Title

HHV-8 Unrelated Primary Effusion Lymphoma-Like Lymphoma, a rare case and review of 48 cases in the literature

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Human Herpesvirus 8–Unrelated Primary Effusion Lymphoma–Like Lymphoma

Report of a Rare Case and Review of 54 Cases in the Literature

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Key Words: Primary effusion lymphoma; PEL; KSHV/HHV-8–unrelated lymphoma; KSHV/HHV-8–negative lymphoma; PEL-like lymphoma; Body cavity–based lymphoma; Effusion-based lymphoma

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ABSTRACT

Objectives: *To report a patient with primary effusion lymphoma who was negative for human herpesvirus-8 (HHV-8), human immunodeficiency virus, Epstein-Barr virus, hepatitis C virus, and hepatitis B virus, as well as review 54 reported cases of HHV-8–unrelated primary effusion lymphoma (PEL)–like lymphoma in the literature to clarify the nature of this entity.*

Methods: *The patients' characteristics, clinical presentation, pathogenesis, morphologic-immunophenotypic features, clinical management, and prognosis were studied.*

Results: *HHV-8–negative PEL-like lymphomas often occur in immunocompetent and elderly patients, are sometimes associated with chronic inflammation–related fluid overload, are mostly large B-cell or large B-cell with plasmacytic differentiation type, and are associated with a better prognosis.*

Conclusions: *In various aspects, HHV-8–unrelated PEL-like lymphoma is a different entity from HHV-8–related PEL. Immunophenotype, morphology, and c-*myc*/8q24 status should be included for differential diagnosis. A test for c-*myc *or 8q24 abnormalities should be recommended for subdividing HHV-8–unrelated PEL-like lymphoma, which may have benefits in patient management.*

Primary effusion lymphoma (PEL) is a rare type of non-Hodgkin lymphoma (NHL) confined to the body cavities, usually without extracavitary tumor mass. It is associated with Kaposi sarcoma–associated herpesvirus/human herpesvirus 8 (KSHV/HHV-8) infection[1] and often coinfected with Epstein-Barr virus (EBV), especially in the setting of human immunodeficiency virus (HIV) infection.[2,3] Both the 2001 and 2008 World Health Organization (WHO) classifications propose that PEL is universally associated with HHV-8.[4,5] However, cases of HHV-8–negative primary lymphomatous effusions have been described and termed *HHV-8–unrelated PEL-like lymphomas*, which may be associated with hepatitis C virus (HCV) infection and other agents.[6-8] Although most cases arise in the setting of HIV infection,[9] PEL has been reported in HIV-negative patients.[10-13] We report a case of HHV-8–unrelated PEL-like lymphoma in the pleural fluid of an HIV-negative 65-year-old woman, who was also negative for HHV-8, EBV, and HCV infection. The patient was never a recipient of a solid organ transplant, nor could the cause of her immunosuppression be identified. Interestingly, the lymphoma cells were B cells with plasmacytic differentiation, and the pleural fluid also showed a monoclonal immunoglobulin (Ig) M spike that was significantly higher than the monoclonal spike observed in the serum. The bone marrow, lymph nodes, and other organs were not involved. These findings suggest that this patient had an atypical presentation of PEL-like lymphoma. To further clarify the HHV-8–unrelated PEL-like lymphoma, in this study, we review an additional 54 reported cases available in literature and discuss the clinical and pathologic characteristics of these cases.

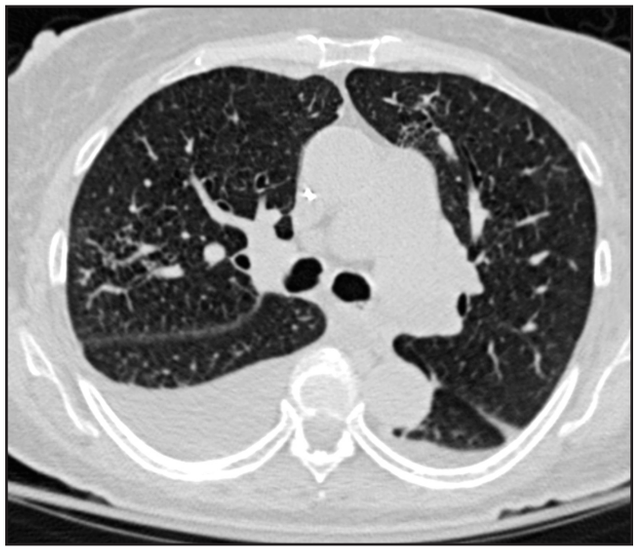

Image 1 Axial chest computed tomography shows bilateral pleural effusions, with the right greater than the left.

Case Report

A 65-year-old woman presented to the emergency room (ER) with a nonproductive cough, shortness of breath, and fatigue. She reported an unintended weight loss of 50 pounds over the course of 1 month but denied night sweats, fevers, or chills. The patient's past medical history is remarkable for IgA dermatitis and a 42-year history of cigarette smoking (1 pack per day). In the ER, the patient exhibited evident hypoxia with an oxygen saturation as low as 86%. Her physical examination was significant for bilateral basal rales, along with palpable inguinal lymph nodes bilaterally. No organomegaly was noted. Her initial peripheral blood counts revealed mild anemia with normal white blood cell and platelet counts. A chest x-ray revealed opacities in both lungs and evidence of bilateral pleural effusions. Chest computed tomography also confirmed the chest x-ray findings **Image 1** and further revealed mildly enlarged mediastinal lymph nodes (less than 1 cm). No masses in the lung and pleura were identified. The patient underwent a thoracocentesis for therapeutic relief as well as for diagnostic interpretation. Cytologic examination of the transudative fluid obtained revealed many large atypical lymphoid cells with a basophilic cytoplasm and a plasmacytoid appearance consistent with a malignant process **Image 2**. By immunohistochemistry, these large atypical cells showed λ restriction and were positive for CD20, CD79a, and MUM-1 with a small subset expressing CD138 and PAX-5 **Image 3**. Staining for HHV-8 by immunohistochemistry and for EBV by in situ hybridization (EBV-encoded RNA) showed negative results. Subsequent fluorescence in situ hybridization (FISH) testing for c-*myc* on paraffin sections of the pleural fluid sample revealed no abnormalities. Conventional cytogenetics was not performed on the fluid sample. Serologies for hepatitis B virus (HBV) and HCV infection were negative. Flow cytometry performed on the pleural fluid showed a λ-restricted B-cell population expressing CD19 and CD20 and a plasma cell population expressing CD138, CD38, and cytoplasmic λ light chain, consistent with a B-cell lymphoma with a plasmacytoid differentiation **Image 4**. An

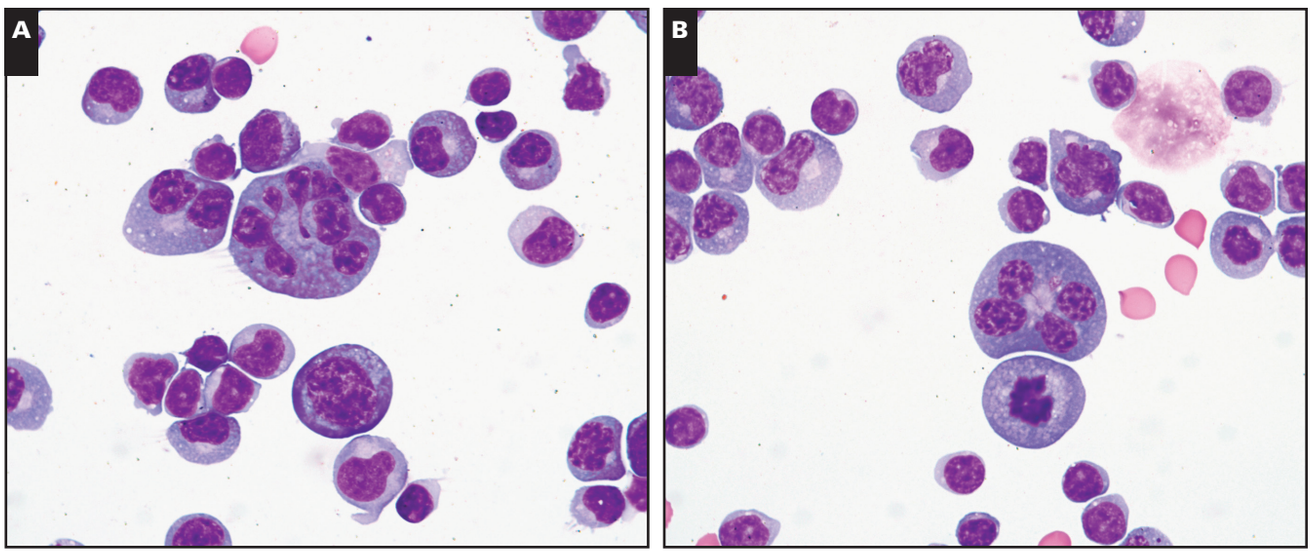

Image 2 Morphologic appearance of malignant cells in pleural fluid. **A**, Malignant cells demonstrate plasmacytoid appearance with multilobulated nuclei, with moderate to severe nuclear atypia. The malignant cells have occasional small cytoplasmic vacuoles (Wright stain, ×1,000). **B**, Frequent mitotic figures are seen (Wright stain, ×1,000).

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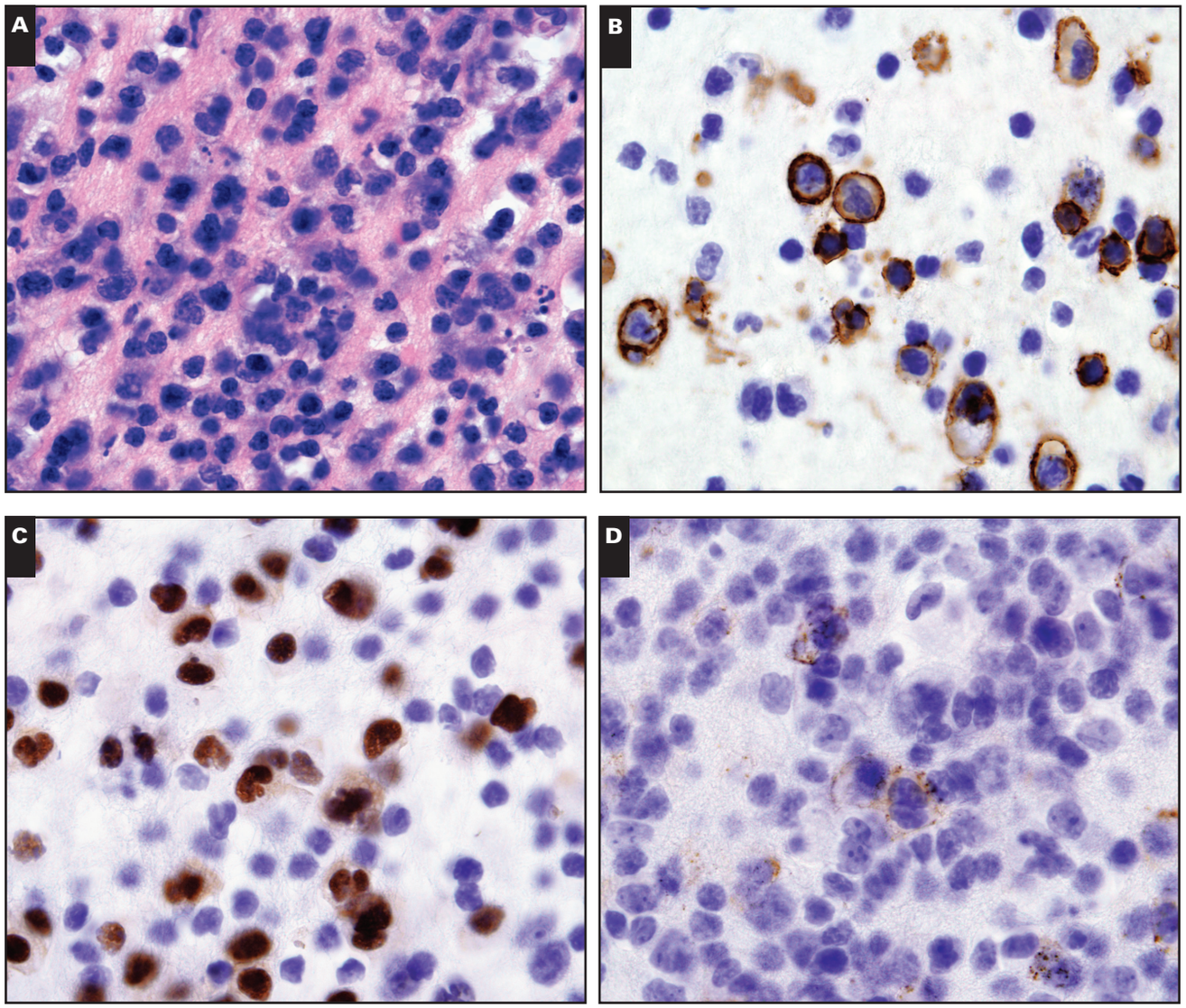

Image 3 Histologic, immunohistochemical, and in situ hybridization findings of malignant cells in pleural fluid. **A**, Malignant cells in cytospin preparation of pleural effusion (H&E, ×1,000). **B, C**, The malignant cells show strong membranous staining for CD20 (**B**, ×1,000) and strong nuclear staining for MUM-1/IRF4 (**C**, ×1,000).

endobronchial, ultrasound-guided, fine-needle aspiration biopsy specimen of the enlarged mediastinal lymph nodes showed no evidence of malignancy. Cervical mediastinoscopy was then performed, and biopsy specimens from mediastinal, peritracheal, and subcarinal lymph nodes mainly showed reactive lymphoid hyperplasia with no definitive evidence of lymphoma by both immunohistochemistry and flow cytometry. An excisional biopsy specimen of an enlarged inguinal lymph node showed necrotizing lymphadenitis with reactive lymphoid hyperplasia. Neither FISH nor cytogenetic testing was done on the lymph node samples. A bone marrow biopsy specimen showed no evidence of involvement by lymphoma or by a plasma cell dyscrasia. Cytogenetic studies performed on the bone marrow aspirate showed a normal female karyotype with no chromosomal abnormalities.

Serum protein electrophoresis and immunofixation showed a paraprotein spike in the γ region. Protein electrophoresis and immunofixation on the pleural fluid revealed an IgM λ monoclonal spike in the γ region of higher magnitude (1.67 g/dL) than that seen in the serum (0.99 g/dL) **Figure 1**. Urine protein electrophoresis showed no evidence of monoclonal paraproteins.

A whole-body positron emission tomography scan showed several consolidative areas in bilateral lung parenchyma (no discrete masses) along with increased uptake

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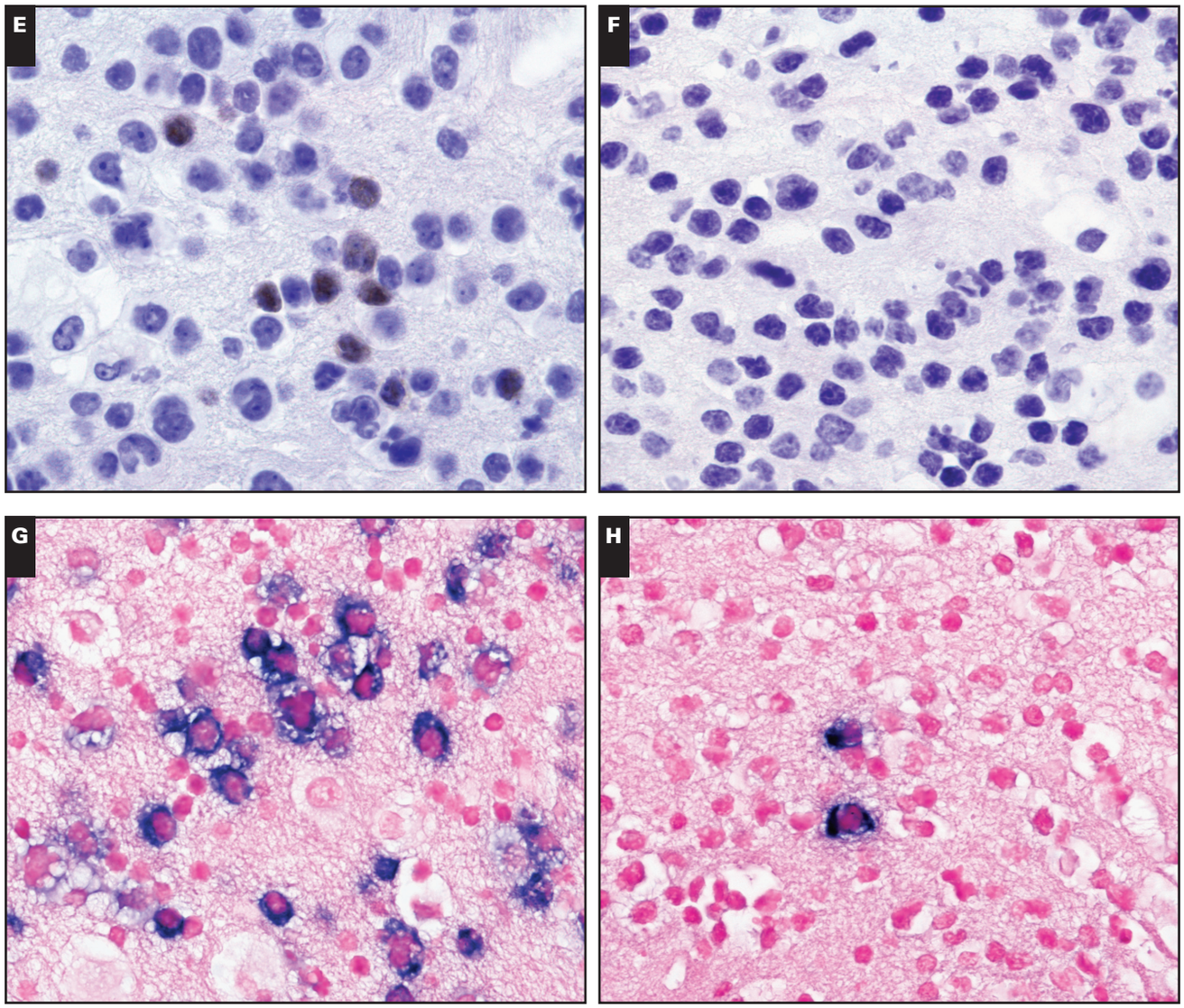

Image 3 (cont) **D, E**, A subset of the malignant cells expresses CD138 (D, ×1,000) and PAX-5 (E, ×1,000). **F**, Herpesvirus 8 staining was negative in malignant cells (×1,000). **G, H**, In situ hybridization for λ (**G**, ×1,000) and κ (**H**, ×1,000) demonstrate a λ-restricted cell population.

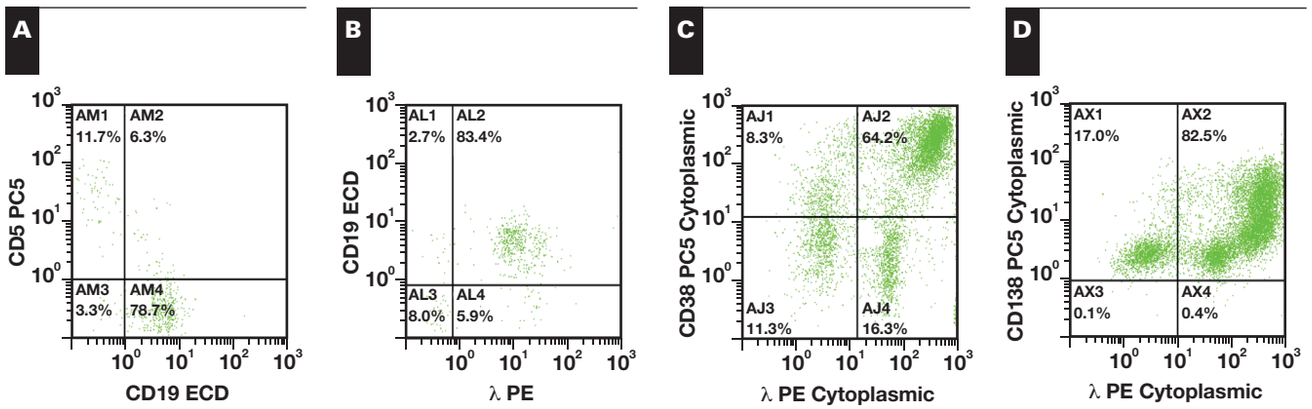

Image 4 Flow cytometric analysis of malignant cells in pleural fluid. **A, B**, Immunophenotyping of the lymphoid gate of pleural fluid reveals that most lymphoid cells are CD19-positive B cells with surface λ light chain restriction. **C, D**, Cytoplasmic CD38 and CD138 with cytoplasmic light chain analyses demonstrate a λ-restricted plasma cell population.

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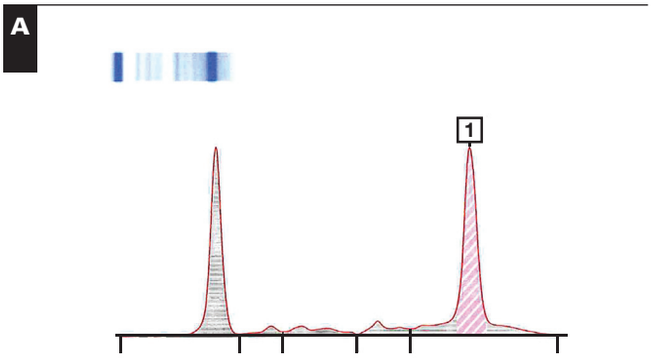
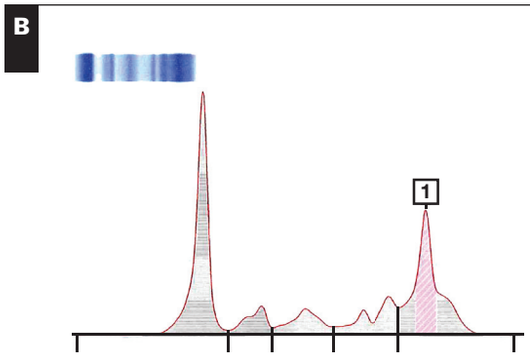


Fractions	%	Ref %
Albumin	35.2	27.0-52.0
α_1	2.7–	4.0-14.0
α_2	5.4–	8.0-22.0
β	5.2–	13.0-30.0
γ	51.5+	4.0-19.0
1	39.7	



Fractions	%	Ref %	g/dL	Ref g/dL
Albumin	38.0	48.0-61.8	2.01–	3.20-5.60
α_1	7.0	2.1-5.4	0.37+	0.15-0.33
α_2	9.1	8.0-16.0	0.48–	0.50-0.90
β	12.8	11.9-21.5	0.68	0.60-1.10
γ	33.1	8.8-15.4	1.75+	0.70-1.70
1	18.7		0.99	

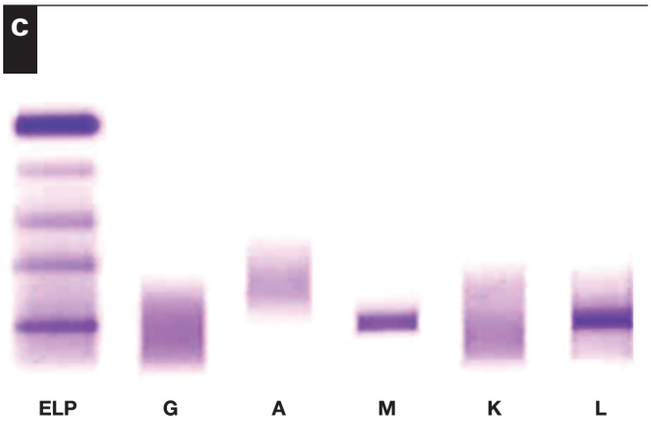


Figure 1 Protein electrophoresis and immunofixation results. **A, B**, Protein electrophoresis of pleural fluid and serum identifies a band with restricted mobility in the γ region. **C**, Serum immunofixation identifies an immunoglobulin (Ig) M λ monoclonal protein. A, IgA; ELP, electrophoresis; G, IgG; K, κ light chains; L, λ light chains; M, IgM.

in enlarged mediastinal, bilateral axillary, right supraclavicular, and retrocrural nodes. No increased uptake was found in the skeletal system. At this point, a diagnosis of HHV-8–unrelated PEL-like lymphoma was made after systemic lymphoma and plasma cell myeloma were ruled out. The patient was treated with rituximab, cyclophosphamide, vincristine, and high-dose prednisone. After 3 cycles of treatment, the patient had persistent malignant cells in the pleural fluid. The last hospital admission was for the continued chemotherapy. However, the patient's respiratory function deteriorated progressively, and she finally became respirator dependent. The patient died after removal of life support according to her family's request. The entire clinical course since the diagnosis of the lymphoma was 5.5 months. No autopsy was requested.

Discussion

Primary effusion lymphoma, also known as body cavity–based lymphoma, is a rare subtype of NHL usually presenting as serous effusions in body cavities without identifiable tumor masses. It was first established as a distinct entity in 1996.[9,14] The WHO describes PEL as a large B-cell lymphoma without expression of pan–B-cell markers such as CD19, CD20, and CD79a; universally positive for KSHV/HHV-8 infection; and with no describable relationship with c-*myc* proto-oncogene rearrangements.[4,5] Although HHV-8–related PEL occurs in HIV-negative patients,[10,15] PEL is usually found in HIV-positive immunosuppressed patients and refers only to lymphomatous effusions associated with HHV-8 infection, indicating that HHV-8 infection plays a key role in lymphomagenesis.[16,17] Reports of

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effusion lymphomas in patients without HHV-8 infection initially raised the question of the role of HHV-8 in PEL lymphomagenesis. Primary lymphomatous effusions not associated with HHV-8 infection are now termed *HHV-8–unrelated PEL-like lymphomas*.[6-8] Lymphomatous effusions that are secondary to systemic lymphomas or to body cavity–based mass-forming lymphomas are excluded from HHV-8–unrelated PEL-like lymphomas. Initially, these HHV-8–unrelated lymphomas were represented by cases of either Burkitt lymphoma or immunoblastic lymphoma, which exclusively or predominantly involved the body cavities.[9,10] More recently, other subtypes of HHV-8–unrelated PEL-like lymphomas, mostly large B-cell lymphomas, have been reported.[6,18] Furthermore, HHV-8–unrelated PEL-like lymphomas were classified by Carbone and Gloghini[7] based on EBV and c-*myc* status. It is important to distinguish PEL from HHV-8–unrelated PEL-like lymphoma because the 2 entities appear to differ in pathogenesis, morphologic-immunophenotypic features, clinical behavior, and prognosis. Compared with PEL, HHV-8–unrelated lymphomas mostly express pan–B-cell markers, are HHV-8 negative, and occur in older patients who are generally HIV negative. Human herpesvirus 8–unrelated lymphomas have better clinical outcomes and responses to therapy compared with PEL.

HIV Status and Related Findings

Review of the literature identified 55 HHV-8–unrelated PEL-like lymphoma cases, including the present case. The clinical and pathologic characteristics of each case are listed in **Table 1** and **Table 2**, respectively,[6,8-13,18-53] and summarized in **Table 3**. Of the 50 cases, 46 (92%) were from HIV-negative patients, and 4 were from HIV-positive patients (Table 3). The HIV status of 5 cases was unknown (Table 1).[25,27,53] Human immunodeficiency virus–negative PEL-like lymphomas occur in older individuals (mean age, 69.3 years, n = 46) (Table 3) compared with patients with HIV-positive PEL-like lymphomas (mean age, 42.8 years, n = 4) ($P < .01$). Although both HIV-negative and HIV-positive PEL-like lymphomas show a male predominance, the male-to-female ratio in the HIV-positive group (3:1 = 3) is much higher than that in the HIV-negative group (26:20 = 1.3), which is typically seen in HHV-8–related PEL. Twenty-two (48%) of the 46 patients with HIV-negative PEL-like lymphoma were alive at the time of report compared with 0 of 4 patients with HIV-positive PEL-like lymphoma, suggesting that HIV-negative PEL-like lymphomas have a less aggressive course. Survival status information was not available for 3 cases.[11,53] Patients with HIV-negative PEL-like lymphoma who died at the time of report lived an average of 8.2 months after diagnosis compared with 4.3 months for patients with HIV-positive PEL-like lymphoma ($P < .05$). In addition, the morphology of the lymphoma cells in HIV-positive PEL-like lymphoma cases consisted of large cell (2/4, 50%) and small Burkitt-like morphology (2/4, 50%). All 4 HIV-positive PEL-like lymphomas were immunophenotypically indeterminate but had a B-cell/plasma cell genotype by B-cell gene rearrangement study in 3 (75%) of 4 cases, with 1 case remaining indeterminate due to a germline IgH profile.[9] The c-*myc* rearrangement was found in 3 (75%) of 4 cases, including the case with an indeterminate phenotype. Furthermore, HIV-positive PEL-like lymphomas involved the peritoneum and/or the pleural space. In contrast, the morphology of PEL-like lymphoma in HIV-negative patients was predominantly large cell type (43/46, 93%) and B-cell/plasma cell type (42/46, 91%). Abnormalities of c-*myc* were identified in 9 (43%) of 21 HIV-negative patients.

Among the 46 HIV-negative and 5 HIV-unknown status cases, most patients were immunocompetent, and only 4 patients appeared in the setting of immunosuppression (1 with common variable immunodeficiency[29] and 3 with a history of transplantation[25,38,53]) (Table 1). This finding is significantly different from PEL.

EBV Status and Related Findings

Epstein-Barr virus is frequently identified in PEL most likely due to immunosuppression in the setting of HIV infection. In the reviewed 55 HHV-8–unrelated PEL-like lymphoma cases, EBV was positive in lymphoma cells from 16 (30%) of 53 patients (Table 3) but negative in 37 (70%) patients. All HIV-positive PEL-like lymphoma cases (4/4) showed evidence of EBV infection. This finding argues against a key role of EBV in the lymphomagenesis of HHV-8–unrelated PEL-like lymphoma. In EBV-positive and EBV-negative patients, age, sex, patient survival time, morphology and immunophenotype of the lymphoma cells, as well as location of the lymphomatous involvement, were similar to those seen in HIV-positive and HIV-negative patients.

HCV Status and Related Findings

Unlike PEL, which is universally associated with HHV-8 infection, no infectious etiology has been definitively established for HHV-8–unrelated PEL-like lymphoma. Previous studies have shown a possible association between HCV infection and HHV-8–unrelated PEL-like lymphoma.[6,8,19,21,34,35] In a review by Kobayashi et al,[6] 7 (33%) of 21 HIV-negative patients with HHV-8–unrelated PEL-like lymphoma tested for HCV were positive for infection. In our review study, 10 (25%) of 40 cases in which HCV testing was performed showed evidence of HCV infection (Table 3). Interestingly, although the patterns affected by age, sex, and survival time in HCV-positive and HCV-negative patients did not differ from those seen in HIV-positive and

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Table 1
Clinical Characteristics of Patients With Herpesvirus 8–Unrelated PEL-Like Lymphoma

Case No.	Reference	Age, y/ Sex	Other Disease	Site Involved	HIV	HCV	HBV	HTLV-1
1	Hermine et al[11]	52/F	ND	Pleura, pericardium	–	ND	ND	ND
2	Carbone et al[10]	90/M	ND	Pleura	–	ND	ND	ND
3	Carbone et al[10]	58/M	ND	Pleura, peritoneum	+	ND	ND	ND
4	Nador et al[9]	33/M	ND	Peritoneum	+	ND	ND	ND
5	Nador et al[9]	36/M	ND	Peritoneum	+	ND	ND	ND
6	Ascoli et al[19]	59/F	Cirrhosis	Peritoneum	–	+	ND	ND
7	Carbone et al[20]	57/M	ND	Peritoneum	–	ND	ND	ND
8	Ichinohasama et al[21]	63/M	Cirrhosis, HCC	Peritoneum	–	+	–	ND
9	Kuwabara et al[22]	59/F	Cholelithiasis	Pleura, peritoneum	–	–	ND	ND
10	Ashihara et al[23]	60/F	Cholesteatoma	Peritoneum	–	–	–	ND
11	Hara et al[24]	65/M	Cirrhosis	Peritoneum	–	+	–	ND
12	Ohori et al[25]	70/M	Hepatitis B, s/p liver transplant, HCC	Pleura	ND	ND	+	ND
13	Rodriguez et al[12]	65/M	Cirrhosis, alcohol abuse	Peritoneum	–	–	–	–
14	Yamamoto et al[26]	72/F	Cerebral aneurysm	Pleura, peritoneum	–	–	–	–
15	Tanaka et al[27]	42/F	ND	Peritoneum	ND	–	ND	ND
16	Ohshima et al[13]	75/M	ND	Pleura	–	ND	ND	ND
17	Ohshima et al[13]	76/M	ND	Pleura	–	ND	ND	ND
18	Ohshima et al[13]	81/M	ND	Pleura	–	ND	ND	ND
19	Saiki et al[28]	58/F	DM, chronic hepatitis, hypothyroidism	Peritoneum	–	+	ND	ND
20	Hisamoto et al[29]	58/F	Common variable immunodeficiency	Pleura, pericardium	–	–	ND	ND
21	Chiba et al[30]	55/M	Autoimmune hemolytic anemia	Peritoneum	–	–	–	–
22	Nakamura et al[31]	51/M	ND	Scrotum	–	–	–	ND
23	Paner et al[8]	58/M	Cirrhosis	Peritoneum	–	+	ND	ND
24	Shimazaki et al[32]	90/F	Atrial fibrillation	Pleura, peritoneum, pericardium	–	–	–	–
25	Inoue et al[33]	70/F	None	Pleura, pericardium	–	–	–	–
26	Nonami et al[34]	32/F	Protein-losing enteropathy, chylothorax	Pleura, peritoneum	–	+	–	–
27	Takao et al[35]	74/F	Cirrhosis, allergic granulomatous angitis	Pleura, peritoneum, pericardium	–	+	ND	ND
28	Fujiwara et al[36]	75/F	None	Pericardium	–	–	ND	ND
29	Jenkins et al[37]	61/M	Chronic liver disease, alcohol abuse	Peritoneum	–	–	–	ND
30	Matsumoto et al[18]	90/M	Pulmonary tuberculosis	Pleura	–	–	ND	ND
31	Matsumoto et al[18]	87/F	ND	Pleura	–	–	ND	ND
32	Venizelos et al[38]	27/F	Chronic renal failure, s/p renal transplantation	Peritoneum	–	ND	ND	ND
33	Youngster et al[39]	88/M	CAD	Pleura, pericardium	–	–	–	ND
34	Kobayashi et al[6]	70/F	ND	Pleura, peritoneum	–	ND	ND	ND
35	Niino et al[40]	78/M	Idiopathic CD4 T-lymphocytopenia	Pleura, pericardium	–	–	–	–
36	Terasaki et al[41]	68/M	None	Pleura	–	–	ND	ND
37	Adiguzel et al[42]	89/M	DM, HTN, CAD	Pleura	–	–	ND	ND
38	Taira et al[43]	68/F	ND	Pleura, pericardium	–	–	–	–
39	De Filippi et al[44]	69/M	Cirrhosis, renal carcinoma	Pleura, peritoneum	–	+	ND	ND
40	Tsagarakis et al[45]	77/M	Idiopathic CD4 T-lymphocytopenia, MI, prostate carcinoma	Pleura	–	–	–	–
41	Takahashi et al[46]	82/M	ND	Pleura, pericardium	–	–	ND	ND
42	Takahashi et al[46]	73/M	ND	Pleura, pericardium, peritoneum	–	–	ND	ND
43	Kagoya et al[47]	74/M	ND	Pericardium	–	–	ND	ND
44	Cooper et al[48]	44/F	DM, asthma, spinal osteoarthritis, alcohol abuse	Pleura, peritoneum	+	+	–	ND
45	Terasaki et al[49]	99/F	ND	Pleura, pericardium	–	–	ND	ND
46	Terasaki et al[49]	85/M	ND	Pleura, pericardium	–	–	ND	ND
47	Wang et al[50]	79/M	HTN, arthritis, dissecting aortic aneurysm	Pleura	–	–	–	ND
48	Sumida et al[51]	58/F	Polycystic kidney disease	Peritoneum	–	ND	ND	ND
49	Kim et al[52]	80/F	HTN, tuberculosis with benign pleural effusion	Pleura	–	–	ND	ND
50	Alexanian et al[53]	85/F	CAD, MI, s/p CABG	Pleura	ND	ND	ND	ND
51	Alexanian et al[53]	29/M	Complex congenital heart disease, s/p surgeries, CHF, cirrhosis	Peritoneum	–	–	–	ND
52	Alexanian et al[53]	45/M	Alcohol-cirrhosis, s/p liver transplant with subsequent HCV	Peritoneum	ND	+	+	ND
53	Alexanian et al[53]	72/M	CAD, MI, s/p angioplasty	Pleura	ND	ND	ND	ND
54	Alexanian et al[53]	51/M	Alcohol-cirrhosis, anasarca, diastolic dysfunction	Pleura	–	–	–	ND
55	Present case	65/F	IgA dermatitis	Pleura	–	–	–	ND

CABG, coronary artery bypass graft; CAD, coronary artery disease; CEOP, cyclophosphamide, epirubicin, vincristine, prednisolone; CHF, congestive heart failure; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; COP, cyclophosphamide, vincristine, prednisolone; DM, diabetes mellitus: HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV-1, human T-cell lymphoma virus 1; HTN, hypertension; MI, myocardial infarction; IgA, immunoglobulin A; ND, not done or not described; PEL, primary effusion lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; SCT, stem cell transplantation; s/p, status post; THP-COP, pirarubicin, cyclophosphamide, vincristine, prednisolone; VNCOP-B, cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin, prednisolone.

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Therapy	Outcome
ND	ND
Chemotherapy	Died, 1 month
None	Died, 5 months
Chemotherapy	Died, 6 months
ND	Died, unknown
None	Died, 2 months
None	Died, 0.25 month
None	Died, 22 months
Chemotherapy, radiation	Died, 27 months
None	Alive, 24 months
Prednisolone, etoposide	Alive, 8 months
Radiation for HCC, prednisone	Alive, 8 months
CHOP	Died, 12 months
VNCOP-B	Died, 5 months
Melphalan, prednisolone	Died, 3 months
CHOP	Died, 15 months
None	Alive, 6 months
None	Alive, 2 months
None	Died, 7 months
Prednisolone, etoposide	Died, 0.5 month
CHOP	Died, 2 months
Chemotherapy, orchiectomy with radiation	Alive, 8 months
COP	Died, 5 months
None	Died, 5 months
THP-COP, sobuzoxane	Alive, 48 months
THP-COP, SCT	Died, 18 months
THP-COP, rituximab	Alive, 26 months
CHOP	Alive, 36 months
Vincristine, cyclophosphamide	Alive, 2 months
THP-COP, etoposide, rituximab	Alive, 38 months
Rituximab	Alive, 32 months
CEOP	Died, 0.75 month
R-CHOP	Alive, 9 months
THP-COP	Died, 26 months
Rituximab, THP-COP	Alive, 30 months
Drainage, R-CHOP	Alive, 22 months
None	Alive, 40 months
CHOP	Died, 7 months
Bortezomib, cyclophosphamide, dexamethasone	Died, 2.25 months
R-CHOP without doxorubicin	Alive, 3 months
Drainage, R-CHOP	Alive, 21 months
Drainage, R-CHOP	Alive, 9 months
Drainage, R-CHOP	Died, 3 months
CHOP, HAART	Died, 2 months
Drainage	Alive, 16 months
Drainage	Alive, 11 months
Pleurodesis with doxycycline instillation	Alive, 55 months
Chemotherapy	Died, 18 months
None	Alive, 18 months
Drainage	ND
Chemotherapy, SCT	Died, 4.5 months
CHOP	Died, 1.5 months
Drainage	ND
Drainage	Died, 0.03 months
Drainage, R-CHOP	Died, 5.5 months

HIV-negative or EBV-positive and EBV-negative patients, large cell morphology and B-cell immunophenotype of PEL-like lymphoma with associated c-*myc* abnormalities were found in HCV-positive patients. In addition, most cases of HCV-associated HHV-8–unrelated PEL-like lymphoma involved the peritoneum, which may be related to liver cirrhosis caused by HCV infection (Tables 1 and 3).[8,19,21,24,35,53] The finding of HCV-RNA in ascitic fluid indicates persistent antigenic stimulation, which promotes clonal expansion of intraperitoneal B cells.[19] This may represent an important step in the pathogenesis of HHV-8–unrelated PEL-like lymphoma. Although HCV infection may contribute to the development of some HHV-8–unrelated PEL-like lymphomas, its role does not appear as crucial as that of HHV-8 infection in the development of PEL. In our review, most (75%) HHV-8–unrelated PEL-like lymphoma cases tested for HCV infection were negative. Two of 22 PEL-like lymphoma cases associated with HBV were found in our study, both EBV positive[25,53] and 1 HCV positive as well.[53] No human T-lymphotrophic leukemia virus type 1–infected HHV-8–unrelated PEL-like lymphoma cases (0/9) were identified in this study (Table 1).

Pathologic Features

Site Involvement

Unlike PEL, in which pleural involvement is dominant, HHV-8–unrelated lymphoma showed frequent involvement of the peritoneum. Peritoneal involvement was seen in 27 (49%) of 55 cases, with exclusive peritoneal involvement in 17 (31%) cases (Table 3). This high frequency of peritoneal involvement is partially due to viral hepatic cirrhosis. Involvement of the pleura was seen in 35 (64%) of 55 cases, with sole involvement of pleura in 16 (29%). Fourteen (25%) of the 55 cases showed pericardial involvement. Sole involvement of the pericardium was seen only in 2 (4%) cases. Involvement of the pericardium was apparently related to the pleural involvement (Table 3). One case with isolated unilateral scrotal involvement was identified in this study.[31] This patient had negative viral tests for HIV, HCV, HBV, EBV, and HHV-8, and the lymphoma cells were large and had a B-cell phenotype and genotype.

Morphology

While most HHV-8–unrelated PEL-like lymphomas (50/55, 91%) demonstrated an anaplastic cellular (large) morphology (Table 3) ▮**Table 4**▮, a small portion of the studied cases (5 of 55, 9%) revealed small- to medium-sized tumor cells that were described as Burkitt-like lymphoma cells.[6,9,19,20] Interestingly, c-*myc* rearrangement was detected in 3 of 5 of these cases, and t(8;22)(q24;q11)[19] was found in 1 of the remaining 2 cases, indicating a possibility of extranodal

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Table 2
Pathologic Features of Herpesvirus 8–Unrelated PEL-Like Lymphomas

Case No.	Reference	Cellular Morphology	Expression of Markers	Phenotype	Genotype
1	Hermine et al[11]	Large, pleomorphic	CD19, CD20, CD22, CD45, HLA-DR	B cell	B cell (IgH rearranged)
2	Carbone et al[10]	Large, pleomorphic	None (CD45, CD15, CD30, EMA)	Indeterminate	B cell (monotypic λ)
3	Carbone et al[10]	Large, pleomorphic	CD45, CD30	Indeterminate	B cell (monotypic κ)
4	Nador et al[9]	Medium, Burkitt-like	Possible null type, not specifically described	Indeterminate	B cell (IgH rearranged)
5	Nador et al[9]	Medium, Burkitt-like	Possible null type, not specifically described	Indeterminate	Indeterminate (IgH germline)
6	Ascoli et al[19]	Small to medium	CD10, CD20, CD24, λ	B cell	ND
7	Carbone et al[20]	Small to medium, Burkitt type	CD10, CD19, CD20, CD22, CD40, CD74, CD79a, CD23, CD38, CD45	B cell	B cell (IgH rearranged, monotypic λ)
8	Ichinohasama et al[21]	Medium to large	CD19, CD20, CD22, CD45, IgG λ	B cell	B cell (IgH rearranged, monotypic λ)
9	Kuwabara et al[22]	Large, pleomorphic	CD10, CD30, CD33, CD71, CD138	Plasma cell	Plasma cell (IgH rearranged, monotypic λ)
10	Ashihara et al[23]	Large, pleomorphic	CD19, CD20, CD22, CD45, HLA-DR, IgG, IgM	B cell	ND
11	Hara et al[24]	Large, cytoplasmic vacuoles	CD19, CD20, CD22	B cell	B cell (IgH rearranged)
12	Ohori et al[25]	Medium to large	CD19, λ	B cell	ND
13	Rodriguez et al[12]	Immunoblastic	CD19, λ	B cell	B cell (IgH rearranged)
14	Yamamoto et al[26]	Large, cytoplasmic vacuoles	CD2, CD3, CD7, CD30, CD38, CD45RO, CD45, TCRαβ	T cell	T cell (TCR rearranged)
15	Tanaka et al[27]	Large, anaplastic cell-like	CD11, CD13, CD16, CD18, CD38, EMA, keratin	Indeterminate	B cell (IgH rearranged)
16	Ohshima et al[13]	Large	CD19, CD20, HLA-DR, IgM κ	B cell	B cell (IgH rearranged)
17	Ohshima et al[13]	Large, Burkitt-like	CD10, CD19, CD20, HLA-DR, IgM λ	B cell	B cell (IgH rearranged)
18	Ohshima et al[13]	Large	CD10, CD19, CD20, HLA-DR	B cell	B cell (IgH rearranged)
19	Saiki et al[28]	Pleomorphic	CD4, CD5, CD19, CD20	B cell	B cell (IgH rearranged)
20	Hisamoto et al[29]	Large	CD19, CD20, CD22, HLA-DR	B cell	ND
21	Chiba et al[30]	Large, multilobated, multinucleated	CD20, CD21, CD79a, CD38, CD45, IgM κ	B cell	B cell (IgH rearranged)
22	Nakamura et al[31]	Medium to large, cytoplasmic vacuoles	CD20, CD79a, CD45	B cell	B cell (IgH rearranged)
23	Paner et al[8]	Large, pleomorphic	CD10, CD19, CD20, CD22, CD45, FMC7, HLA-DR, κ	B cell	B cell (IgH rearranged)
24	Shimazaki et al[32]	Large	CD20, CD79a, BCL-2	B cell	B cell (IgH rearranged)
25	Inoue et al[33]	Large	CD8, CD10, CD19, CD20, CD22, CD24, CD38, CD45, CD71	B cell	B cell (IgH rearranged)
26	Nonami et al[34]	Large, cytoplasmic vacuoles	CD10, CD19, CD20, HLA-DR	B cell	B cell (IgH rearranged)
27	Takao et al[35]	Class V cytology, conclusive for malignancy	CD19, CD20, CD25, CD45, HLA-DR, IgM κ	B cell	B cell (IgH rearranged)
28	Fujiwara et al[36]	Large, cytoplasmic vacuoles	CD20, CD79a	B cell	B cell (IgH rearranged)
29	Jenkins et al[37]	Large, pleomorphic	CD38, CD138, high Ki-67	Plasma cell	ND
30	Matsumoto et al[18]	Large, cytoplasmic vacuoles	CD19, CD20, CD30	B cell	B cell (IgH rearranged)
31	Matsumoto et al[18]	Large	CD19, CD20, CD30, κ	B cell	ND
32	Venizelos et al[38]	Large to very large	CD3, CD8, CD30	T cell	T cell (TCR oligo, IgH not rearranged)
33	Youngster et al[39]	Large	CD20, CD30, CD45, CD79a	B cell	ND
34	Kobayashi et al[6]	Small to medium	CD4	Indeterminate	B cell (IgH rearranged, TCRβ-germline)
35	Niino et al[40]	Large, cytoplasmic vacuoles	CD19, CD20, CD22, HLA-DR, IgM λ	B cell	ND
36	Terasaki et al[41]	Large, atypical	CD20, CD79a	B cell	B cell (IgH rearranged)
37	Adiguzel et al[42]	Large	CD7, CD30, CD38, CD45, CD71, HLA-DR	Indeterminate	ND
38	Taira et al[43]	Malignant	CD10, CD19	B cell	B cell (IgH rearranged)
39	De Filippi et al[44]	Large, plasmacytoid	CD30, CD38, CD45, CD138, cytoplasmic λ	Plasma cell	ND
40	Tsagarakis et al[45]	Large, atypical	CD19, CD20, CD30, CD38, CD22	B cell	ND
41	Takahashi et al[46]	Medium to large	CD20, CD79a, light chain restriction	B cell	ND
42	Takahashi et al[46]	Large, atypical	CD20	B cell	ND
43	Kagoya et al[47]	Medium to large	CD20, high Ki-67	B cell	ND
44	Cooper et al[48]	Large, pleomorphic, cytoplasmic vacuoles	CD10, CD38, CD45	Indeterminate	B cell (monotypic κ)
45	Terasaki et al[49]	Medium to large with mitoses	CD5, CD19, CD20, CD25, IgM, IgD, λ	B cell	B cell (rearranged)
46	Terasaki et al[49]	Medium to large sized	CD20	B cell	B cell (rearranged)
47	Wang et al[50]	Large, centroblast-like	CD20, CD79a, BCL-2, BCL-6, MUM-1, CD45	B cell	B cell (rearranged)
48	Sumida et al[51]	Large, cytoplasmic vacuoles	B-cell immunophenotype	B cell	ND
49	Kim et al[52]	Medium to large	CD20, BCL-2	B cell	ND
50	Alexanian et al[53]	Large, pleomorphic	CD45, CD20, CD79a, CD138, BOB1, OCT-2, κ	B cell and plasma cell	ND
51	Alexanian et al[53]	Large, pleomorphic	CD45, CD38, CD79a, CD138, PAX-5, BOB1, OCT-2, κ	B cell and plasma cell	B cell (rearranged)
52	Alexanian et al[53]	Large, pleomorphic	CD45, CD38, CD56, CD138, κ	Plasma cell	Plasma cell (IgH germline)
53	Alexanian et al[53]	Large, pleomorphic	CD45, CD20, CD30, CD43, BCL-2	B cell	ND
54	Alexanian et al[53]	Large, pleomorphic	CD45, CD25, CD30, CD38, BLIMP1, Granzyme, MUM-1, TIA	Indeterminate	ND
55	Present case	Large, plasmacytoid	CD20, CD79a, MUM-1, CD138, PAX-5, λ	B cell and plasma cell	ND

EBV, Epstein-Barr virus; FISH, fluorescence in situ hybridization; IgD, immunoglobulin D; IgG, immunoglobulin G; IgH, immunoglobulin heavy chains; IgM, immunoglobulin M; ND, not done or not described; PEL, primary effusion lymphoma; TCR, T-cell receptor.

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Karyotype	*c-myc* Abnormalities	EBV
ND	ND	–
ND	No	–
ND	No	+
ND	Yes (rearranged)	+
ND	Yes (rearranged)	+
48,XX,t(8;22)(q24;q11),+16,+20(20)	ND	–
46,XY,t(8;22)(q24;q11)	Yes (rearranged)	+
Complex	Yes (rearranged)	–
ND	ND	–
der(8)t(2;8)(q31;q24) with complex karyotype	No	+
ND	No	–
ND	ND	+
ND	ND	+
del(1)(p11p22),+i(7)(q10), t(11;14)(q23;q11)	ND	–
Normal	No	–
Complex	Yes (amplification)	–
Complex	No	–
Complex	Yes (amplification)	–
Hyperdiploid	Yes (rearranged)	–
Normal	No	+
Complex	ND	+
ND	ND	–
ND	ND	–
ND	Yes (rearranged)	–
Complex	No	–
Complex	Yes (amplification)	–
ND	Yes (amplification)	–
Complex with t(1;22)(q21;q11), t(14;17)(q32;q23)	No	–
ND	ND	ND
Complex with add(8)(q24)	ND	–
ND	ND	–
ND	ND	–
ND	ND	–
ND	ND	+
Complex with add(3)(q27)	No	+
Normal	No	–
ND	ND	–
ND	ND	–
ND	ND	+
ND (FISH trisomy 18)	No	+
ND	ND	+
ND	ND	–
ND	ND	–
Complex with t(8;14)(q24;q32)	Yes (rearranged)	+
ND	Yes (amplification)	–
Complex	No	–
ND	ND	–
ND	ND	ND
ND	ND	–
ND	ND	–
Inv 10q	ND	–
ND	ND	+
ND	ND	–
ND	ND	–
ND	No	–

Burkitt lymphoma. This finding was not described in PELs. Otherwise, the morphology of HHV-8–unrelated PELs was mostly described as large cell with pleomorphic nuclei and an abundant vacuolated cytoplasm. Plasmacytoid appearance was also reported similar to the present case (Image 2). It is believed that the fluid environment may act as a culture media, providing readily accessible nutrients to tumor cells. Therefore, the tumor cells may display extremely abnormal growth patterns, as can be seen in cultured cell lines.

Immunophenotype

Forty 40 (73%) of 55 reviewed HHV-8–unrelated PEL-like lymphomas expressed pan–B-cell markers such as CD19, CD20, and CD79a by immunohistochemistry and/or flow cytometry, and an additional 6 cases with indeterminate phenotype were further confirmed to be a B-cell genotype by rearranged IgH (Tables 2 and 4). The B-cell phenotype/genotype of most PEL-like lymphoma cases (46/55, 84%) was strikingly different from PEL, which typically lacks expression of pan–B-cell markers. In addition, some of the B-cell cases (8/55) demonstrated coexpression of CD10 with CD19 and/or CD20 (Table 2), indicating a germinal center origin of tumor cells. In addition, 13 of 55 cases showed CD30 expression (5 with B-cell type, 4 with indeterminate type, 2 with plasma cell type, and 2 with T-cell type) (Table 2), indicating cellular activation. These findings support the hypothesis that persistent antigenic stimulation caused by chronic inflammation promotes clonal B-cell expansion.[19] The best example of lymphoma related to chronic inflammation is diffuse large B-cell lymphoma (DLBCL) associated with chronic inflammation (2008 WHO classification),[54] formerly known as pyothorax-associated lymphoma (PAL).[55] Pyothorax-associated lymphoma was initially defined as an NHL of an exclusively B-cell phenotype developing in the pleural cavity of patients with more than a 20-year history of chronic pyothorax and recently as a prototypic form of DLBCL associated with chronic inflammation.[54] The latter is a lymphoid neoplasm occurring in the context of long-standing chronic inflammation and showing an association with EBV. B-cell NHL is well known to be associated with antecedent autoimmune diseases, including Sjögren syndrome, rheumatoid arthritis, and Hashimoto thyroiditis.[56] In addition to autoimmune mechanisms, chronic inflammatory stimulation of a non-autoimmune nature could also be an etiologic factor in the development of these B-cell lymphomas. Pyothorax-associated lymphoma and mucosa-associated lymphoid tissue lymphoma are included in this category, which is generally referred to as malignant lymphomas developing in chronic inflammation.[57] Interestingly, about 70% of PALs are also associated with EBV infection but not HIV infection. Although HHV-8 has not been identified in most patients with PAL, rare cases of HHV-8–positive PAL have been reported.[58,59] In addition,

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Table 3
Summary of Clinical and Pathologic Characteristics Based on HIV, EBV, and HCV Status

		Site Involved						Cell Morphology		Immunophenotype		c-*myc*/8q24	
Status	Cases, %	Pl	Pt	Pc	Pl/Pt	Pl/Pc	Pl/Pt/Pc	Large	Small-Medium	B or Plasma Cell	Other	Positive	Negative
HIV status													
Positive	4 (8)	0	2	0	2	0	0	2	2	3	1	3	1
Negative	46 (92)	13	13	2	5	9	3	43	3	42	4	12	14
Unknown	5	3	2	0	0	0	0	5	0	5	0	0	1
EBV status													
Positive	16 (30)	2	7	0	4	3	0	12	4	15	1	5	5
Negative	37 (70)	14	8	2	3	6	3	36	1	33	4	10	11
Unknown	2	0	2	0	0	0	0	2	0	2	0	0	0
HCV status													
Positive	10 (25)	0	6	0	3	0	1	9	1	10	0	6	1
Negative	30 (75)	9	6	2	2	8	2	30	0	27	3	3	4
Unknown	15	7	5	0	2	1	0	11	4	13	2	6	2
Total	55 (100)	16	17	2	7	9	3	50	5	50	5	15	16

EBV, Epstein-Barr virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; Pc, pericardium; Pl, pleura; Pt, peritoneum.
[a] $P < .01$ compared with HIV-positive group.
[b] $P < .05$ compared with HIV-positive group.

Table 4
c-*myc*/8q24 Status Related to Lymphoma Cell Morphology and Immunophenotype

	Morphology (Cell Size), No./Total No. (%)		Immunophenotype/Genotype			
			B-Cell Type			
	Large	Small to Medium	B-Cell Phenotype[a]	B-Cell Phenotype/ B-Cell Genotype[b]	B-Cell/Plasma Cell Phenotype[c]	Indeterminate Phenotype/ B-Cell Genotype[d]
c-*myc*/8q24[h]						
Positive (15/31, 48%)	11/27 (41)	4/4 (100)	3	9	0	2
Negative (16/31, 52%)	16/27 (59)	0	3	7	2	3
Not done (24/55, 44%)	23	1	9	6	1	1
Total, No. (%)	50 (91)	5 (9)	15/55 (27)	22/55 (40)	3/55 (5)	6/55 (11)

IgH, immunoglobulin heavy chain; TCR, T-cell receptor.
[a] CD19 and CD20, CD22, or CD79a.
[b] CD19 and CD20, CD22, or CD79a/IgH rearrangement or monotypic light chain.
[c] CD19 and CD20, CD22. or CD79a/CD138.
[d] CD30, CD45, CD38, or EMA/IgH rearrangement or monotypic light chain.
[e] CD38 and CD138.
[f] CD30, CD45, CD38, or EMA.
[g] CD3 and CD2, CD7, CD8, or CD45RO/TCR rearrangement.
[h] c-*myc* by molecular study and 8q24 by karyotyping.

PAL commonly demonstrates a pleural-based mass lesion, which facilitates differentiation from PEL.[60] Apparently, HHV-8–unrelated PEL-like lymphoma does not meet the diagnostic criteria of DLBCL associated with chronic inflammation due to the lack of long-standing (usually more than 10 years) chronic inflammation and association with EBV. Whether HHV-8–unrelated PEL-like lymphoma should be classified as a variant of DLBCL remains undetermined and needs further study and discussion. However, HHV-8–unrelated PEL-like lymphoma is similar to DLBCL in many aspects, including morphology, immunophenotype, and c-*myc* abnormalities (rearrangement and/or amplification) and is clearly different from PEL except for the location.

In our reported case, the patient had a long history of tobacco smoking, which may have served as a stimulator for chronic inflammation of the lung and contributed to lymphomagenesis. It is difficult to further clarify because none of the reviewed cases demonstrated the relationship between smoking and PEL-like lymphoma.

In addition to B-cell type, other types of PEL-like lymphomas were identified, including plasma cell type (4/55, 7%), indeterminate type (3/55, 5%), and T-cell type (2/55, 4%). Plasma cell differentiation is in line with a terminal B-cell differentiation and does not indicate a process of plasma cell myeloma based on the clinical presentation of those cases. The nature of 2 of 3 indeterminate lymphomas remained

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Mean Age, y	M:F	Deceased, No./ Total No. (%)	Mean Survival, Deceased, mo
42.8	3:1	4/4 (100)	4.3
69.3[a]	26:20	23/46 (50)	8.2[b]
62.8	3:2	2/3 (67)	2.3
59.8	12:4	11/16 (69)	5.8
68.9	19:18	17/34 (50)	7.7
59.5	1:1	1/2 (50)	18.0
56.7	5:5	8/10 (80)	7.5
70.8	17:13	12/30 (40)	6.2
62.6	10:5	9/12 (75)	8.2
65.3	32:23	29/52 (56)	7.4

Immunophenotype/Genotype		
Plasma Cell Phenotype[c]	Indeterminate Phenotype or Genotype[f]	T-Cell Phenotype/ T-Cell Genotype[g]
0	1	0
0	0	1
4	2	1
4/55 (7)	3/55 (5)	2/55 (4)

undetermined because further genotypic studies were not performed. As mentioned above, the third indeterminate case had germline IgH but with c-*myc* rearrangement. The 2 T-cell cases[26,38] had genotypic confirmation (T-cell receptor rearranged) and were not associated with HIV, EBV, or a history of hepatitis. One case[38] was significant for immunosuppression due to a 5-year history of renal transplant and may represent a special type of posttransplant lymphoproliferative disease.

*Relevance to c-*myc *Abnormalities*

It has been suggested that cases of HHV-8–unrelated PEL-like lymphoma with c-*myc* translocations be classified as special variants of Burkitt lymphoma.[9] Classification of PEL based on the presence of HHV-8, EBV, c-*myc* rearrangements, and morphologic features has been proposed[61]: HHV-8–positive PEL (HHV-8 positive, EBV positive or negative, and negative for c-*myc* rearrangements) and HHV-8–negative PEL, under which are extranodal Burkitt lymphomas (HHV-8 negative, positive for c-*myc* rearrangements and EBV, and small noncleaved cell morphology) and extranodal large cell lymphomas (HHV-8 negative, negative for c-*myc* rearrangements, EBV positive or negative, and immunoblastic or anaplastic cell morphology). In this classification, the presence or absence of c-*myc* classifies 2 different types of HHV-8–negative PEL. c-*myc* is a major controller of cellular proliferation, and its deregulation is a common cause of malignancies. Frequent c-*myc* deregulation occurs in lymphomas due to chromosomal translocations, as seen in Burkitt lymphoma[62,63] and gene amplification in a subset of DLBCL.[64] Although aberrant c-*myc* appears to be important for lymphomagenesis, its role in HHV-8–unrelated PEL-like lymphoma is still not clear. In our study, 15 (48%) of 31 HHV-8–unrelated PEL-like lymphoma cases had c-*myc*/8q24 abnormalities, including translocations/rearrangements and amplifications by both molecular study and karyotyping (Tables 3 and 4). According to the proposed classification of PEL, 3 cases with positive EBV, positive c-*myc* rearrangement, and small to medium cell morphology could be considered extranodal Burkitt lymphoma.[9,20] However, using c-*myc*/8q24 as a segregated marker to classify HHV-8–unrelated PEL-like lymphomas may not be adequate because the translocation involving c-*myc* is not specific. Multiple factors, including morphology and EBV and HIV status, should be considered as well. In our study, when separated by HIV status, 3 (75%) of 4 HIV-positive PEL-like lymphomas were positive for c-*myc* abnormalities compared with 12 (46%) of 26 HIV-negative PEL-like lymphomas (Table 3). Similar to HIV-positive cases, c-*myc* abnormalities were detected in 6 (86%) of 7 HCV-positive PEL-like lymphomas and 3 (43%) of 7 HCV-negative PEL-like lymphomas. These results suggest that c-*myc* abnormalities may have a more important role in the development of HHV-8–unrelated PEL-like lymphomas in HIV-positive and/or HCV-positive patients. The possibility also exists that HHV-8–unrelated PEL-like lymphomas in HIV-positive patients represent unusual manifestations of other lymphomas, particularly Burkitt lymphoma, which is more commonly seen in patients with HIV. However, c-*myc* abnormalities can also be observed in other hematopoietic disorders such as DLBCL and plasma cell myeloma.[65] Table 4 summarizes the relationships between c-*myc*/8q24, cell morphology, and immunophenotype. As mentioned previously, 4 of 5 cases with small to medium cellular morphology showed c-*myc* rearrangement (the remaining case was not tested for c-*myc*), which indicates the possibility of Burkitt lymphoma. Eleven (40%) of 27 cases with large cell morphology showed c-*myc*/8q24 abnormalities. In addition, most cases with c-*myc*/8q24 abnormalities were B-cell lymphomas (14/15, 93%), mainly because only rare non–B-cell lymphomas in this study were tested for c-*myc*.

The presence of c-*myc*/8q24 abnormalities not only serves diagnostic or prognostic purposes but also may be important for potential treatment purposes because *myc* is a

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promising target for anticancer drugs, and modulating *myc* expression may be sufficient to stop tumor cell proliferation and induce apoptosis.[66]

Immunoglobin Light Chains in Lymphomatous Fluid

In our reported case of PEL-like lymphoma, the patient was negative for HHV-8, HIV, EBV, HCV, and HBV infection. Morphologic and immunophenotypic features were more consistent with large B-cell lymphoma with plasma cell differentiation (non-Burkitt). The lymphoma was limited to the pleural spaces. Significant past medical history included IgA dermatitis and tobacco smoking. Interestingly, protein electrophoresis and immunofixation on pleural fluid and serum samples from our patient showed a monoclonal IgM spike in both serum and pleural fluid. However, the IgM spike in the pleural fluid was greater than the IgM spike in serum, which has not been described in HHV-8–unrelated PEL-like lymphomas. This pattern may be due to a gradual outflow of IgM proteins from the pleural fluid into the serum. Despite a pre–plasma cell or plasma cell genotype and gene expression signature,[1,67] PEL arises from mature postgerminal center B cells, which rarely express surface immunoglobulins due to the defective expression of B-cell–specific transcription factors.[68,69] The PEL cells from HIV-positive patients have expressed intact immunoglobulins in only 20% of cases,[9] but monoclonal light chains have been detected more frequently in tumor cells from HIV-negative PEL and HHV-8–unrelated PEL-like lymphoma cases.[6] It was previously reported that clonal serum free light chains (sFLC) were elevated in HIV-negative PEL-like lymphoma[44] and that measurement of sFLC may be useful in guiding therapy. Measurement of monoclonal immunoglobulin levels may also be beneficial in the therapeutic monitoring of HHV-8–unrelated PEL-like lymphoma. Although no FLC was detected in the urine of our patient, the presence of monoclonal IgM in the lymphomatous fluid confirms the B-cell/plasma cell immunophenotype of the lymphoma cells. In addition, the higher concentration of the clonal immunoglobulins in the pleural fluid than in the serum supports that the lymphoma was primary rather than secondary. The direct measurement or detection of immunoglobulins in lymphomatous fluid is not frequently performed in patients with PEL or HHV-8–unrelated PEL-like lymphomas. This may be a potential topic for further study to gain better understanding of these 2 different entities.

Treatment and Outcome

Due to the limited case numbers of HIV-negative, HHV-8–unrelated PEL-like lymphoma, there is no standard therapeutic regimen recommended for treatment. However, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)–like therapy had been used for most of the reported cases, with a combination of rituximab (R-CHOP) in some cases because of the B-cell immunophenotype of most HHV-8–unrelated PEL-like lymphoma, which provides an additional treatment choice compared with PEL. In this study, the mean survival time for patients treated with conventional CHOP or R-CHOP was 10 months in patients deceased at time of report (n = 11) and 22.6 months in patients still alive (n = 11). However, the mean survival time in patients without treatment was 4.3 months in patients reported deceased (n = 4) and 18 months in living patients (n = 6). In addition, Alexanian et al[53] reported that the rate of complete remission or partial remission in patients with HHV-8–unrelated PEL-like lymphoma who had chemotherapy was 82.1% compared with 39.6% in patients with HHV-8–positive PEL. These findings further support that HHV-8–unrelated patients may benefit from the more specific chemotherapy for B-cell lymphoma in addition to having a better survival time than HHV-8–positive PEL patients.[53]

Modified Classification

The term *HHV-8–unrelated PEL-like lymphoma* was originally created to differentiate HHV-8–negative PEL from HHV-8–positive PEL.[6-8] To better understand HHV-8–unrelated PEL-like lymphoma, an initial proposal for classifying NHL involving the body cavities was described by Carbone and Gaidano in 1997.[61] This proposal emphasized the clinical, morphologic, and molecular heterogeneity of effusion lymphomas and was established based on the HHV-8 positivity, EBV status, the presence or absence of c-*myc*, and cellular morphology. In 1998, Ichinohasama et al[21] proposed a 3-tiered classification system based on HHV-8 and c-*myc* status. More recently, Carbone and Gloghini[7] further defined their initial classification with more definitive terminology on PELs: (1) PEL has features that are HHV-8 positive, EBV positive or negative, c-*myc* negative, and morphologically immunoblastic/anaplastic; (2) extranodal large cell lymphoma (HHV-8–unrelated PEL-like lymphoma) has features that are HHV-8 negative, EBV positive or negative, c-*myc* negative, and morphologically immunoblastic/anaplastic; and (3) extranodal Burkitt lymphoma has features that are HHV-8 negative, EBV positive, and c-*myc* positive. Reviewing all cases in this study, we believe that immunophenotypic features are also important in HHV-8–negative lymphomas in addition to the key features used by previous authors for the classification. A modified classification is provided in **Figure 2** based on the system described by Carbone and Gloghini.[7] In this modified proposal, immunophenotypic features, including B cell, plasma cell/indeterminate, and T cell, were added to define each type of HHV-8–negative lymphoma prior to further classification using c-*myc*/8q24, EBV status, and morphology. Using this classification, only the HHV-8–negative effusion lymphoma with plasma cell/indeterminate phenotype would be referred to as HHV-8–negative

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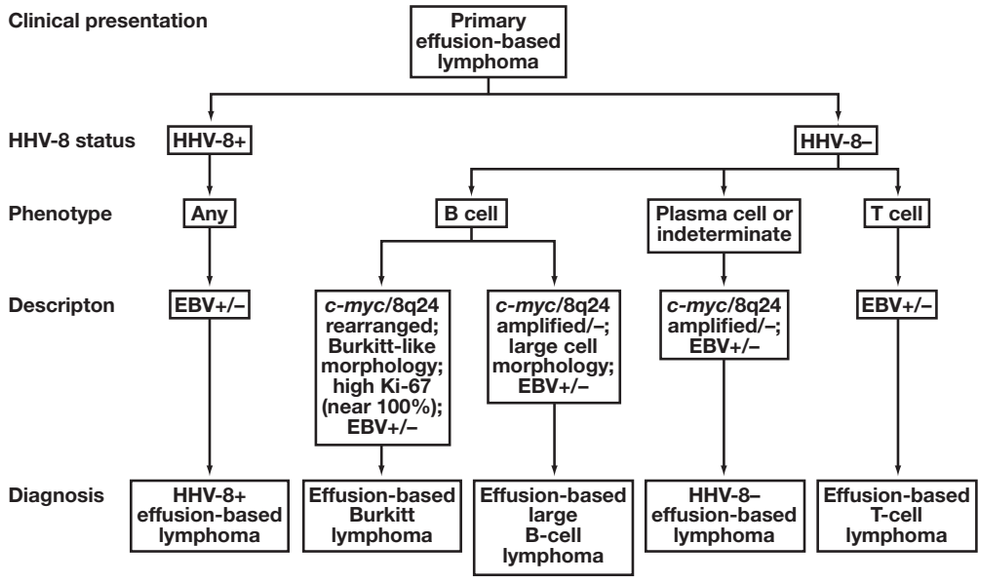

Figure 2 Modified classification of primary effusion-based lymphoma. The hierarchy is modified from the classification system of Carbone and Gloghini[7] by including the immunophenotypic features of HHV-8–unrelated PEL-like lymphomas. HHV-8, human herpesvirus 8; EBV, Epstein-Barr virus; PEL, primary effusion lymphoma.

effusion-based lymphoma as opposed to HHV-8–positive effusion-base lymphoma. All B-cell–type HHV-8–negative lymphomas are divided into effusion-based Burkitt lymphoma and effusion-based large B-cell lymphoma based on the c-*myc* status and morphology. Both these lymphomas essentially belong to Burkitt lymphoma and DLBCL not otherwise specified, respectively, according to the 2008 WHO classification. T-cell type HHV-8–negative lymphomas are classified as effusion-based T-cell lymphoma. Differentiating effusion-based large B-cell lymphoma from effusion-based Burkitt lymphoma when c-*myc* abnormality is present may be challenging, as is the case with some solid lymphomas.

Conclusion

In conclusion, HHV-8–unrelated PEL-like lymphoma is a rare but distinct entity with heterogeneities. Although the mechanism of lymphomagenesis is still largely unknown, it is clear that patients with HHV-8–unrelated PEL-like lymphoma often are immunocompetent and elderly patients, some with underlying medical conditions associated with chronic inflammation that cause fluid overload in body cavities. Most patients test negative for HIV and EBV. The lymphoma cells are large B cells or large B cells with plasmacytic differentiation. The prognosis of HHV-8–unrelated PEL-like lymphoma is better partially due to the targeted treatment available for B-cell lymphoma. Dividing PEL and HHV-8–unrelated PEL-like lymphoma into 2 subgroups will be helpful in managing patients because of the difference in pathogenesis, immunophenotype, clinical behavior, management, and prognosis. Further dividing HHV-8–unrelated PEL-like lymphomas based on immunophenotype in addition to c-*myc*/8q24 abnormalities and morphology is proposed and subject to further study and discussion. Therefore, testing for c-*myc*/8q24 abnormalities should be recommended.

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