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CASE REPORT

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HHV8-unrelated primary effusion lymphoma in a patient with HBV-related liver cirrhosis: A case successfully treated with rituximab and lenalidomide

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Abstract

Human herpesvirus type 8 (HHV-8) unrelated primary effusion lymphoma (PEL) like lymphoma (PEL-LL) is an exceedingly rare non-Hodgkin lymphoma with no characteristic symptoms and consensus on the optimal treatment. This case report presents a 55-year-old man with prior HBV-related Child-Pugh B liver cirrhosis and developing activity-related dyspnea. A moderate amount of pleural effusion was identified without tumor masses, and cytological studies confirmed a diagnosis of PEL-LL. The patient received rituximab and lenalidomide, albeit with HBV infection, and is currently on maintenance therapy with resolving symptoms but without HBV reactivation. Hence, the R2 protocol (rituximab and lenalidomide) might be clinically effective and safe for PEL-LL patients with HBV infection and Child-Pugh B liver cirrhosis.

KEYWORDS

HBV, HHV-8, lenalidomide, PEL-LL, rituximab

1 | BACKGROUND

Primary effusion lymphoma (PEL) is a rare subtype of non-Hodgkin lymphoma (NHL), characterized by malignant pleural, pericardial, or peritoneal primary effusions without distinguishable extra-cavitary tumor masses and is found tightly associated with human herpesvirus type 8/Kaposi sarcoma-associated herpes virus (HHV8/KSHV) and sometimes coinfected with Epstein–Barr virus (EBV).[1] Although HHV8-unrelated PEL-like lymphoma (PEL-LL) is morphologically indistinguishable from PEL, they present with distinctive cell markers. PEL-LL is universally positive for pan-B cell markers (CD19, CD20, and CD79a), commonly expressing BCL-2 and MUM1, rarely positive for plasma cell differentiation markers (CD138), and negative for CD10 and light chain restriction, whereas PEL is negative for pan-B cell markers (CD19, CD20, CD79a) but usually positive for CD45, CD30, CD38, CD71, epithelial membrane antigen, CD138, VS38c, and MUM-1/IRF4.[2,3] Recent studies found PEL-LL to be associated with underlying medical conditions (e.g., liver cirrhosis) and fluid overload.[4] In clinical practice, despite the relatively indolent nature of PEL-LL, the high prevalence of underlying medical conditions such as HBV-related liver cirrhosis

still significantly challenged treatment planning. Herein, we report a case of HHV8-unrelated PEL-LL with underlying HBV-related liver cirrhosis successfully treated with rituximab and lenalidomide (R^2 protocol).

2 | CASE REPORT

A 55-year-old male patient visited his primary medical care for progressing activity-related dyspnea within 20 days. He was on anti-HBV therapy (Entecavir, p.o., 0.5 mg, qd) due to HBV infection and liver cirrhosis. He was identified with a moderate amount of right-sided pleural effusion and a mild amount of ascites but no pulmonary or pleural masses by physical examination and chest CT and was referred to our institute for further workup.

His initial blood count revealed pancytopenia (leukocytes: 3.31 × 109/L [ref: 3.50–9.50109/L]; erythrocytes: 3.55 × 1012/L [ref: 4.30–5.80 × 1012/L]; hemoglobulin: 72 g/L [ref: 130-175 g/L]; and platelets: 14 × 109/L [ref: 125–350 × 109/L]). A hepatic evaluation revealed Child-Pugh B liver cirrhosis (album: 2.69 g/dL↓ [ref: 4, 5.5 g/dL], partial thromboplastin time:16.9 s, and mild ascites), inactive HBV infection (HBV surface antigen: 6086.000COI [ref: <0.9999 COI], HBV-DNA < 20.00 IU/mL), and slightly elevated γ-Glutamyl transpeptidase 95 U/L↑ (ref: 10–60 U/L). Although hepatic hydrothorax might manifest as a right-sided pleural effusion, the moderate dysfunction (Child-Pugh B liver cirrhosis) and unsatisfactory response despite active anti-HBV treatment lead to a further workup to exclude malignancies.

Paracentesis of the right pleural cavity was performed, and the cytological study identified a large amount of atypical large cells which are positive for CD20 (+++), CD79a (+++), Bcl6 (+), MUM1 (30%+), Bcl2 (>90%+), c-myc (30%+), and Ki67 (50%+), but negative for HHV8-LAN1, EBER, and CD10 in immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) studies (Figure 1). Subsequent bone marrow biopsy identified no malignancy, and a whole-body PET/CT scan found no active malignancies other than effusions (Figure 2). Therefore, we concluded the diagnosis of HHV8-unrelated PEL-LL.

Considering the HBV-related Child-Pugh B liver cirrhosis, we continued the anti-HBV therapy and initiated a less intensive chemotherapy protocol (R^2 protocol, 28 days per cycle: Rituximab, 375 mg/m2 i.v., Day 1; lenalidomide 25 mg p.o. qn, Days 1-21) for 8 cycles, after achieving an improvement of ECOG performance status (PS 1 from 2) by intensive supportive care. The patient was on lenalidomide maintenance and anti-HBV therapies for 14 months with resolved symptoms without reactivation of HBV infection; however, unfortunately, he succumbed to COVID-19-related pneumonia.

3 | DISCUSSION

The diagnosis of PEL-LL can be highly challenging, as the histological evidence sometimes can be difficult to acquire, and it might necessitate multiple attempts to conclude the diagnosis. On the contrary, single-sided malignant pleural effusion was more frequently caused by malignancies arising from the lung or pleura. Hence, PET/CT might help with the diagnosis, and multiple cytological studies might be necessary to confirm the diagnosis. Although hepatic

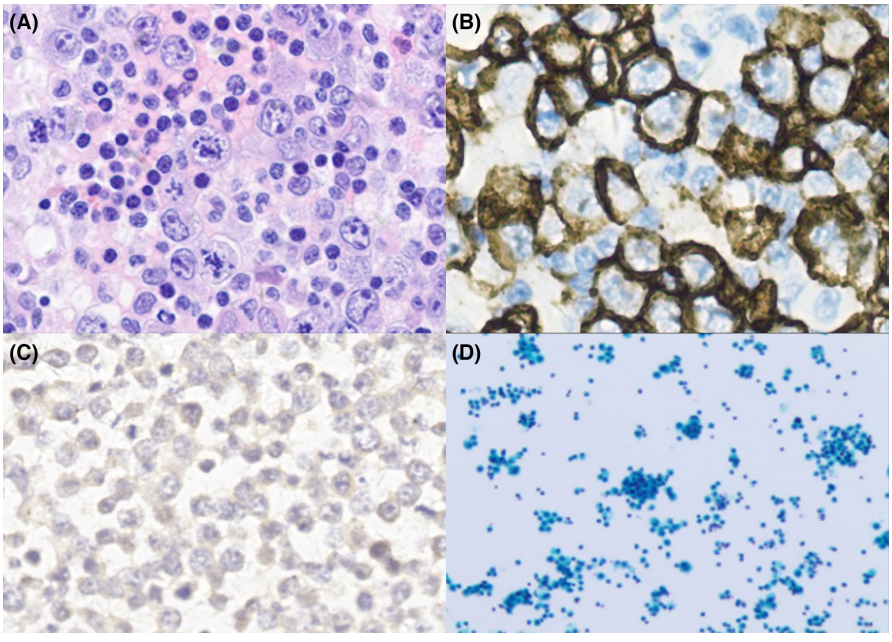

FIGURE 1 Histological findings of thin-prep cytological test (TCT) made from the pleural effusions. Pretreatment histological examination found abundant atypical cells with pathological mitoses in hematoxylin and eosin staining with a magnification of 400 (A). These cells are strongly positive for CD20 (B) but negative for HHV8-LAN1 (C). Mid-treatment histological study revealed no atypical cells (D).

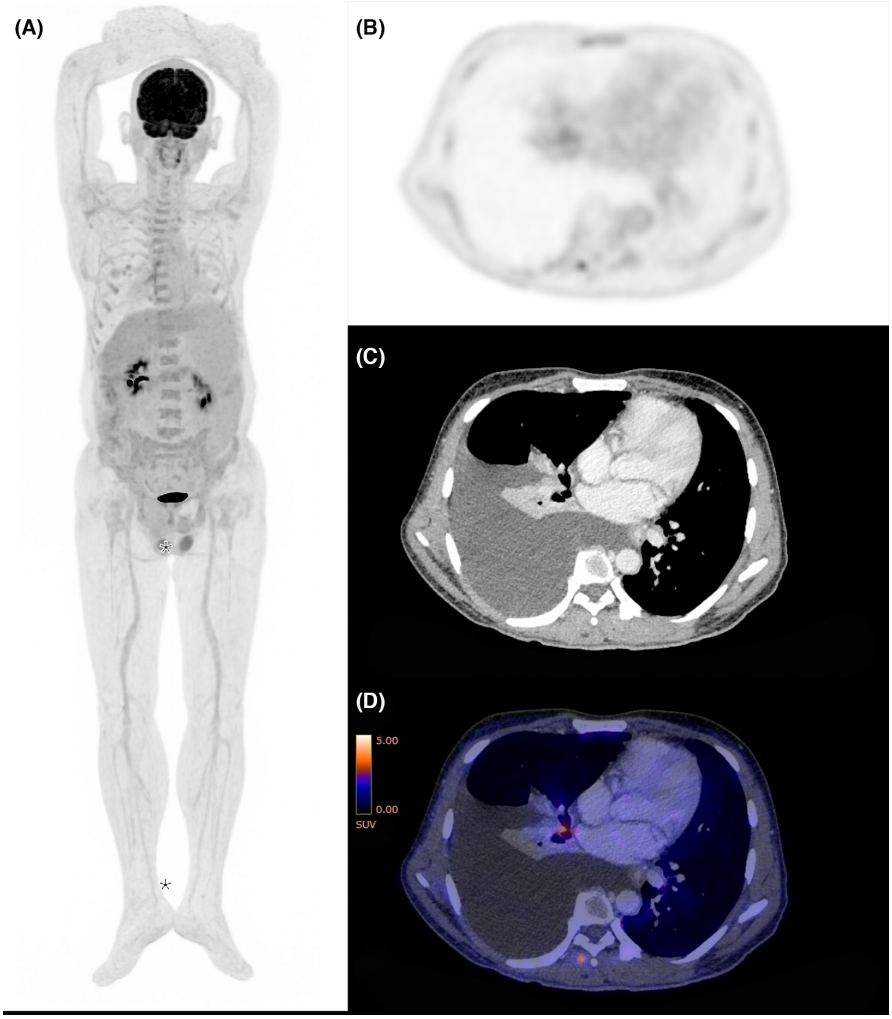

FIGURE 2 Whole-body PET/CT with contrast enhancement. (A): whole-body PET imaging in the maximum intensity projection (MIP) showed unremarkable findings. (B, C), and (D): the PET, contrast-enhanced CT, and fusion imaging in the transaxial plane showed a moderate amount of right-sided pleural effusion (asterisk) with no active pulmonary or pleural malignancies.

hydrothorax, a situation common in patients with liver cirrhosis, usually causes right-sided pleural effusion,[5,6] we did not conclude this diagnosis mainly due to the limited response to aggressive clinical management of liver cirrhosis.

The optimal treatment for PEL-LL with synchronous HBV-related liver cirrhosis is yet under debate. Prior studies found chemotherapies such as R-CHOP, CHOP, Hyper-CVAD (reduced dose), DA-EPOCH, or even single agent treatment, such as rituximab or methylprednisolone alone, effective for PEL-LL.[2,7] Some patients might experience disease resolution even with single pleural paracentesis.[7] However, in our case, the treatment planning was a dilemma. As this patient is positive for CD20, rituximab might be optimal. However, rituximab is known to reactivate the HBV infection and promote the development of liver failure.[8] On the contrary, lenalidomide, an immune modulator, was found to induce apoptosis of B-cell-originated malignancies and inhibit HBV reactivation. Although there lenalidomide-related HBV reactivation was reported, the incidence was extremely low, and continuing anti-HBV treatment is sufficient to inhibit HBV reactivation and therefore to reduce the risk of liver failure.[9] Hence, the combination of the R2 protocol and anti-HBV treatment might be clinically feasible and effective.[10]

4 | CONCLUSIONS

PEL-LL presents with no characteristic clinical symptoms and might be masked by other diseases, such as HBV-related liver cirrhosis. R^2 protocol (rituximab and lenalidomide) might be clinically effective and safe for PEL-LL patients with Child-Pugh B liver cirrhosis.

AUTHOR CONTRIBUTIONS

Peng-Jun Liao: Study design, data collection, data interpretation, literature search and manuscript preparation. **Hui Yuan**: Data interpretation, literature search, and manuscript preparation. **Xiao-Juan Wei**: Project management, study design, data interpretation, literature search, and manuscript preparation.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

DATA AVAILABILITY STATEMENT

The data supporting this study's findings are available from the corresponding author, XJ Wei, upon reasonable request.

CONSENT STATEMENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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