericardial effusion were as follows: blood urea nitrogen, 16.1 mg/dL; creatinine, 0.91 mg/dL; brain natriuretic peptide, 81.6 pg/mL; thyroid stimulating hormone, 5.88 μ IU/mL; free triiodothyronine 3, 2.57 pg/dL; free thyroxine, 1.03 ng/dL; rheumatoid factor, <3 IU/mL; antinuclear antibody, <40; anti-deoxyribonucleic acid antibody, ≤2.0 IU/mL; T-SPOT.TB, negative; carcinoembryonic antigen, 1.1 ng/mL; cytokeratin 19 fragment, 0.9 ng/mL; and pro-gastrin-releasing peptide, 61.7 pg/mL. The serum antibody tests for HIV, hepatitis C virus (HCV), human T-cell leukemia virus type 1, and HHV-8 yielded negative results, whereas that for Epstein–Barr virus (EBV) yielded positive results, indicating a prior infection. Analysis of the pericardial effusion showed protein of 5.4 g/dL; hematocrit, 10.8%; nucleated cells, 6345/μL, adenosine deaminase, 461.8 U/L, and a negative tuberculosis polymerase chain reaction. Bacterial culture of the

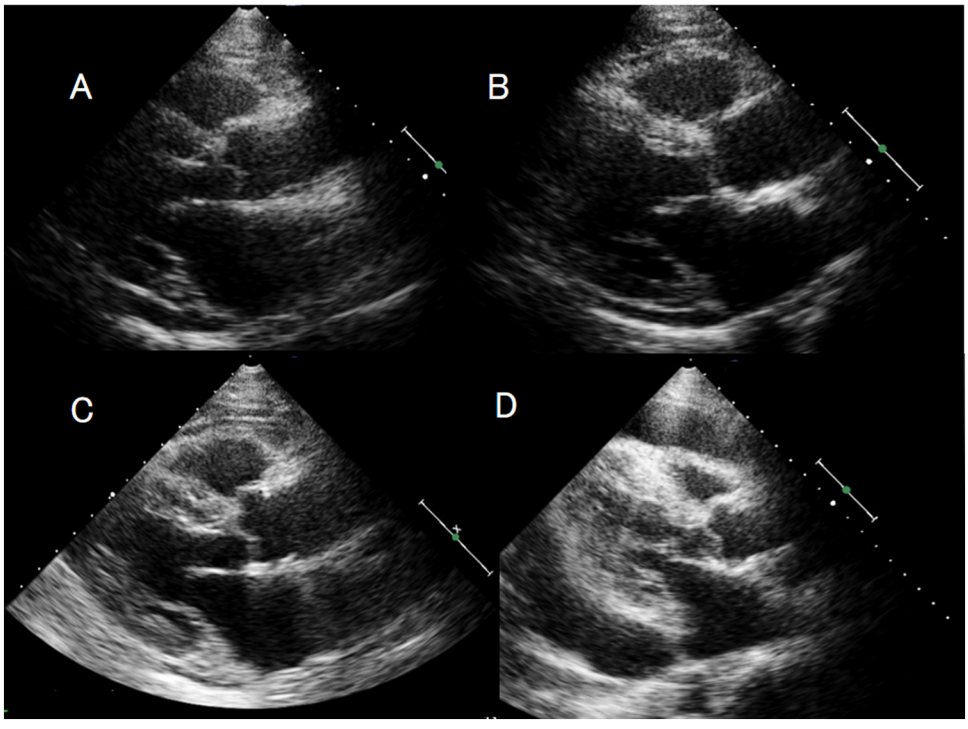

Fig. 1. Parasternal diastolic long-axis view of the patient's echocardiograms. (A) October 28, 2011 (first visit): the echocardiogram showed an echo-free space approximately 10 mm in diameter behind the posterior left ventricular wall. It also showed left atrial enlargement (45 mm), a thickened interventricular septum (12 mm) and left ventricular posterior wall (11 mm), and normal left ventricular end-diastolic diameter (44 mm). The ejection fraction (EF) was 63.3%. (B) August 19, 2015: the echocardiogram showed an echo-free space approximately 5 mm in diameter behind the posterior left ventricular wall. (C) March 2, 2017: the echocardiogram showed a minor echo-free space behind the posterior left ventricular wall. (D) June 22, 2017 (emergency visit): the echocardiogram showed a large amount of pericardial effusion surrounding the heart and a decreased left ventricular end-diastolic diameter (41 mm). There was an echo-free space approximately 30 mm in diameter behind the posterior left ventricular wall and another approximately 25 mm in diameter anterior to the right ventricular wall. The EF was 76.0%.

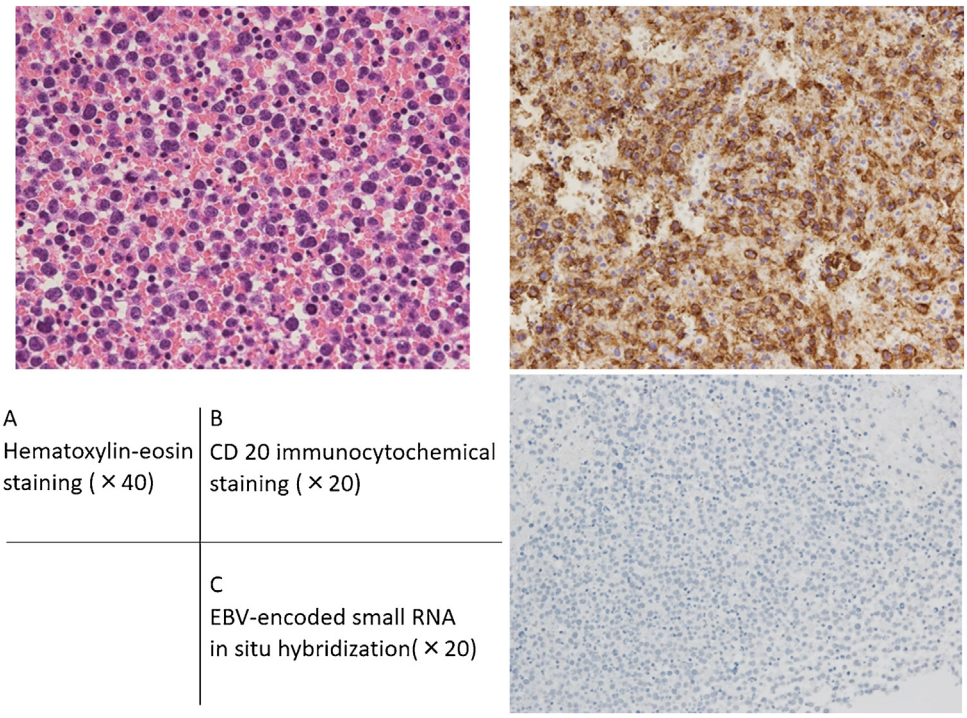

Fig. 2. Pathology of the cell-block specimens of the pericardial effusion. (A) Hematoxylin-eosin staining (×40). Hematoxylin-eosin staining shows numerous cells with an increased nuclear/cytoplasm ratio accompanied by nuclear allotypes. Nuclear fission is also observed, but intercellular adhesion is not clear. (B) CD20 immunocytochemical staining (×20).
CD20 immunocytochemical staining is positive in large heterozygous and diffuse large B cells.
(C) EBV-encoded small RNA in situ hybridization (EBER-ISH) (×20). EBER-ISH is negative.
EBV, Epstein-Barr virus; RNA, ribonucleic acid.

pericardial effusion yielded negative results and mycobacterial culture showed a Gaffky number of 0 after 8 weeks. Cytopathological examination, immunocytochemical staining, lymphocyte surface marker analysis, and cytogenetic examination were performed using cell-block specimens of pericardial effusion. Hematoxylin-eosin staining showed numerous cells with an increased nuclear/cytoplasm ratio accompanied by nuclear allotypes. Nuclear fission was also observed but intercellular adhesion was not apparent (Fig. 2A). CD20 immunocytochemical staining was positive in large heterozygous and diffuse large B cells (Fig. 2B). EBV-encoded small ribonucleic acid (RNA) in situ hybridization (EBER-ISH) staining was negative (Fig. 2C). The results of the lymphocyte surface marker analysis were as follows: CD20 = 95.1%, SMIg-κ = 88.9%, SMIg-λ = 2.4%, CD56 = 2.9%, and CD3 = 2.6%. The results indicated SMIg-kappa type light chain restriction (clonality) of the CD20 lymphocyte line. Cytogenetic examination revealed a complex karyotype with multiple structural and numerical abnormalities including a mutual translocation of chromosomes 3 and 22.

Based on the above findings, he was diagnosed with PEL-LL and received 8 doses of rituximab 375 mg/m^2 over a 2-month period. At the time of writing, he has remained in complete response for 12 months.

Discussion

We present herein a rare case of PEL-LL in a male patient, who was only diagnosed after 6 years of continuous observation of his pericardial effusion. Our case presents the possibility that indolent PEL-LL may exist in the pericardial effusion for a long period of time.

Non-Hodgkin's lymphoma, which is only found in the body's fluid cavities, such as the pericardial, pleural, and peritoneal cavities and the scrotum, and wherein tumor formation or lymph node enlargement are not observed in patients infected with HIV and KSHV (similar to HHV-8), was reported by Cesarman et al. [2] in 1995. Thereafter, this condition was termed PEL according to the World Health Organization classification system of hematologic neoplasms in 2001 [1]. However, lymphoma occurring locally in the pericardial and pleural cavities in patients who were negative for HIV and KSHV (HHV 8) was reported by Hermine et al. [3] in 1996 and was called PEL-LL.

PEL-LL is considered to have a different etiology and onset mechanism from PEL, because almost all reported cases are in elderly individuals without immunodeficiency and HIV infection. However, the pathophysiology of PEL-LL has not yet been elucidated. Wu et al. [4] reported 55 cases, wherein 56.3% of the patients were Japanese, and Alexanian et al. [5] reviewed 45 reports on PEL-LL in 2013 and showed that 60.0% of the patients were Japanese as well. PEL-LL is at times reported during conference proceedings in Japan. Regarding the site of fluid retention, Alexanian et al. [5] reported that effusion most commonly arose within the pleura (66.7%), followed by the peritoneum (37.8%) and pericardium (26.7%), with multiple sites found in 31.1% of patients. Twenty pericardial effusion cases had been reported in PubMed by the end of 2017 [3,6–22] (Table 1). Among these, only 7 cases of PEL-LL, including our case, had simple pericardial effusion without pleural effusion and ascites. In such cases, diagnosis is difficult because soluble interleukin-2 receptor, which is an indicator of malignant lymphoma, may be normal, as previously reported in two cases of PEL-LL [13,22]. Therefore, pericardiocentesis with cytopathological analysis of the pericardial effusion is required.

Table 1 Pericardial effusion of PEL-LL in the English literature by the end of 2017.

Year	Reference	Age/Sex	Clinical history	Effusion	HIV	EBV	HCV	Therapy	Effect	Overall survival(M)	Outcome
1996	Hermine [3]	52/F	ND	PL,PC	–	–	ND	ND	ND	ND	ND
2003	Hisamoto [6]	58/F	CVID	PL,PC	–	+	–	D + Prednisolone	NR	18days	Died
2003	Simazaki [7]	90/F	AF	PL,PC,(PT)[a]	–	–	–	Thoracentesis	NR	5	Died
2004	Inoue Y [8]	70/F	ND	PL,PC	–	–	–	CHOP,THP-CO, sobuzoxane	CR	18	Alive
2004	TaKao [9]	74/F	[b]	PL,PC,PT	–	–	+	THP-COP + R	CR	26	Alive
2005	Fujiwara [10]	75/F	No disease	PC	–	–	–	A + CHOP	CR	36	Alive
2006	Youngster [11]	88/M	IHD	PL,PC	–	–	–	R + CHOP	CR	11	Alive
2006	Inoue S [12]	67/F	RA	PC	–	-(skin)	ND	A + CHOP	NR	16	Died
2008	Niino [13]	78/M	No disease	PL,PC	–	+	–	R + THP-COP	CR	>30	Alive
2009	Taira [14]	69/F	Pituitary tumor surgery	PL,PC	–	–	–	D + CHOP	NR	7	Died
2010	Takahashi [15]	82/M	ND	PL,PC	–	+	–	D + R + CHOP	CR	21	Alive
2010	Takahashi [15]	73/M	ND	PL,PC,PT	–	–	–	D + R + CHOP	CR	9	Alive
2011	Kagoya [16]	74/M	ND	PC	–	–	–	R + CHOP	effectiveness	7 courses	Died
2011	Terasaki [17]	99/F	ND	PL,PC	–	–	–	Drainage	Spontaneous CR	16	Died of old age
2011	Terasaki [17]	85/M	HT,AF	PL,PC	–	–	–	Drainage	Spontaneous CR	11	Alive
2014	Mohammad [18]	76/M	HT,AF	PL,PC	–	–	–	Drainage	CR	14	Alive
2014	Patil [19]	71/F	No disease	PC	ND	–	–	Chemotherapy	ND	ND	ND
2015	Nakamura [20]	85/M	PVC	(PL)[c],PC	–	+	–	Drainage	CR	24	Alive
2017	Kim [21]	73/M	ND	PC	–	–	–	R + CHOP	NR	3	Died
2017	Koeda [22]	75/M	ND	PL,PC	–	+[d]	–	D + R + CHOP	CR	ND	Alive
2017	Our patient	75/M	Osteoarthritis	PC	–	–	–	D + R	CR	12	Alive

ND, no description; PL, pleura; PC, pericardium; CVID, common variable immunodeficiency; D, drainage; NR, no response; AF, atrial fibrillation; PT, peritoneum.
[a] Autopsy findings; CHOP, cyclophosphamide, hydroxydoxorubicin, oncovine or vincristine, and prednisolone; THP-CO, pirarubicin, cyclophosphamide, and oncovine; CR, complete response.
[b] Cirrhosis and allergic granulomatous angitis; THP-COP, pirarubicin, cyclophosphamide, oncovine or vincristine, and prednisolone; R, rituximab; A, aspiration; IHD, ischemic heart disease; RA, rheumatoid arthritis; HT, hypertension; PVC, premature ventricular contraction.
[c] Disappeared after pericardiocentesis.
[d] High Epstein-Barr virus antibody titer.

Regarding the involvement of viral infections in PEL-LL, Alexanian et al. [5] reported that seropositivity for HCV and EBV was observed in 26.5% and 28.9% of patients, respectively. In the 21 pericardial effusion cases, including our case, seropositivity for HCV and EBV was observed in 5.3% (1/19) and 23.8% (5/21) of patients, respectively (Table 1). However, determining whether EBV infection is simply a prior infection or a trigger of PEL-LL through a serum antibody test is difficult. In Nakamura's case, wherein bilateral pleural effusion disappeared after pericardiocentesis in a manner similar to our case, the patient's EBER-ISH result was positive [20]; however, our patient's EBER-ISH result was negative. Hence, the involvement of EBV infection in PEL-LL should be determined not only through a serum antibody test, but also through EBER-ISH.

The prognosis of PEL-LL is variable. In the 21 patients with pericardial effusion, 6 died while 4 had complete response after management with drainage only without chemotherapy. Of these, 3 patients are still alive (Table 1).

Our patient had a rapid deterioration of his pericardial effusion over the course of 6 years. To our knowledge, there are no reported cases of PEL-LL that were diagnosed after long-term observation. It is impossible to retroactively determine whether diffuse large B cells were present in the pericardial effusion of our patient at its initial detection 6 years earlier. However, our case demonstrates the possibility of long-term existence of indolent PEL-LL in mild-to-moderate pericardial effusion and shows the diagnostic challenges faced in such patients who hesitate to undergo pericardiocentesis. Finally, we want to emphasize that cardiologists should consider PEL or PEL-LL as a differential diagnosis in patients with unexplained pericardial effusion.

Conflict of interest

The authors declare that there is no conflict of interest.

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