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KSHV/HHV8-negative Effusion-based Lymphoma, a Distinct Entity Associated With Fluid Overload States

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Abstract

Human herpesvirus-8 (HHV8)-positive effusion-based lymphomas have been termed primary effusion lymphoma (PEL) in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Kaposi sarcoma herpesvirus (KSHV)/ HHV8-negative effusion-based lymphomas (KSHV/HHV8-negative EBLs) resembling PELs have been reported in the literature and in many cases have been (mis)classified as PEL-like lymphomas. Herein, we present a series of cases and a review of KSHV/HHV8-negative EBLs. This lymphoma, although cytomorphologically resembling PEL, is a distinct entity with characteristic clinical and pathologic features. Patients are older, generally human immunodeficiency virus negative and not immunosuppressed, frequently hepatitis C positive compared with the population baseline, and often have an underlying medical condition leading to fluid overload. The lymphoma cells express pan-B-cell antigens in 86.7%, and CD20 is expressed in 71.1% of the cases. The lymphoma is often of germinal center B or mixed germinal center B/activated B-cell signature with the Hans classifier, and Epstein-Barr virus is positive in nearly 30% of cases. Rare T-cell lymphomas were also reported. Clinical outcomes and response to therapy, including isolated aspiration, are relatively favorable compared with cases of PEL. We suggest that HHV8-negative effusion-based lymphoma is a distinct entity associated with fluid overload states.

Keywords

KSHV/HHV8-associated lymphoma; PEL-like lymphoma; primary effusion lymphoma; body cavity lymphoma; HHV8/KSHV-unrelated lymphoma; effusion lymphoma

Primary effusion lymphoma (PEL) is an uncommon, high-grade, large cell non-Hodgkin lymphoma typically of B-cell lineage that most often presents in immunocompromised patients as serous effusions without a primary tumor mass. Within the World Health Organization (WHO) classification schema, PEL remains unique, as its definition universally mandates the presence of Kaposi sarcoma herpesvirus (KSHV), also named human herpesvirus-8 (HHV8), in neoplastic cells.[1] Morphologically, PEL is characterized by large pleomorphic cells displaying myriad appearances from immunoblastic to anaplastic.

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The characteristic immunophenotypic profile lacks pan-B-cell markers such as CD19, CD20, and CD79a, and both surface and cytoplasmic immunoglobulin with preservation of immunoglobulin heavy-chain hypermutation and lack of MYC gene rearrangements.[1,2]

Numerous reports have emerged in the last 15 years on KSHV/HHV8-negative effusion-based lymphomas (KSHV/HHV8-negative EBL), which demonstrate remarkably similar cytomorphologic characteristics to PEL but differ in immunophenotype, demographics, response to treatment, and clinical outcome. However, without standardized nomenclature to categorize these entities, terms such as PEL-like lymphoma, HHV8-unrelated PEL, body cavity–based high-grade lymphoma, and others have been used in the literature to describe these lymphomas. The resulting confusion and nonuniform diagnoses have thwarted accurate assessment of the pathogenesis, natural history, treatment, and prognosis of such lesions; this situation is made no less frustrating by the abysmal prognosis of classic PEL compared with reportedly better prognosis in PEL-like lymphomas.

Herein we discuss a series of 5 patients seen at our institution, as well as the largest literature review to date of the aforementioned entity, designated as KSHV/ HHV8-negative EBL. We believe that this represents a clinically and pathologically distinct entity compared with PEL; as such, its diagnostic criteria and nomenclature should be standardized in the interest of maintaining international uniformity.

MATERIALS AND METHODS

Cases in the literature were collected through a retrospective analysis of all reports indexed on Pubmed using a combination of the following search terms in both MeSH and non-MeSH queries: Primary Effusion Lymphoma; PEL; KSHV/HHV8 negative effusion lymphoma; Human Herpes Virus 8 lymphoma; and body cavity lymphoma. Cases were included in our study if they met the following inclusion criteria: lack of associated primary solid lymphoid malignancies; cytomorphologic features resembling PEL; and lack of KSHV/HHV8 expression.[3–36] Six cases were excluded because their cytomorphology resembled that of Burkitt lymphoma and/or because of the presence of t(8:22)(q24;q11). We identified 40 cases from the published data and added a series of 5 new cases collected from our institution, bringing the total number of cases to 45.

Individual features of each case were studied, including patient demographics, clinical presentation and site of effusion, lymphoma morphology, immunophenotype, cytogenetic/ molecular characteristics, method of therapeutic intervention, and eventual outcome (Tables 1–3). Cases are listed in order of their appearance in the literature and/or our institution.

Our study was reviewed and approved by the UCLA Institutional Review Board.

Report of Internal Cases

We have summarized the patient demographics, lymphoma characteristics, and clinical outcomes for the internal cases (cases 41 to 45) alongside the data from our literature review (Tables 1–3). The presenting scenario for our patients has been briefly described below.

Case 41—An 85-year-old woman with a history of coronary artery disease status post myocardial infarction and 2-vessel coronary artery bypass graft presented with chest pain and shortness of breath. No lymphadenopathy, or-ganomegaly, or history of lymphoma was noted. Imaging revealed a large left-sided pleural effusion without associated mass lesion. Laboratory studies revealed a white blood cell (WBC) count of 12,960/μL, hematocrit of 33.7%, a platelet count of 469,000/μL, and lactate dehydrogenase (LD) of 586 U/L. Human immunodeficiency virus (HIV) and hepatitis status was unknown. Thoracocentesis extracted 1.2 L of dark tea-colored fluid with an LD of 2161 U/L. Microbiological studies were all negative. Cytomorphologic examination revealed large atypical lymphoid cells with irregular nuclei, multiple prominent nucleoli, coarse chromatin, and moderate cytoplasm. Many cells demonstrated plasmacytoid morphology. The patient declined treatment and opted to be transferred to hospice care, at which point she was lost to follow-up (Tables 1–3).

Case 42—A 29-year-old Egyptian man with a history of complex congenital heart disease status post multiple surgical corrections presented with congestive heart failure. Imaging showed hepatic cirrhosis with splenomegaly and ascites with no lymphadenopathy or other mass lesions. Laboratory studies revealed a WBC count of 7910/μL, hematocrit of 42.9%, a platelet count of 180,000/μL, and an LD of 1104 U/L. HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) studies were all negative. Paracentesis yielded 1.9 L of brown fluid with an LD of 6522 U/L. Microbiological studies were all negative. Cytomorphologic examination revealed neoplastic cells similar in morphology to those described in case 41.

The patient was treated with ifosphamide, carboplatin, and etoposide, followed by an additional round of BCNU, etoposide, cytarabine, melphalan, and an autologous stem cell transplant. However, he developed massive ascites and expired approximately 4½ months after the original lymphoma diagnosis (Tables 1–3).

Case 43—A 45-year-old man with a history of alcoholic cirrhosis status post orthotopic liver transplantation complicated by contraction of HCV presented with altered mental status and worsening abdominal distention. The imaging studies demonstrated an atrophic liver and diffuse abdominal and pelvic ascites without mass lesion or lymphadenopathy. Laboratory studies demonstrated a WBC count of 8300/μL, hematocrit of 33%, a platelet count of 107,000/μL, and an LD of 269 U/L. HBV and HCV studies were positive. Paracentesis extracted 1.9 L of clear fluid. Microbiological studies were all negative. Cytomorphologic features were similar to those described in previous cases (Fig. 1).

The patient received 1 cycle of cyclophosphamide, doxorubicin, vincristine, and prednisolone therapy with resulting neutropenia and sepsis requiring readmission. Rapid decompensation ensued, and the patient expired approximately 1½ months after the initial lymphoma diagnosis (Tables 1–3).

Case 44—A 72-year-old man with a history of coronary artery disease and myocardial infarction status post angioplasty presented to our institution with dyspnea and cough. Imaging demonstrated a pleural effusion. Laboratory studies revealed a WBC count of 7300/μL, hematocrit of 40.8%, and a platelet count of 147,000/μL. Hepatitis and HIV status

was unknown. Cytologic examination of the pleural fluid demonstrated features similar to those described in the previous cases. The patient was subsequently lost to follow-up (Tables 1–3).

Case 45—A 51-year-old man with a history of alcoholic cirrhosis presented with several days of worsening lower extremity edema and paroxysmal nocturnal dyspnea. Imaging revealed mild left-ventricular diastolic dysfunction, a cirrhotic liver, bilateral pleural effusions, borderline splenomegaly, and mild ascites without any lymphadenopathy or mass lesions. Laboratory studies revealed a WBC count of 3600/μL, hemoglobin of 8.3 g/ dL, a platelet count of 48,000/μL, and an LD of 1090 U/ L. HIV, hepatitis A virus, HBV, and HCV studies were all negative. Cytomorphologic examination of the pleural fluid demonstrated numerous large atypical cells similar in morphology to those previously described. The patient's multiple confounding conditions and poor overall constitution led to rapid decompensation, and he expired on the day the lymphoma diagnosis was rendered (Tables 1–3).

RESULTS

Patient Demographics and Clinical Presentation of KSHV/HHV8-negative EBLs

The demographics and clinical characteristics are described in detail in Table 1. The patients were generally elderly (median 70 y) with a slight male-to-female predilection (62.2%). A striking proportion of patients were Japanese (60.0%), and more than half had a documented history of an underlying medical condition leading to fluid overload, including cirrhosis (1 due to HBV, 5 due to HCV, and 4 due to alcohol abuse), protein-losing enteropathy (2 patients), cardiac problems (10 patients), and a ventriculoperitoneal shunt placed 30 years before (1 patient). Seropositivity was observed in 4.9% and 26.5% of patients for HIV and HCV, respectively. Effusions most commonly arose within the pleura (66.7%), followed by the peritoneum (37.8%) and pericardium (26.7%). Multiple sites of effusion were demonstrated in 31.1% of cases, whereas in 1 case the effusion was entirely confined to the scrotum.[16]

Lymphoma Cytology, Immunophenotype, and Molecular Characteristics

The characteristics of lymphomatous cells are described in detail in Table 2. The neoplastic cells were morphologically medium to large with pleomorphic, immunoblastic, or plasmacytoid/plasmablastic morphology. Pan-B-cell antigens, defined as CD19, CD20, CD22, CD79a, or cytoplasmic/surface immunoglobulin, were present in 39 of 45 cases (86.7%). Thirty-two of 45 cases (71.1%) expressed CD20. One case lacked pan-B-cell antigens but demonstrated B-cell gene rearrangement. Two cases showed a T-cell immunophenotype, whereas 3 cases were indeterminate by either immunophenotype or the gene rearrangement studies. Twenty-four of 25 cases (96.0%) in which IgH gene rearrangement was performed demonstrated clonal rearrangement, whereas 1 case demonstrated T-cell gene rearrangement. Eleven of 17 (64.7%) cases carried a complex karyotype. Eleven of 38 cases (28.9%) demonstrated the presence of Epstein-Barr virus (EBV) sequences in malignant cells. The MYC gene demonstrated a germline configuration in 19 of 23 cases (82.6%).

Treatment and Clinical Outcome

Details of the treatment strategy and clinical outcome are outlined in Table 3. Patients were treated with either aspiration/pleurodesis alone (31.0%) or aspiration followed by chemotherapy regimens (69.0%). Three patients received postchemotherapy stem cell transplants, whereas 1 patient underwent an orchiectomy. Three patients had an unknown treatment/intervention course.

Data on the effects of the intervention strategy were available in the majority of cases; of these, complete remission (CR) or partial remission (PR) was achieved in 7 of 10 (70%) of postaspiration-only patients versus 23 of 28 (82.1%) of postchemotherapy patients. Survival and outcome data were available in 38 cases; of these, a subset of patients died of causes not attributable to the underlying lymphoma.[4,5,6,11,17,20,24,33] Of the remaining 30 patients, the mean and the median survival were estimated to be 14.5 and 10 months, respectively, with 46.7% of patients surviving for at least 1 year after diagnosis.

DISCUSSION

In this study, we highlight our experience and published literature on KSHV/HHV8-negative EBLs, the majority of which is seen in individuals with an underlying medical condition such as cirrhosis and heart failure leading to fluid overload states. These cases often present with diagnostic/semantic dilemma for the pathologist, partly because they have not been specifically described in the current WHO classification.

On comparing our data of the 45 cases of KSHV/ HHV8-negative EBLs with a recent literature review of 142 KSHV/HHV8-positive PEL cases,[37] the patterns that emerge strongly suggest that KSHV/HHV8-negative EBL is a distinct entity demonstrating unique demographic, immunophenotypic, and treatment response/survival characteristics (Table 4).

Compared with PELs, patients afflicted with KSHV/HHV8-negative EBLs are older with a median age of 70 years versus 44 years. Patients are less frequently male (62.2% vs. 94.9%). HIV positivity in KSHV/HHV8-negative EBL is uncommon compared with PEL (4.9% vs. 77.5%).[37] Patients of Japanese origin account for 60.0% of reported KSHV/HHV8-negative EBL cases, and more than half of the overall cases occur in patients with a documented history of a medical condition leading to fluid overload, although such a clinical history was not available for PEL cases.

The frequent null phenotype with lack of pan-B-cell markers has historically rendered PEL difficult to diagnose without ancillary studies.[1,2] Although the reported overall expression of pan-B-cell markers in PEL has increased in recent years, its incidence was recently estimated at 39.8%.[37] In the current series of KSHV/HHV8-negative EBL cases (Table 2), 86.7% of cases demonstrated pan-B-cell markers, with most cases expressing multiple such antigens. It is particularly noteworthy that given its therapeutic importance, CD20, the primary target of rituximab, demonstrates striking differential expression; 71.1% in our series versus 15.1% in reported PEL cases.[37] A majority of cases in our series (7 of 9) were demonstrated to have either germinal center B or mixed germinal center B/activated B-cell immunosignatures unlike PEL in which lesional cells are typically of activated B-cell type.[1]

EBV sequences were found in 28.9% of KSHV/HHV8-negative EBL when compared with the 65.6% of PEL.[37] IgH rearrangements are slightly more prevalent in KSHV/HHV8-negative EBL compared with PEL, with a rate of 96.0% versus 81.6%.[37]

In terms of prognosis, whereas PEL confers a uniformly abysmal clinical course on patients, KSHV/ HHV8-negative EBL appears less aggressive overall and may be associated with a more favorable prognosis. Treatments are often more efficacious with aspiration-only or chemotherapy interventions resulting in CR/PR in 70% and 82.1% of KSHV/HHV8-negative EBL patients versus 18.2% and 39.6% of PEL patients, respectively.[37] The response to aspiration-only measures is particularly noteworthy for oncologists given that the older cohort of patients with KSHV/HHV8-negative EBL may be unable to tolerate chemotherapy and will seek alternative treatment modalities with acceptable outcomes; this sort of spontaneous regression has generated much speculation as regards the pathogenesis of KSHV/ HHV8-negative EBL, discussed below. In addition, overall survival encompassing all treatment modalities is considerably improved with a median and >1-year survival rate of 8 months and 42.1% in KSHV/HHV8-negative EBL versus 4 months and 17.3% in PEL, respectively.[37] As previously described, survival statistics further improve when deaths from nonlymphoma causes are excluded, although no comparison data are available.

Numerous reports have in the past tried to address KSHV/HHV8-negative effusion lymphomas to better understand this entity. Ichinohasama et al[5] proposed a potential 3-tiered classification system for effusion lymphomas on the basis of KSHV/HHV8 and MYC status: type I PEL (KSHV/HHV8 positive, germline MYC), type II PEL (KSHV/HHV8 negative, rearranged MYC), and type III PEL (KSHV/HHV8 negative, germline MYC), with the first 2 groups preferentially affecting HIV-sero-positive patients. Although this scheme has been referenced in numerous publications, we do not favor its usage for several reasons. The WHO has clearly stated that the term PEL be restricted to the cases that are KSHV/HHV8 positive. Furthermore, in the proposed system, the authors have labeled as type II PEL cases that were KSHV/ HHV8 negative with MYC gene rearrangement, which may be categorized as Burkitt lymphomas as further pointed out by Nador and colleagues.[2,5]

In a more recent review, Carbone and Gloghini[38] classified effusion lymphomas using a constellation of features including cytomorphology, effusion location, presence of mass lesions, and EBV, KSHV/HHV8, and MYC status; lymphomas were subsequently categorized as primary lymphomas including PEL (KSHV/HHV8 positive, EBV negative, and MYC negative), Burkitt lymphoma (KSHV/HHV8 negative, EBV positive, MYC positive), and possibly KSHV/HHV8-unrelated EBL (KSHV/HHV8 negative, EBV positive or negative, and MYC negative) versus effusion lymphomas arising secondarily from lymphoid malignancies or body cavity–based masses that were KSHV/HHV8 negative. Although intuitive, this model raises the question of whether or not KSHV/HHV8-negative EBL is truly a “primary” lymphoma that arises in effusions secondary to other medical conditions leading to fluid overload. Unlike the classic “secondary” lymphoma, diffuse large B-cell lymphoma associated with chronic inflammation, and its prototype pyothorax association lymphoma, KSHV/HHV8-negative EBL maintains a distinct clinical picture;

there is no radiologically evident thickening of serosal membranes, striking male predominance, or strong association with EBV.[39]

Theories regarding the pathogenesis of KSHV/ HHV8-negative effusions have failed to demonstrate a definite cause. Ichinohasama et al[5] suggested that aberrations in PAX5, a B-cell-specific antigen, may play a role. Ohshima et al[12] subsequently proposed that multistep genomic abnormalities including trisomy 8 and alterations of MYC were involved in lymphomagenesis. Previous epidemiologic studies have shown an association between HCV and B-cell non-Hodgkin lymphoma, which may be partially explained by the lymphotropic properties of HCV triggering clonal B-cell expansion.[40–43] Co-infection with HCV was demonstrated in 26.5% of our cases of KSHV/HHV8-negative EBL, over an order of magnitude higher than the baseline prevalence rate of 2% for hepatitis C in the general population of the United States.[44]

A final suspect in the mechanism of lymphomagenesis that cannot be excluded is the effusion itself. A direct comparison may be drawn with diffuse large B-cell lymphoma associated with chronic inflammation, in which longstanding chronic inflammation of a site hosting EBV-transformed B-cells leads to escape from immune surveillance and subsequent malignant transformation.[1] Rodriguez et al[6] proposed that dysregulation of cytokines in the setting of chronic inflammation may predispose to KSHV/HHV8-negative EBL, a concept furthered by Ashihara et al[7] who argued that localized serositis, in their case due to inflow of cerebrospinal fluid, may lead to transformation of an effusion into a malignant lymphoma. Several features in our case series support this possibility: more than half of the patients in our series had a documented medical condition either predisposing to or immediately causing a fluid overload state; 3 patients had a documented longstanding history of a benign effusion that demonstrated malignancy only after multiple aspirations; 7 of 10 patients achieved spontaneous remission after complete aspiration of their effusion without any additional treatment; 5 patients treated with chemotherapy experienced CR of the malignancy, whereas a benign effusion remained. Although none of these observations rises to the level of a causative association, they all support the concept that the lymphoma may in fact be secondary to a preexisting effusion.

Our study is not, however, without its inherent limitations. Although we have made every effort to meticulously collect data from all reported cases of KSHV/ HHV8-negative EBLs, our study is not a meta-analysis. Individual patients did not possess a standardized work up for their lymphoma in terms of immunophenotypic or cytogenetic/molecular diagnostic panels. Furthermore, the true length of time during which a patient had an effusion before a potential malignant transformation remains unknown in most cases. Finally, whereas the aggregate data demonstrate a favorable overall survival compared with PEL, 3 of our 5 internal cases succumbed to their illness within 4 months of diagnosis. However, given our status as a tertiary-care referral center, our patients tend to present with more advanced disease and liver dysfunction, exacerbating intolerance to treatment and potentially accounting for their poor outcomes.

Although the data above delineate a clear set of unique features in KSHV/HHV8-negative EBL, characteristics similar to PEL remain and have been the impetus for vague

nomenclature over the years. The distinct cytomorphology, location of effusions, lack of solid malignancy, and lack of MYC rearrangements all parallel to that of PEL, and it is precisely this mimicry that has spawned confusing labels such as PEL-like lymphoma and HHV8-unrelated PEL, which is of particular concern given this entity's reported frequency at 20% of overall primary lymphomatous effusions.[38] However, such labels do no service to pathologists, who may be unable to render accurate diagnoses in the absence of agreed-upon criteria, clinicians, who struggle with ideal treatment regimens and inconsistent response data, and patients, who no longer know what survival statistics to believe. So then the question remains—given their uniqueness, where and how should these lymphomas be classified in the pantheon of B-cell lymphomas?

In summary, we have presented data from the largest overall series of KSHV/HHV8-negative EBL cases, including the largest single-institution collection. Our analysis demonstrates that KSHV/HHV8-negative EBLs, although sharing cytomorphologic characteristics with PEL, is a distinct entity: lymphoma cells are KSHV/ HHV8 negative and express pan-B-cell antigens; patients are older with less male predominance, are generally HIV negative, often hepatitis C positive, and often have an underlying medical condition leading to fluid overload; and clinical outcomes and response to therapy are much improved. Furthermore, the striking association with underlying fluid overload states predating the malignant effusion raises the possibility that these lymphomas are in fact secondary to chronic serosal stimulation. Although the WHO description of PEL alludes to reports of KSHV/HHV8-negative EBL arising in the peritoneal cavities of patients with HCV cirrhosis, we believe such patients represent a small subset of a more global entity related to fluid overload at different sites with lymphomagenesis not inextricably tied to HCV.[1] Given the distinct clinicopathologic features of KSHV/HHV8-negative EBL, a provisional subtype of effusion-based KSHV-negative lymphomas may be a consideration.

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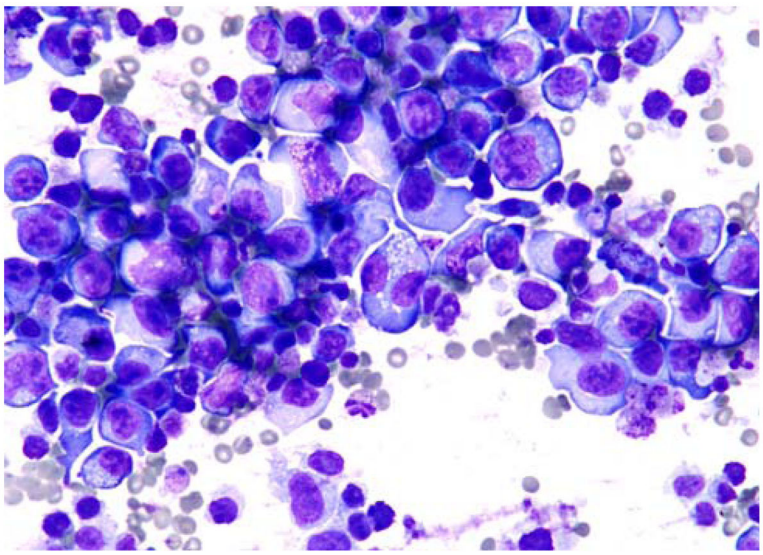

FIGURE 1.

Large, pleomorphic, atypical lymphoid cells with prominent nucleoli, basophilic cytoplasm, and clear vacuoles (Wright-Giemsa).

TABLE 1

Patient Demographics

Case	References	Age	Sex	Clinical History	Effusion	HCV	HIV
1	Hermine et al[3]	52	F	NA	PL, PC	NA	−
2	Carbone et al[4]	58	M	NA	PL, PT	NA	+
3	Carbone et al[4]	90	M	NA	PL	NA	−
4	Ichinohasama et al[5]	63	M	HCV-C; HCC	PT	+	−
5	Rodriguez et al[6]	65	M	EtOH-C; peritonitis, longstanding ascites	PT	−	−
6	Ashihara et al[7]	60	F	Cholesteatoma 30 y earlier with VPS tube	PT	−	−
7	Hara et al[8]	65	M	HCV-C	PT	+	−
8	Yamamoto et al[9]	72	F	NA	PL, PT	NA	−
9	Ohori et al[10]	70	M	HBV-C, s/p OLT 12 y earlier; recurrent HBV-C	PL	NA	NA
10	Saiki et al[11]	58	F	DM; hypothyroidism	PT	+	−
11	Ohshima et al[12]	75	M	NA	PL	NA	−
12	Ohshima et al[12]	32	F	PLE	PT	NA	−
13	Ohshima et al[12]	81	M	NA	PL	NA	−
14	Paner et al[13]	58	M	HCV-C	PT	+	−
15	Hisamoto et al[14]	58	F	CVID	PL, PC	−	−
16	Shimazaki et al[15]	90	F	AF; orthopnea	PL	−	−
17	Nakamura et al[16]	51	M	NA	Scrotal	−	−
18	Chiba et al[17]	55	M	NA	PT	−	−
19	Inoue et al[18]	70	F	DOE	PL, PC	−	−
20	Takao et al[19]	74	F	HCV-C; allergic granulomatous angitis	PL, PC	+	−
21	Nonami et al[20]	32	F	PLE; lymphangiomas; repeated systemic edema and years of chylous ascites	PL, PT	+	−
22	Fujiwara et al[21]	75	F	NA	PC	−	−
23	Jenkins et al[22]	61	M	EtOH-C	PT	−	−
24	Matsumoto et al[23]	90	M	Pulmonary tuberculosis without chronic pyothorax or pneumothorax	PL	−	−
25	Matsumoto et al[23]	87	F	WNL	PL	−	−
26	Venizelos et al[24]	27	F	Renal transplant 5 y earlier	PT	NA	−
27	Youngster et al[25]	88	M	Ischemic heart disease	PL	−	−

Case	References	Age	Sex	Clinical History	Effusion	HCV	HIV
28	Terasaki et al[26]	68	M	WNL	PL	−	−
29	Niino et al[27]	78	M	WNL	PL, PC	−	−
30	Adiguzel et al[28]	89	M	CAD; diabetes; HTN	PL	−	−
31	Tsagarakis et al[29]	77	M	MI; prostate cancer s/p radiation	PL	−	−
32	De Filippi et al[30]	69	M	HCV-C; renal cancer	PL, PT	+	−
33	Taira et la[31]	68	F	NA	PL, PC	−	−
34	Takahashi et al[32]	82	M	NA	PL, PC	−	−
35	Takahashi et al[32]	73	M	NA	PL, PC, PT	−	−
36	Cooper et al[33]	44	F	OA; DM; asthma; cholecystitis; EtOH abuse	PL	+	+
37	Kagoya et al[34]	74	M	DOE	PC	−	−
38	Wang et al[35]	79	M	HTN; OA; AD; DOE	PL	−	−
39	Terasaki et al[36]	99	F	WNL	PL, PC	−	−
40	Terasaki et al[36]	85	M	HTN; AF	PL, PC	−	−
41	This study	85	F	CAD; MI s/p CABG	PL	NA	NA
42	This study	29	M	Complex congenital heart disease s/p multiple surgeries; CHF; cirrhosis	PT	−	−
43	This study	45	M	EtOH-C; s/p OLT & redo OLT with subsequent HCV	PT	+	NA
44	This study	72	M	CAD; MI s/p angioplasty	PL	NA	NA
45	This study	51	M	EtOH-C; anasarca, diastolic dysfunction	PL	−	−

AD indicates aortic dissection; AF, atrial fibrillation; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CVID, common variable immunodeficiency; DM, diabetes mellitus; DOE, dyspnea on exertion; EtOH-C, alcohol-related cirrhosis; HBV-C; HBV-related cirrhosis; HCC, hepatocellular carcinoma; HCV-C, HCV-related cirrhosis; HTN, hypertension; MI, myocardial infarction; NA, not applicable; OA, osteoarthritis; OLT, orthotopic liver transplant; PC, pericardium; PL, pleura; PLE, protein-losing enteropathy; PT, peritoneum; s/p, status post; WNL, within normal limits.

TABLE 2

Lymphoma Characteristics

Case	Morphology	Immunophenotype	EBV	Ph/Ge	IgH	Cytogenetics	*MYC*
1	Large	CD45, CD19, CD20, CD22, HLA-DR	−	B	R	NA	NA
2	Large, pleomorphic	CD45, CD30, LLC	+	B	NA	NA	G
3	Large, pleomorphic	KLC	−	B	NA	NA	G
4	Large	CD45, CD19, CD20, CD22, LLC	−	B	R	t(9:14) & complex karyotype	G
5	Immunoblastic	CD19, LLC	−	B	R	NA	NA
6	Large, pleomorphic	CD45, CD7, CD19, CD20, CD22, HLA-DR	+	B	NA	Complex	G
7	Large, pleomorphic	CD19, CD20, CD22	−	B	R	NA	G
8	Large	CD3, CD7, TCR α-β	NA	T	NA	del(1) (p11p22), +i(7)(ql0), and t(11:14) (q23;q11)	NA
9	Medium to large	CD19, CD20, LLC	+	B	R	NA	NA
10	Pleomorphic	CD4, CD5, CD19, CD20	−	B	R	Hyperdiploid	R
11	Large	CD19, CD20, HLA-DR, KLC, IgM	−	B	R	Complex	G-A
12	Large	CD10, CD19, CD20, HLA-DR	−	B	R	Complex	G-A
13	Large	CD5, CD10, CD19, CD20, HLA-DR	−	B	R	Complex	G-A
14	Large, pleomorphic	CD45, CD10, CD19, CD20, CD22, FMC7, HLA-DR, KLC	−	B	R	NA	NA
15	Large, pleomorphic	CD19, CD20, CD22, HLA-DR	+	B	NA	No anomalies	G
16	Large, pleomorphic	CD20, CD79a, BCL2	−	B	R	NA	R
17	Medium to large	CD19, CD20, CD45, CD79a	−	B	R	46XY	NA
18	Large, plasmacytoid	CD20, CD38, CD45, CD79a, IgM, KLC	+	B	R	Complex	G
19	Large, pleomorphic	CD45, CD8, CD10, CD19, CD20, CD22, CD24, CD71, HLA-DR	−	B	R	Complex	G
20	NA	CD45, CD19, CD20, CD25, HLA-DR, KLC	−	B	R	NA	G-A
21	Large, pleomorphic	CD10, CD19, CD20, HLA-DR	−	B	NA	Complex	G-A
22	Large	CD20, CD79a	−	B	R	t(1;22)(q21;q11),t(14;17)(q32;q23)	G
23	Medium to large, plasmacytoid	CD38, CD138	NA	ID	NA	NA	NA
24	Large, pleomorphic	CD19, CD20, CD30	NA	B	R	Complex	R
25	Large	CD19, CD20, CD30, KLC	NA	B	NA	NA	NA
26	Immunoblastic to anaplastic	CD45, CD3, CD8, CD30	−	T	TCR	NA	NA
27	Large, pleomorphic	CD45, CD20, CD30, CD79a	NA	B	NA	NA	NA
28	Large, pleomorphic	CD20, CD79a	NA	B	R	NA	G

Case	Morphology	Immunophenotype	EBV	Ph/Ge	IgH	Cytogenetics	*MYC*
29	Large, pleomorphic	CD19, CD20, CD22, HLA-DR, LLC, IgM, IgD	+	B	NA	Complex	G
30	Large, immunoblastic	CD45, CD30, CD38, CD71, HLA-DR	−	ID	NA	NA	NA
31	Large, pleomorphic	CD45, CD19, CD20, CD30, CD38, CD66, CD71, CD79a, EMA, LLC	+	B	NA	NA	G
32	Large, plasmacytoid	CD45, CD30, CD38, CD138, LLC	+	B	NA	NA	NA
33	NA	CD10, CD19	NA	B	R	NA	NA
34	Medium to large, plasmacytoid	CD20, CD79a, LLC	+	B	NA	NA	NA
35	Large, pleomorphic	CD20	−	B	NA	NA	NA
36	Large, pleomorphic	CD45, CD10, CD38	+	B	R	NA	R
37	Medium to large	CD20, high Ki67	−	B	NA	NA	NA
38	Large, pleomorphic to centroblastic	CD45, CD20, CD79a, BCL2, BCL6, MUM1	−	B	R	NA	NA
39	Medium to large	CD5, CD19, CD20, CD25, LLC, IgM, IgD	−	B	R	NA	G-A
40	Medium to large	CD20	−	B	R	Complex	G
41	Large, pleomorphic	CD45, CD20, CD79a, CD138, BOB1, OCT2, BCL6, MUM1	−	B	NA	NA	NA
42	Large, pleomorphic	CD45, CD38, CD79a, CD138, PAX5, BOB1, OCT2, KLC	−	B	R	Constitutional paracentric inversion 10q	NA
43	Large, pleomorphic	CD45, CD38, CD56, CD138, KLC, Ki67 > 90%	+	B	G	NA	NA
44	Large, pleomorphic	CD45, CD20, CD30, CD43, BCL2	−	B	NA	NA	NA
45	Large, plasmablastic	CD45, CD25, CD30, CD38, BLIMP1, granzyme, MUM1, TIA1	−	B	NA	NA	NA

G indicates germline; G-A, germline but amplified; ID, indeterminate; KLC, κ light chain restricted; LLC, λ light chain restricted; NA, not applicable; Ph/Ge, phenotype/genotype; R, rearranged.

TABLE 3

Treatment/Clinical Outcome

Case	Therapy	Effect	Overall Survival	Outcome
1	NA	NA	NA	NA
2	Aspiration	NA	5 (mo)	Died (AIDS dementia)
3	Unspecified chemo	Aborted due to toxicity	1	Died
4	Aspiration	Spontaneous CR	2	Died (complications of HCC)
5	CHOP	CR; ascites remained	12	Died (traumatic subdural)
6	Aspiration	Spontaneous CR	24	Alive
7	Prednisolone, etoposide	CR	8	Alive
8	NA	NA	NA	Died
9	NA	NA	8	Alive
10	Aspiration	Spontaneous CR	7	Died (unrelated cerebral bleeding)
11	CHOP	CR	15	Died
12	CHOP, SCT	CR	13	Alive
13	Aspiration	NR	2	Alive
14	COP	PR, multiple recurrences	5	Died
15	Prednisolone	NR	0.6	Died
16	Aspiration	NR	5	Died
17	Orchiectomy, MEP-carboplatin, local radiation	CR	8	Alive
18	CHOP	CR	5	Died (pneumonia/pancreatitis)
19	CHOP, THP-COP, sobuzoxane	CR	18	Alive
20	R+THP-COP	CR	26	Alive
21	THP-COP, SCT	CR	18	Died (extensive bleeding from hemangioma)
22	CHOP	CR	36	Alive
23	Vincristine & cyclophosphamide	CR	NA	Alive
24	R+THP-COP, etoposide	PR	25	Alive
25	Rituximab	CR	28	Alive
26	Endoxan, farmorubicin, oncovin, prezolon	NA	0.7	Died (operative complications)
27	R+CHOP	CR	9	Alive
28	R+CHOP	Spontaneous CR after aspiration maintained after chemo	22	Alive
29	R+THP-COP	CR	30	Alive
30	Aspiration	Spontaneous CR; ascites returned without lymphoma	40	Alive
31	R+COP	NR	3	Alive
32	VelCD	Initial response, then recurrence	2.1	Died
33	CHOP	NR	7	Died
34	R+CHOP	CR; ascites remained	12	Alive
35	R+CHOP	CR; ascites remained	NA	Alive

Case	Therapy	Effect	Overall Survival	Outcome
36	CHOP	PR	2	Died (complications of Mallory Weiss tear)
37	R+CHOP	CR; ascites remained	NA	Died
38	Pleurodesis	Spontaneous CR	55	Alive
39	Aspiration	Spontaneous CR	16	Died
40	Aspiration	Spontaneous CR	11	Alive
41	Aspiration	NA	NA	NA
42	ICE, BCNU-ECM, SCT	Initial response, then recurrence	4.5	Died
43	CHOP	Aborted due to toxicity	1.5	Died
44	Aspiration	NA	NA	NA
45	Aspiration	NR	0.03	Died

AIDS indicates acquired immunodeficiency syndrome; BCNU-ECM, BCNU, etoposide, cytarabine, melphalan; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; COP, cyclophosphamide, vincristine, prednisolone; ICE, ifosphamide, carboplatin, etoposide; MEP, mitoxantrone, etoposide, and prednisone; NA, not applicable; NR, no response; R, rituximab; SCT, stem cell transplant; THP-COP, pirarubicin, vincristine, cyclophosphamide, prednisolone; VelCD, bortezomib cyclo-phosphamide dexamethasone.

TABLE 4

Comparison of KSHV/HHV8-negative EBL and PEL

	KSHV/HHV8- negative EBL	Traditional PEL*
No. cases	45	142
Demographics		
Age, median (range)	70 (27–99)	44 (26–101)
Sex (M/F) [n (%)]	28/45 (62.2)	129/136 (94.9)
Japanese origin [n (%)]	27/45 (60.0)	NA
PMH leading to fluid overload [n (%)]	23/45 (51)	NA
HIV+ [n (%)]	2/41 (4.9)	110/142 (77.5)
Hepatitis C [n (%)]	9/34 (26.5)	8/31 (25.8)
Effusion site		
Pericardium [n (%)]	12/45 (26.7)	33/140 (23.6)
Peritoneum [n (%)]	17/45 (37.8)	53/140 (37.9)
Pleura [n (%)]	30/45 (66.7)	106/140 (75.7)
Multiple [n (%)]	14/45 (31.1)	46/140 (32.9)
Phenotype		
HHV8+ [n (%)]	0/45 (0)	142/142 (100)
Pan-B-cell markers† [n (%)]	39/45 (86.7)	43/108 (39.8)
CD20+ [n (%)]	32/45 (71.1)	15/99 (15.1)
EBV+ [n (%)]	11/38 (28.9)	80/122 (65.6)
IgH rearrangement [n (%)]	24/25 (96.0)	71/87 (81.6)
Achieved CR/PR		
Aspiration only [n (%)]	7/10 (70.0)	6/33 (18.2)
Chemotherapy [n (%)]	23/28 (82.1)	19/48 (39.6)
Survival—all		
Mean (mo)	12.8	NA
Median (mo)	8	4
Survival >1 y [n (%)]	16/38 (42.1)	22/127 (17.3)
Survival—select‡		
Mean (mo)	14.5	NA
Median (mo)	10	NA
Survival >1 y [n (%)]	14/30 (46.7)	NA

*Compared against previously published review from Kobayashi et al.[37]

†Pan-B-cell markers defined as CD19, CD20, CD22, CD79a, and cytoplasmic or surface immunoglobulin.

‡Survival statistics exclude deaths unrelated to lymphoma (traumatic and complications of other underlying medical problems).

PMH indicates past medical history.