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CASE REPORT

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Primary age-related EBV-associated effusion-based lymphoma successfully treated with rituximab and thoracentesis

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Abstract

EBV-positive HHV8-negative EBL is part of the spectrum of EBV-positive diffuse large B-cell lymphoma NOS. This entity can be labeled as primary age-related EBV-associated EBL and appears to respond well to rituximab and thoracentesis.

KEYWORDS

aEBV-EBL, age-related EBV-associated effusion-based lymphoma, EBL, EBV-positive DLBCL-NOS, EBV-positive HHV8-negative effusion-based lymphoma

1 | INTRODUCTION

We report a 98-year-old patient with primary age-related EBV-associated effusion-based lymphoma (aEBV-EBL) in the setting of persistent transudative pleural effusion. He was treated with rituximab and thoracentesis achieving complete remission. We suggest that aEBV-EBL is a subtype of EBV-positive HHV8-negative EBL, which is part of the EBV-positive DLBCL-NOS spectrum.

Primary human herpesvirus 8-negative effusion-based lymphoma (HHV8-negative EBL) is a distinct category of non-Hodgkin lymphoma which manifests as a serous effusion without a distinct tumor mass. The hallmark of a HHV8-negative EBL diagnosis is negativity for HHV8 infection, thereby distinguishing itself from primary effusion lymphoma (PEL) which requires the presence of HHV8 infection.[1] HHV8-negative EBL has been found in association with hepatitis C virus (HCV) infection, fluid overload, liver cirrhosis, renal dysfunction, cardiac arrhythmias, myocardial infarction, and heart failure.[2-5] Epstein-Barr virus (EBV) infection has been reported in 13% of HHV8-negative EBL cases.[3] EBV-positive and HHV8-negative EBL have been reported in patients with liver disease, HIV, lymphocytopenia, common variable immunodeficiency, solid organ transplant, and renal disease.[2,6-10]

EBV-positive DLBCL-NOS is a well-defined entity in the World Health Organization (WHO) classification of B-cell lymphomas. EBV-positive and HHV8-negative EBL can be defined as EBV-positive DLBCL-NOS primarily presenting as EBL. Age-related EBV-associated DLBCL, another well-known entity seen in elderly patients, is also recognized as part of the spectrum of EBV-positive DLBCL-NOS.[11,12] This entity is known to follow an aggressive clinical course when compared against EBV-negative DLBCL.[13,14]

Herein, we report an extremely rare case of primary age-related EBV-associated effusion-based lymphoma in a 98-year-old man who achieved complete remission following rituximab monotherapy and thoracentesis. We further discuss

EBV-positive and HHV8-negative EBL based on medical literature review.

2 | CASE REPORT

A 98-year-old man with a history of congestive heart failure (CHF) with preserved ejection fraction and related chronic bilateral small to moderate sized pleural effusions for 3 years (right > left), permanent atrial fibrillation, coronary artery disease, and hypertension presented with progressive shortness of breath, fatigue, and 10 pound weight loss over the course of 3 months. His history is significant for recurrent worsening of his right-sided pleural effusion with no evidence of malignant cells on repeated thoracentesis.

However, upon his presentation with worsening shortness of breath approximately twenty months prior to writing this report, he underwent thoracentesis with cytology testing leading to the diagnosis of effusion-based large B-cell lymphoma. Immunohistochemistry (IHC) studies were performed on the paraffin-embedded cell block. Cytospin slides with modified Giemsa-Wright (GW) stain showed markedly increased atypical large mononucleated cells with abundant blue cytoplasm, open chromatin, and prominent nucleoli (Figure 1A); these atypical large cells were also present in the hematoxylin and eosin (H&E) stained slide from cell block (Figure 1B). These large cells expressed B-cell markers including CD20 (Figure 1C) and CD79a. They were also positive for BCL2 and BCL6 (focal), and CD30 with high proliferative rate (~90%) by Ki-67. In situ hybridization for EBV-encoded small RNA (EBER ISH) was positive. The IHC for HHV8 (Figure 1D-I), CD15 and CD138 were negative.

A computed tomography (CT) scan of the chest and abdomen with contrast did not show any evidence of disease outside the right pleural cavity. Positron emission tomography

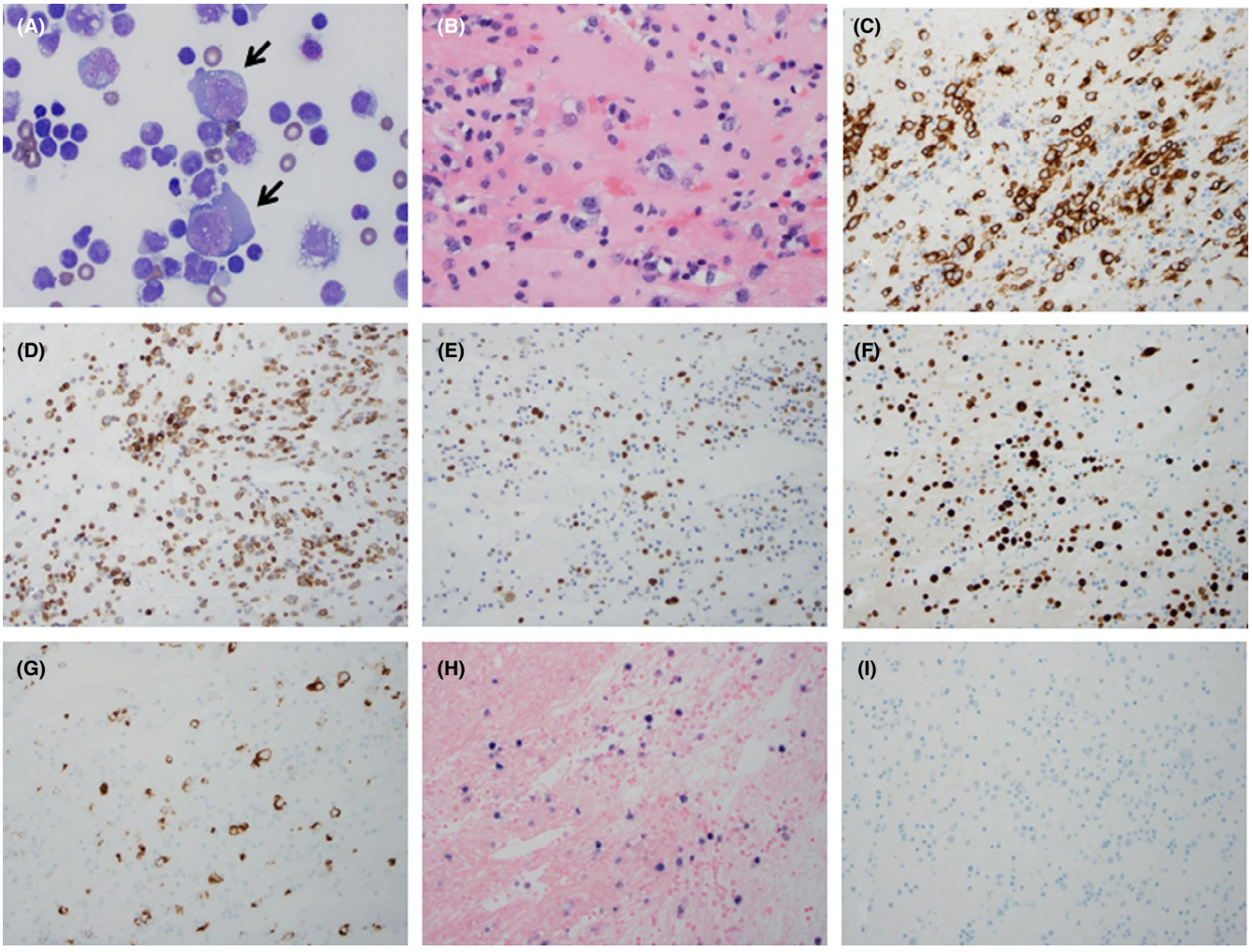

FIGURE 1 The slides from cytospin and cell block revealed large atypical cells (A, GW stain x 50, arrows; B, H&E stain x 40). Immunohistochemical studies demonstrated that the neoplastic lymphocytes were positive for CD20 (C, x20), BCL2 (D, x20), BCL6 (E, x20), with a high proliferative rate by KI-67 (F, x20). A subpopulation was positive for CD30 (G, x20) and EBER ISH (H, x20). Immunostaining for HHV8 was completely negative (I, x20)

(PET) scan confirmed the CT scan findings, demonstrating a right-sided pleural effusion without any corresponding hypermetabolic activity in the right pleural cavity (Figure 2). HBV, HCV, and HIV serological testing were negative. EBV testing by polymerase chain reaction was positive on peripheral blood. The patient was deemed a poor candidate for intensive therapy with chemo-immunotherapy regimen due to his age and multiple comorbidities. He was treated with an 8-week course of weekly rituximab 375mg/m2. The patient tolerated the treatment well. Follow-up chest x-rays were conducted every 1-3 months, demonstrating mild to moderate residual effusion volumes which were stable. Following completion of rituximab therapy, the patient eventually required another right-sided thoracentesis approximately seventeen months after initial presentation for recurrent effusion, but the cytology results were negative for any lymphoma cells indicating pathologic remission. As such, the patient's persistent effusion was related to CHF and not secondary to lymphoma. Further, quantitative testing for EBV PCR following treatment with rituximab returned negative. Consequently, the patient is deemed to be in remission and has been alive and clinically stable for over 22 months since the time of diagnosis.

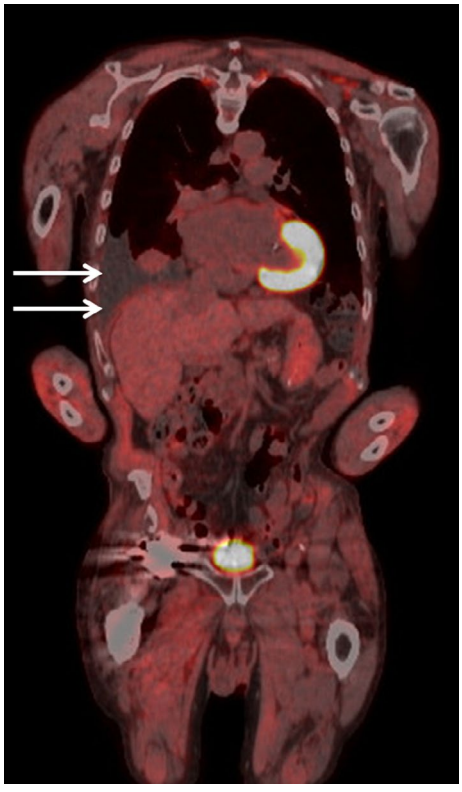

FIGURE 2 PET scan demonstrating right-sided pleural effusion with no corresponding hypermetabolism (arrows). Effusion confined to right pleural cavity; no hypermetabolic activity noted elsewhere

3 | DISCUSSION

In contrast to PEL, HHV8-negative EBL is characterized by the absence of HHV-8 infection and is an etiologically heterogeneous group of lymphomas.[1] Because it is such a rare disease, the relative prevalence of HHV8-negative EBL is not definitively known. Typically affecting older adults, one case series involving 17 patients with HHV8-negative EBL reported a median diagnostic age of 86 years.[9] Unlike PEL, which typically carries a poor prognosis due to resistance to chemotherapy, the estimated overall survival for patients with HHV8-negative EBL at 2 years following diagnosis has recently been reported to be as high as 84.7%.[3] Alexanian et al also reported that the overall response to chemotherapy in patients with HHV8-negative EBL was 82.1% compared with 39.6% in patients with PEL.[2] In another review, treatment with aspiration only or chemotherapy in HHV8-negative EBL patients was far more efficacious than in PEL patients; complete or partial remission was attained by aspiration or chemotherapy in 70% and 82% of HHV8-negative EBL patients versus 18% and 39% of PEL patients, respectively.[15] These and other similar findings support the necessity for distinguishing HHV8-negative EBL from PEL as the prognosis and treatment options differ significantly between these two entities.

In order to properly diagnose and distinguish HHV8-negative EBL from other entities such as PEL, IHC and morphology examination is extremely important. Unlike PEL, whose morphology is either large cell or small Burkitt-like, morphology in HHV8-negative EBL is predominantly large cell type with B-cell phenotype. Morphologically, HHV8-negative EBL typically consist of predominantly large cells with irregular nuclear contours, coarse chromatin, multiple conspicuous nucleoli that are often pleomorphic, and abundant vacuolated cytoplasm.[16] IHC usually confirms B-cell origin in HHV8-negative EBL. In one case series, 86.7% of HHV8-negative EBL cases demonstrated pan-B-cell markers whereas the incidence of pan-B-cell markers in PEL has been reported at 39.8%.[2,15] The same series showed that 71% of HHV8-negative EBL patients carried CD20 positivity versus 15% in PEL. As such, CD20-targeted therapy using monoclonal antibodies such as rituximab can be employed in most cases of HHV8-negative EBL. Moreover, CD20 expression is a biomarker for better overall survival in HHV8-negative EBL patients.[17]

In the case of our patient, CD20 positivity provided us with a targetable and less toxic treatment option in comparison to standard chemotherapy. Furthermore, immunostaining for HHV8 and plasma cell marker CD138 were both negative, eliminating a possible PEL diagnosis. It is also worth noting that a diagnosis of diffuse large B-cell lymphoma associated with chronic inflammation/pyothorax was ruled out in our patient because of a lack of history of long-standing chronic inflammation or pyothorax.

TABLE 1 Clinical characteristics of 16 patients with HHV8(-) and EBV(+) effusion-based lymphoma reported in the medical literature

Author	Case	Age/Sex	Site	Comorbidities	Therapy & Outcome
Ohori et al 2001[6]	#1	70/M	Pleura	Hepatitis B (HBV), liver transplant, Hepatocellular carcinoma (HCC)	Radiation for HCC; prednisone; Alive; 8 mo
Tsagarakis et al 2009[8]	#2	77/M	Pleura	Myocardial infarct, Idiopathic CD4 T-lymphocytopenia, prostate carcinoma	Rituximab, cyclophosphamide, vincristine, prednisone; Alive; 3 mo
Usmani et al 2015[9]	#3	57/M	Peritoneum	ESRD on dialysis, s/p heart transplant	CHOP; Lost to follow-up at 6 mo
Ashihara et al 2001[29]	#4[a]	60/F[a]	Peritoneum	Cholesteatoma	Alive; 24 mo
Rodriguez et al 2001[7]	#5	65/M	Peritoneum	Cirrhosis, alcohol abuse	Cyclophosphamide, doxorubicin, vincristine, prednisone; Died; 12 mo
Chiba et al 2003[25]	#6	55/M	Peritoneum	Autoimmune hemolytic anemia	Cyclophosphamide, doxorubicin, vincristine, prednisone; Died; 2 mo
Alexanian et al 2013[2]	#7	45/M	Peritoneum	Alcohol-cirrhosis, liver transplant with subsequent HCV and HBV	Cyclophosphamide, doxorubicin, vincristine, prednisone; Died; 1.5 mo
Koboyashi et al 2007[15]	#8[a]	70/F[a]	Pleura/ Peritoneum	None described	Pirarubicin, cyclophosphamide, vincristine, prednisolone; Died; 26 mo
De Filippi et al 2009[30]	#9	69/M	Pleura/ Pericardium	Cirrhosis, renal cell carcinoma, Hepatitis C	Bortezomib, cyclophosphamide, dexamethasone; Died; 2.25 mo
Hisamoto et al 2003[10]	#10	58/F	Pleura/ Pericardium	Common variable immunodeficiency	Prednisolone, etoposide; Died; 0.5 mo
Niino et al 2008[31]	#11	78/M	Pleura/ Pericardium	Idiopathic CD4 T-lymphocytopenia	Rituximab, pirarubicin, cyclophosphamide, vincristine, prednisolone; Alive; 30 mo
Takahashi et al 2010[36]	#12[a]	82/M[a]	Pleura/ Pericardium	None described	Drainage; rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; Alive; 21 mo
Cooper et al 2010[26]	#13	44/F	Pleura/ Peritoneum	HIV, HCV, DM, asthma, alcohol abuse, spinal osteoarthritis	Cyclophosphamide, doxorubicin, vincristine, prednisone, HAART; Died; 2 mo
Carbone et al 1996[27]	#14	58/M	Pleura/ Peritoneum	HIV	None; Died; 5 mo
Nador et al 1996[28]	#15	33/M	Peritoneum	HIV	Chemotherapy; Died; 6 mo
Nador et al 1996[28]	#16	36/M	Peritoneum	HIV	None described; Died; Unknown

[a]Possible cases of primary age-related EBV-associated effusion-based lymphoma.

Due to the limited number of cases of HHV8-negative EBL, there is no standard therapeutic regimen for treatment. However, therapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) had been used for most reported cases in combination with rituximab (R-CHOP) when CD20 is positive. Rituximab targeting CD20 has demonstrated significant benefit in selected patients according to multiple reports.[18] One case of HHV8-negative EBL in the pericardium was treated with 8 doses of rituximab over a 2 month period, resulting in complete response for >12 months.[19] In another report, two older patients with HHV8-negative EBL, ages 90 and 87, were treated with rituximab alone and demonstrated complete remission.[18] Interestingly, reports of patients being treated with thoracentesis alone have also demonstrated positive responses in older patients with a poor functional status.[20] One report

documented an 89-year-old patient treated with thoracentesis and pleurodesis before remaining in complete remission for 40 months.[21] This excellent response to aspiration alone is significant as HHV8-negative EBL afflicts primarily older patients who often carry a poor functional status and predictably poor outcome in the setting of toxic effects from systemic chemotherapy.

In the absence of HHV8 infection, EBV can be a driver of EBL. In our patient, EBL appears to be EBV-driven and fits the profile of age-related EBV-associated DLBCL-NOS, which has been described in predominantly elderly patients without any predisposing immunodeficiency or HIV infection.[12] Age-related EBV-positive DLBCL-NOS, also known as "EBV-positive DLBCL of the elderly," is thought to be related to waning of T-cell-mediated EBV immunity and physiological immunosenescence associated with the aging process.[22,23] Typically manifesting at nodal sites, age-related EBV-positive DLBCL-NOS can also infrequently present at extranodal sites, including the skin, lung, stomach, tonsils, and pleural effusion.[12,24] We propose that EBV-positive HHV8-negative EBL in otherwise immunocompetent elderly patients is a part of the spectrum of age-related EBV-positive DLBCL-NOS and represents a unique entity which can be labeled as primary age-related EBV-associated effusion-based lymphoma (aEBV-EBL).

Our literature review identified sixteen cases of EBV-positive HHV8-negative EBL (Table 1).[2,6-8,10,15,27-31] Composed of etiologically heterogeneous patients, the majority had some form of immunodeficiency as indicated by a prior history of immunodeficiency syndromes, HIV, and orthotopic liver transplant (OLT). The two OLT patients appeared to develop EBV-positive post-OLT lymphoproliferative disorder manifesting as primary EBL. Similar to our patient, three out of the sixteen patients did not appear to have any evidence of immunodeficiency. These three patients, aged 60, 70, and 82, likely had aEBV-EBL. Although the mechanism behind homing of the lymphoma to effusion fluid is unknown, it is possible that EBV-directed homing and cytokine milieu in the effusion fluid results in EBV-positive EBL.[32] Mechanistically, activated NF-kB and JAK/STAT signaling pathways promoting cell proliferation and survival play an important role in the biology of age-related EBV-positive DLBCL.[33,34] It is also worth mentioning that age-related EBV-positive DLBCL has been described as an aggressive lymphoma since worst outcomes are associated with EBV-positive DLBCL when compared against EBV-negative DLBCL.[14,24,35] However, in the three cases of possible aEBV-EBL, survival outcomes appear to be quite favorable. Similarly, our patient has done quite well with the least intensive approach, indicating that age-related EBV-positive DLBCL-NOS presenting as EBL may carry a better prognosis.

In conclusion, aEBV-EBL is a rare and unique subtype of age-related EBV-positive DLBCL and appears to be quite responsive to CD20-targeted therapy with an excellent survival outcome. Additional research is warranted to further define this lymphoma entity.

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CONFLICT OF INTEREST

The authors have no potential conflict of interest in regards to the contents of this manuscript.

AUTHOR CONTRIBUTIONS

Dr Justin J. Kuhlman: Conceptualization, writing—original draft preparation, reviewing, and editing. Dr Muhamad Alhaj Moustafa: supervision, conceptualization, formal analysis, reviewing, and editing. Alexander J. Tun: conceptualization, writing, reviewing, and editing. Dr David M. Menke: methodology for pathology contributions, reviewing, and editing. Dr Han W. Tun: supervision, project administration, formal analysis, conceptualization, reviewing, and editing. Dr Liuyan Jiang: supervision, project administration, methodology for pathology contributions, reviewing, and editing.

ETHICAL APPROVAL

The authors attest that the current work is an original manuscript without direct overlap with other texts and that there has been no ethical misconduct during the preparation or submission of this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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