Human herpesvirus 8-negative effusion-based lymphoma with indolent clinical behavior in an elderly patient: A case report and literature review

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Abstract. Primary effusion lymphoma (PEL) is a B-cell non-Hodgkin's lymphoma that is usually characterized by lymphomatous effusions in the body cavity without any detectable tumor masses. According to the World Health Organization (WHO) schema for tumor classification, PEL is defined by the presence of human herpesvirus 8 (HHV8) in malignant lymphoid cells. However, a subset of effusion-based B-cell lymphoma is not HHV8-positive and exhibits different clinicopathological characteristics. The 2017 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues does not list HHV8-negative effusion-based lymphoma, which remains an underappreciated B-cell lymphoma, as an individual entity. The present study reports a case of this rare type of lymphoma with indolent clinical behavior in a 75-year-old male patient receiving only symptomatic treatment. Additionally, a review of similar cases reported in the English literature is presented.

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Abbreviations: CT, computed tomography; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HHV8, human herpesvirus 8; HIV, human immunodeficiency virus; PEL, primary effusion lymphoma; PET-CT, positron emission tomography-computed tomography; TTE, transthoracic echocardiogram; WHO, World Health Organization

Key words: human herpesvirus 8-negative effusion-based lymphoma, primary effusion lymphoma, indolent non-Hodgkin's lymphoma

Introduction

Primary effusion lymphoma (PEL) is a rare and distinct type of non-Hodgkin's lymphoma typically characterized by serous effusions without any detectable tumor masses (1). It accounts for ~4% of all human immunodeficiency virus (HIV)-related non-Hodgkin lymphoma (NHL) cases and <1% of all non-HIV-related NHL cases in the United States (between 2001 and 2012) (1). According to the 2017 World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues (2), human herpesvirus 8 (HHV8) infection is commonly detected in neoplastic lymphoid cells. Most cases of PEL are associated with an immunocompromised status, particularly human immunodeficiency virus (HIV) infection, and frequently, there is co-infection with Epstein-Barr virus (EBV) (3). Neoplastic tumor cells exhibit a wide range of cytological appearances, from immunoblastic to anaplastic morphology (3). Although HHV8-negative effusion-based lymphoma, a rare and underappreciated subgroup of non-Hodgkin's lymphoma, is cytomorphologically similar to PEL, it exhibits several distinct clinicopathological characteristics since it generally develops in older patients with better outcomes; unlike PEL, the neoplastic cells in HHV8-negative effusion-based lymphoma express pan-B-cell markers (4).

In the present report, a 75-year-old male with an indolent variant of HHV8-negative effusion-based lymphoma is described. In addition, a brief review of similar cases reported in the literature is presented.

Case report

A 75-year-old male patient presented with cough and shortness of breath, which lasted for 1 month. The patient was admitted to Severance Hospital (Seoul, South Korea) in December 2018. Written informed consent for participation in the present study was obtained from the patient. The patient had a medical history of hypertension and tuberculosis, which was treated with anti-tuberculous drugs 50 years ago. The patient was a

former smoker (1 pack/day for 10 years) but stopped smoking 45 years ago. Chest X-ray revealed cardiomegaly and mild pleural effusion. Electrocardiogram revealed atrial fibrillation with a right bundle branch block. A complete blood count provided results within the normal ranges [white blood cell (WBC), 6,540/μl (normal range, 4,000-10,800/μl); red blood cell (RBC), 5.01x10^6/μl (normal range, 4.4-6.1x10^6/μl); hemoglobin, 15.4 g/dl (normal range, 13.0-17.4 g/dl); hematocrit, 46.1% (normal range, 40-52%)]. The amounts of lactate hydrogenase and total protein in the blood serum were 205 IU/l (normal, 119-247 IU/l) and 7.0 g/dl (normal, 6.0-8.0 g/dl), respectively. Immunoassays for the detection of HIV antibody, hepatitis B surface antigen and hepatitis C virus (HCV) antigen were performed following routine hospital procedures and the results were all negative (data not shown). Transthoracic echocardiogram (TTE) revealed enlarged left and right atria, mild pulmonary hypertension (right ventricular systolic pressure, 43 mmHg) with dilated inferior vena cava, and a moderate amount of pericardial effusion. The patient refused hospital admission for a further diagnostic work-up. Diuretics were administered to control the pericardial effusion. After 6 months, the patient presented with aggravated dyspnea and a continuous low-grade fever. Chest computed tomography (CT) demonstrated pleural thickening and effusion (Fig. 1A), but neither hilar lymphadenopathy nor a mass lesion was detected. A positron emission-CT (PET-CT) scan showed mildly increased 18F-fluorodeoxyglucose uptake in the left pleura (Fig. 1B). A follow-up TTE revealed constrictive pericarditis, as well as persistent left atrial enlargement and pleural effusion. A thoracentesis was performed under a tentative diagnosis of tuberculous pericarditis and pleurisy. Pleural fluid analysis revealed the following counts: RBC, 30,000/μl (normal range, 0-100,000/μl); WBC, 10,446/μl (normal range, 0-10,000/μl); protein, 4,800 mg/dl (normal range, 0-2000 mg/dl); glucose, 16 mg/dl (normal range, 0-60 mg/dl); lactate dehydrogenase, 4,355 IU/l (normal range, 100-300 IU/l); and adenosine deaminase, 698.4 IU/l (normal range, 0-40 IU/l). Microbiological tests for tuberculosis, including an acid-fast bacilli smear, quantitative polymerase chain reaction and cultures, were performed according to routine procedures, and the results were all negative (data not shown).

Morphological analysis of the pleural fluid revealed the presence of numerous apoptotic figures and large atypical cells with cytomorphological features of centroblasts in the pleural fluid (Fig. 2A).

For immunohistochemistry, the cytology cell block from the pleural fluid aspiration was fixed with 10% buffered neutral formalin at room temperature overnight and embedded in paraffin. Tissue sections (4-μm-thick) from paraffin-embedded cell blocks were deparaffinized and rehydrated with xylene and a descending alcohol series. Immunostaining was performed using automatic immunostaining instruments, namely Ventana Benchmark XT automated staining system (Ventana Medical Systems) or Dako Omnis (Dako; Agilent Technologies, Inc.), according to the manufacturer's recommendations. Antigen retrieval was performed using Cell Conditioning Solution (Ventana Medical Systems) or EnVision FLEX Target Retrieval Solution, High pH (Dako; Agilent Technologies, Inc.). Endogenous peroxidase activity was blocked using 3% hydrogen peroxide at room temperature for 15 min. The sections were then incubated with primary antibodies at 37˚C for 32 min against CD45 (mouse monoclonal; clone 2B11; 1:50; cat. no. M0701; Agilent Technologies, Inc.), CD20 (mouse monoclonal; clone L26; 1:50; cat. no. M0755; Dako; Agilent Technologies, Inc.), CD79a (mouse monoclonal; clone JCB117; 1:50; cat. no. M7050; Dako; Agilent Technologies, Inc.), paired box 5 (PAX5; rabbit monoclonal; clone SP34; 1:100; cat. no. 790-4420; Ventana Medical Systems, Inc.), CD138 (mouse monoclonal; clone MI15; 1:100; cat. no. M7228; Dako; Agilent Technologies, Inc.), MYC (rabbit monoclonal; clone EP121; 1:50; cat. no. 395R-15; Cell Marque; Merck KGaA), BCL-2 (mouse monoclonal; clone 124; 1:100; cat. no. M0887; Dako; Agilent Technologies, Inc.), BCL-6 (mouse monoclonal; clone G1191E/A8; 1:100; cat. no. 227M-96; Cell Marque; Merck KGaA), CD3 (rabbit polyclonal; 1:100; cat. no. A0452; Dako; Agilent Technologies, Inc.), CD68 (mouse monoclonal; clone PG-M1; 1:200; cat. no. M0876; Dako; Agilent Technologies, Inc.), calretinin (mouse monoclonal; clone DAK-Calret 1; 1:50; cat. no. M7245; Dako; Agilent Technologies, Inc.), Ki-67 (mouse monoclonal; clone MB-1; 1:150; cat. no. M7240; Agilent Technologies, Inc.) and HHV8 (mouse monoclonal; clone 13B10; 1:100; cat. no. 760-4260; Ventana Medical Systems, Inc.). After chromogenic visualization using an ultraView Universal DAB Detection kit (Ventana Medical Systems; cat. no. 760-500, including secondary antibody incubation at 37˚C for 8 min using ultraView Universal HRP Multimer), sections were counterstained with hematoxylin at 37˚C for 8 min. Light microscopy (BX43 System Microscope; Olympus Corporation; magnification, x40-400) was used to observe the sections. Appropriate positive controls were stained concurrently to validate the staining method. Negative controls were prepared by substituting non-immune serum (mouse monoclonal IgG κ isotype control; clone P3.6.2.8.1; cat. no. AB_1944423; Invitrogen; Thermo Fisher Scientific, Inc.) for the primary antibody. No staining was detected in the negative controls.

Immunohistochemistry analysis revealed that the atypical cells were uniformly positive for CD45 and that a subset of these cells exhibited varying degrees of CD20 expression (Fig. 2B), CD79a and PAX5. The cells were negative for CD138 (Fig. 2C). Although 10% of the atypical cells were positive for focal MYC (Fig. 2D), they were negative for BCL-2 (Fig. 2E), BCL-6 (Fig. 2F), CD3, CD68 and calretinin. The Ki-67 labeling index was 73.5%, accounting for the average of four high-power fields (Fig. 2G). The atypical cells were negative for HHV8 (Fig. 2H), and EBV-encoded RNA was not detected in the nuclei of the atypical cells (Fig. 2I) using *in situ* hybridization, which was performed as previously described (5). Pathological features in the patient suggested the possibility of an unusual variant of PEL or diffuse large B-cell lymphoma associated with chronic inflammation. As the patient's symptoms remained stable, symptomatic treatment was provided and the patient was closely followed up. The mild pleural effusion persisted over a 1-year follow-up period. Repeated pleural fluid analysis revealed large atypical cells with the same cytological features of centroblasts and immunophenotypic features. Some large atypical cells expressed MUM1, but were negative for HHV8, CD30 and CD138. Polymerase chain reaction analysis of immunoglobulin heavy chain (IgH) gene rearrangement was performed using BIOMED-2

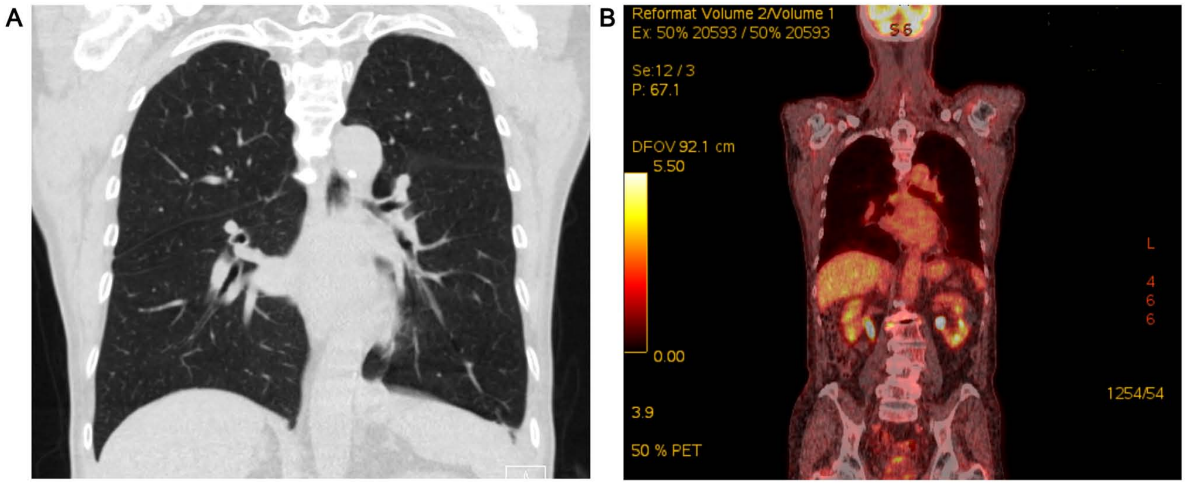

Figure 1. Chest CT and PET-CT scans of the patient. (A) Chest CT revealing left pleural thickening and effusion. (B) PET-CT scan showing mildly increased 18F-fluorodeoxyglucoseuptake uptake in the left pleura. CT, computed tomography; PET-CT, positron emission tomography-CT.

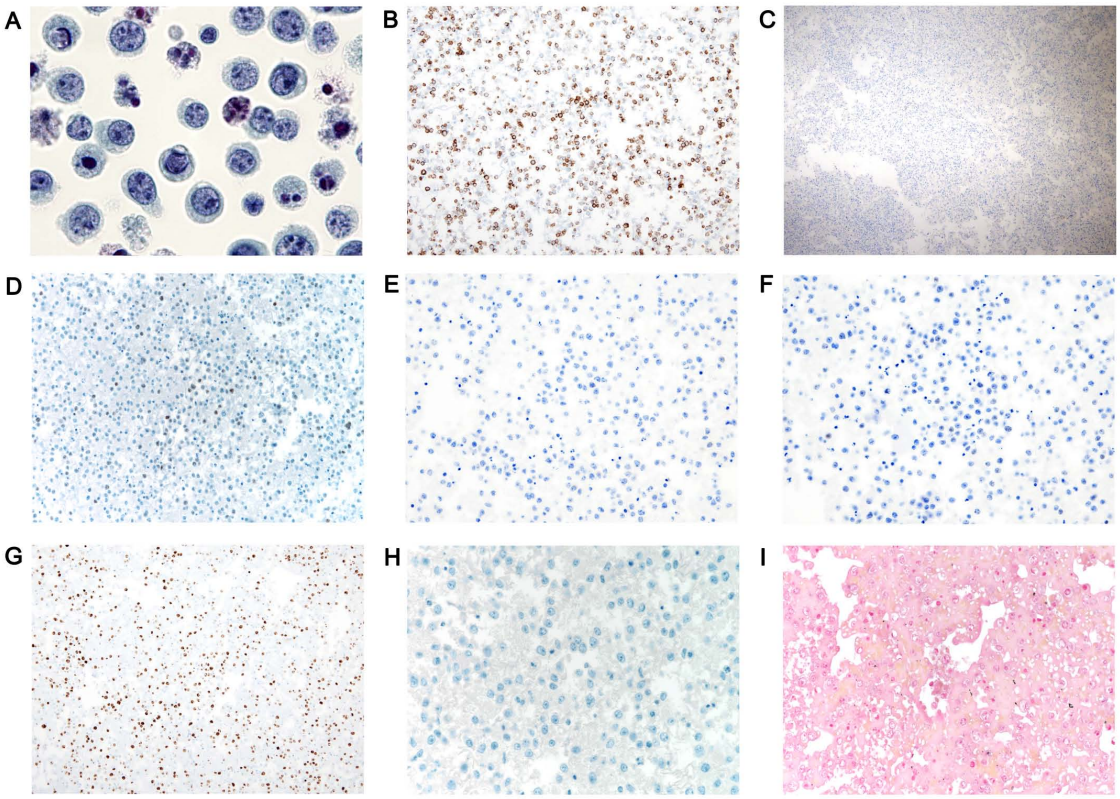

Figure 2. Histopathological and immunohistochemical findings in HHV8-negative effusion-based lymphoma. (A) Cytomorphological appearance of malignant lymphoid cells in the pleural fluid (magnification, x1,000). Malignant cells showing (B) membranous CD20 staining (magnification, x100) and (C) no staining for CD138 (magnification, x40). Tumor cells showing (D) focal positivity (10% of tumor cells) for c-MYC (magnification, x200) and no staining for (E) BCL-2 (magnification, x200) and (F) BCL-6 (magnification, x200). (G) Immunohistochemical staining for Ki-67 revealed a labeling index of 73.5% (magnification, x100). (H) Immunohistochemical staining for HHV8 (magnification, x400) and (I) Epstein-Barr virus-encoded RNA *in situ* hybridization (magnification, x400) of the pleural fluid was negative. HHV8, human herpesvirus 8.

multiplex primers in accordance with the manufacturer's protocol (Invivoscribe, Inc.) as previously described (6). The reaction assays for the IgH rearrangement tests involved a full set of five reactions targeting the IGH (IGH_A, FR1-JH; IGH_B, FR2-JH; IGH_C, FR3-JH; IGH_D, DH1-6-JH; and IGH_E, DH7-JH). The results demonstrated clonal rearrangement of the IgH gene (Fig. 3). The pathological diagnosis of HHV8-negative effusion-based lymphoma was made on the basis of clinicopathological findings noted 6 months after the first visit of the patient. The pleural effusion resolved following the insertion of a drainage catheter. Systemic imaging including a PET-CT scan demonstrated no other lesions. Thus, the patient was closely observed without chemotherapy. Follow-up chest CT, which was performed at 10 months post-diagnosis,

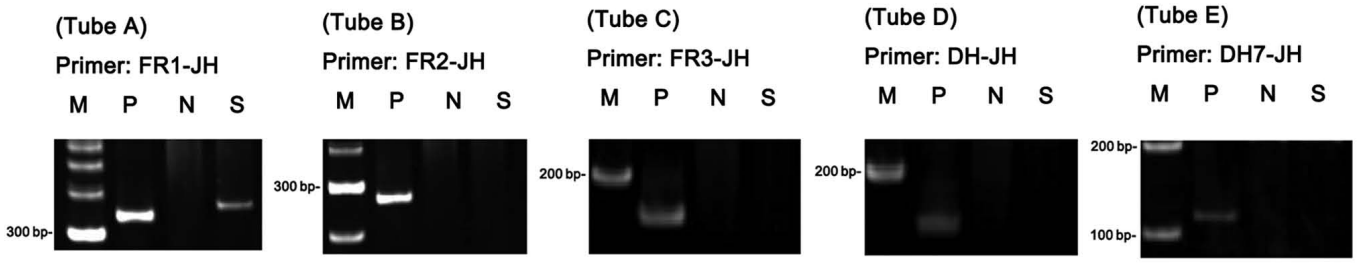

Figure 3. Immunoglobulin heavy chain gene rearrangement test results for HHV8-negative effusion-based lymphoma. Detection of the clonal rearrangement of immunoglobulin heavy chain gene was consistent with the presence of a clonal B-cell population based on the polymerase chain reaction-based analysis of the immunoglobulin heavy chain gene rearrangement. Tube A, B and C contain the framework regions FR1-JH, FR2-JH and FR3-JH, respectively. Tube D and E contain the diversity and joining regions (DH1-6-JH and DH7-JH). M, size marker; P, positive control; N, negative control; S, sample (patient).

did not reveal an increase in pleural effusion or suspicious pleural enhancement. At a regular 2-month follow-up for six visits in total, the patient was alive without any symptoms for 13 months post-diagnosis.

Discussion

The present study reports a case of HHV8- and EBV-negative pleural effusion-based lymphoma with indolent clinical behavior in an elderly patient. Typical PEL occurs in immune-compromised patients, particularly in those with HIV infection (7). HHV8 universally infects malignant lymphoid cells and encodes proteins that are essential for the proliferation and survival of tumor cells (8). Although EBV co-infection is found in most cases of HHV8 infection, it is not considered to play an important role in the pathogenesis (9). The etiology of HHV8-negative effusion-based lymphoma is still unclear. EBV infection is seen in 28.9% of patients with HHV8-negative effusion-based lymphoma and 65.6% of patients with PEL (10). Paner *et al* (11) suggested a possible association between HHV8-negative effusion-based lymphoma and HCV; however, a subsequent study demonstrated HCV infection in only 10% of patients with HHV8-negative effusion-based lymphoma (3). Ohshima *et al* (12) proposed that the genetic alteration of MYC may be involved in the pathogenesis of HHV8-negative effusion-based lymphoma, and Ichinohasama *et al* (13) suggested that PAX5 aberration may play a role in the lymphomagenesis of HHV8-negative effusion-based lymphoma. Effusion or chronic serositis itself could create ideal body conditions for lymphomagenesis, similar to fibrin-associated diffuse large B-cell lymphoma and diffuse large B-cell lymphoma associated with chronic inflammation (10). A large proportion of HHV8-negative effusion-based lymphoma is associated with fluid overload caused by different oedematous disorders, such as liver cirrhosis or heart failure. A study of 55 HHV8-negative effusion-based lymphoma cases reported cirrhosis and heart disease in 10 (18.2%) and 9 (16.4%) cases, respectively (3). The present case was also associated with localized fluid overload caused by heart disease and tuberculous pleurisy that occurred several years previously.

As was observed in the present case, HHV8-negative effusion-based lymphoma typically occurs in elderly patients with a median age of 70 years (10). Studies consistently report a higher incidence of HHV8-negative effusion-based lymphoma in males compared with that in females (3,10). In a previous study, the median age of patients at presentation with PEL was 42 years in an HIV-infected group, compared with 73 years in an immune-competent group (2). The immunocompromised state is likely to be associated with the earlier onset of PEL as there is no substantial difference in median age between patients with HHV8-positive and HIV-negative PEL and HHV8-negative effusion-based lymphoma.

Tumor cells in HHV8-negative effusion-based lymphoma exhibit cytological features ranging from immunoblasts to highly pleomorphic cells, which sometimes resemble Hodgkin cells commonly found in PEL (14). However, the tumor cells in HHV8-negative effusion-based lymphoma more commonly demonstrate either centroblast-like or Burkitt-like cytomorphology compared with those in PEL (3,14). In the present case, most tumor cells exhibited the cytomorphological features of centroblasts.

Unlike in PEL, in which the tumor cells usually lack pan B-cell markers, the majority of tumor cells in HHV8-negative effusion-based indolent lymphoma express pan B-cell markers and do not express an activation marker or plasma cell-associated antigen (15). The tumor cells in the present case also expressed pan B-cell markers, although not all cells demonstrated uniform and strong expression of pan B-cell marker; no tumor cells expressed activation markers or plasma cell-associated antigens except MUM1.

Regarding genetics, HHV8-negative effusion-based lymphoma demonstrates complex genomic aberrations (12). Although cytogenetic analysis could not be performed in the present study, Ohshima *et al* (12) reported gain in 19 out of 24 chromosomes in a comparative genomic hybridization study. They also reported complex chromosomal abnormalities in both number and structure, including t(8;22) or +8 chromosome and c-myc amplification. Terasaki *et al* (16) also reported cases of HHV8-negative effusion-based lymphoma with complex karyotype abnormalities in a G-band study.

HHV8-negative effusion-based lymphoma exhibits a less aggressive clinical course compared with PEL (17). Zaimoku *et al* (17) reported a markedly higher survival rate in patients with HHV8-negative effusion-based lymphoma (1-year survival rate, 60.1%) compared with those with PEL (1-year survival rate, 39.3%). Notably, the present case demonstrated no progression of disease over 1 year without chemotherapy. To the best of our knowledge, 12 patients

Table I. Clinicopathological characteristics of human herpesvirus 8-negative effusion-based lymphoma with an indolent clinical course.

First author, year	Sex	Age, years	Other disease(s)	Site	Histology	HIV	EBV	HCV	HBV	C-MYC	Therapy	Survival (at date of last follow-up)	Duration of follow-up, months	Refs.
Ashihara *et al*, 2001	F	60	Cholesteatoma	Peritoneum	Large, pleomorphic	-	+	-	-	None	None	Yes	24	(18)
Adiguzel *et al*, 2009	M	89	DM, HTN, CAD	Pleura	Large, pleomorphic	-	-	-	N/A	N/A	None	Yes	40	(19)
Terasaki *et al*, 2011	F	99	N/A	Pleura, Pericardium	Medium to large sized	-	-	-	N/A	A	Drainage	Yes	16	(16)
Wang *et al*, 2011	M	79	HTN, arthritis, aortic dissection	Pleura	Large, centroblast-like	-	-	-	-	N/A	Pleurodesis with doxycycline instillation	Yes	55	(20)
Kim *et al*, 2012	F	80	HTN, tuberculosis	Pleura	Medium, centroblast-like	-	-	-	N/A	N/A	None	Yes	18	(21)
Saini *et al*, 2013	F	87	CHF, HTN, AF, Dyslipidemia, degenerative joint disease	Pleura, pericardium	Large, pleomorphic	-	-	N/A	N/A	N/A	talc pleurodesis	Yes	29	(7)
Mohammad *et al*, 2014	M	76	HTN, AF	Pleura, pericardium	Large, pleomorphic	-	-	-	-	N/A	None	Yes	14	(22)
Nakatsuka *et al*, 2013	M	70	Prostate cancer	Pleura, pericardium	Large, pleomorphic	-	-	N/A	N/A	N/A	N/A	Yes	14	(23)
Nakatsuka *et al*, 2013	M	70	N/A	Pleura, pericardium	Large, pleomorphic	-	-	N/A	N/A	N/A	N/A	Yes	25	(23)
Nakamura *et al*, 2015	M	85	PVC	Pleura, pericardium	Medium to large, anaplastic	-	+	-	-	N/A	Drainage	Yes	24	(24)
Usmani *et al*, 2015	F	89	CHF	Pleura	NA	N/A	-	N/A	N/A	N/A	None	Yes	120	(15)
Usmani *et al*, 2015	F	82	PAD, CAD, HTN, metastatic breast cancer	Pericardial	N/A	N/A	-	N/A	N/A	N/A	None	Yes	14	(15)
Present study	M	75	AF, tuberculosis	Pleura, pericardium	Large, centroblast-like	-	-	-	-	-	None	Yes	22	

F, female; M, male; N/A, not available; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CHF, chronic heart failure; AF, atrial fibrillation; PVC, premature ventricular contraction; PAD, peripheral artery disease; A, amplification.

with indolent HHV8-negative effusion-based lymphoma who survived longer than 1 year without treatment have been previously described, as identified by searching Pubmed (https://pubmed.ncbi.nlm.nih.gov/) using the key words 'HHV-8', 'non-Hodgkin lymphoma', 'effusion', 'immune compromised' and 'primary effusion lymphoma' (7,15,18-24) (Table I). Among the 13 cases (including the present case), there were 7 males and 6 females, with an age range of 60-99 years (mean age, 80.1 years). The cases were either determined to be negative for HIV infection, hepatitis B virus infection and HCV infection, or the data were unavailable. Heart disease, including coronary artery disease and arrythmia, and chronic heart failure, were observed in 8 (61.6%) and 2 (15.4%) patients, respectively. EBV co-infection in lymphoma cells was detected in 2 cases (15.4%). c-MYC amplification was observed in 1 case (7.7%). Cytomorphologically, centroblast-like or small- to medium-sized Burkitt-like malignant lymphoid cells were observed more frequently in the cases summarized in Table I (3/13; 23.1%) than in a previous study on HHV8-negative effusion-based lymphoma (5/55; 9%) (3). Taken together, HHV8-negative effusion-based lymphoma with an indolent clinical course tends to occur in older patients with fewer comorbidities, a lower rate of related virus infections (such as HCV) and fewer aggressive cytomorphological features compared with conventional HHV8-negative effusion-based lymphoma. This suggests that HHV8-negative effusion-based lymphoma can be categorized into subgroups according to prognostic factors.

In summary, the present study reports a case of HHV8-negative effusion-based lymphoma with unusual indolent clinical behavior and presents a review of the characteristics of 13 biologically similar cases reported in the literature. The results suggest the existence of an indolent variant of HHV8-negative effusion-based lymphoma. In order to predict indolent clinical behavior in this rare type of lymphoma, a clinicopathological analysis of more cases is needed.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

AYL provided the conception and design of the manuscript. MK and JA drafted the manuscript. JA and SOY analyzed the previous articles regarding HHV8-negative effusion-based lymphoma. MK, SOY and WIY interpreted the results of immunohistochemistry, Epstein-Barr virus-encoded RNA *in situ* hybridization and PCR. AYL, SHY and JSK interpreted the patient clinical data. SOY, AYL and WIY carefully reviewed and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent for participation in the study was obtained from the patient.

Patient consent for publication

The patient provided written informed consent for the publication of associated data and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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