

Original Research

Clinicopathologic and molecular features of primary effusion lymphoma and fluid overload-associated large B-cell lymphoma: A retrospective study

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ABSTRACT

Primary effusion lymphoma (PEL) and fluid overload-associated large B-cell lymphoma (FO-LBCL) are rare B-cell neoplasms presenting as serous effusions without solid masses, distinguished primarily by human herpesvirus-8 status. We analyzed three PEL and seven FO-LBCL cases using immunohistochemistry, Epstein-Barr virus-encoded RNA in situ hybridization, immunoglobulin heavy chain (*IGH*), T-cell receptor beta (*TRB*) and T-cell receptor gamma (*TRG*) gene rearrangement analyses, and targeted next-generation sequencing. The median age was 72 years for PEL and 83 years for FO-LBCL. All PEL cases lacked CD20, whereas FO-LBCL tumors retained pan-B-cell markers. Aberrant T-cell antigen expression was observed in two PEL cases, both showing clonal T-cell receptor rearrangements in addition to *IGH* clonality. FO-LBCL harbored recurrent alterations involving *CD79B*, *PIM1*, and *MYD88*, suggesting partial molecular overlap with the molecular features characteristic of the MCD subtype of diffuse large B-cell lymphoma (DLBCL). Clinically, all patients with PEL died of disease, whereas FO-LBCL appeared to have a more favorable clinical course, with four patients remaining alive at the last follow-up. Despite morphologic overlap, PEL and FO-LBCL showed distinct immunophenotypic, genetic, and clinical features. These preliminary findings support further investigation of B-cell receptor/NF- κ B-related signaling pathways in FO-LBCL and may contribute to improved molecular classification and future therapeutic stratification.

Introduction

Primary effusion lymphoma (PEL) and fluid overload-associated large B-cell lymphoma (FO-LBCL) are rare B-cell neoplasms that present as serous effusions without detectable tumor masses [1,2]. Although PEL and FO-LBCL have overlapping cytomorphologies, these entities differ in their virologic associations, immunophenotypes, and clinical courses. PEL is uniformly associated with human herpesvirus-8 (HHV-8) and frequently shows a loss of pan-B-cell markers with aberrant expression of T-cell antigens [3,4]. In contrast, FO-LBCL is consistently HHV-8 negative, retains B-cell lineage markers, and generally demonstrates a

more indolent clinical behavior [2,5].

In parallel, advancements in genomic profiling have refined the molecular taxonomy of diffuse large B-cell lymphoma (DLBCL), leading to the recognition of distinct genetic subtypes. Among these, the *MYD88/CD79B* (MCD) subtype—defined by co-occurring *MYD88*^{L265P} and *CD79B* mutations—has been particularly associated with the non-germinal center/activated B-cell phenotype and a predilection for immune-privileged sites, such as the central nervous system and testes [6–8]. Although FO-LBCL has not been formally assigned to this framework, limited genomic reports have identified *MYD88* and *CD79B* mutations in some cases [9,10] suggesting a potential biological link to

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the MCD subtype.

Despite these observations, PEL and FO-LBCL have not been fully defined at the molecular level, and to the best of our knowledge, no prior studies have integrated their genetic differences with the underlying pathogenesis or contextualized them within a broader DLBCL spectrum. Given the diagnostic and therapeutic challenges associated with effusion-based lymphomas, a better understanding of their molecular basis is essential for elucidating their cellular origin and pathogenic mechanisms, which may ultimately improve clinical management. We hypothesized that PEL and FO-LBCL, despite their morphologic similarity, represent biologically distinct entities with differing pathogenetic mechanisms and genetic profiles. To address this, we performed an integrated clinicopathological and molecular analysis to delineate their biological differences and provide insights for future diagnostic and therapeutic strategies.

Methods

Case selection

All cases of PEL and FO-LBCL were retrospectively collected from Korea University Anam Hospital and Guro Hospital between 2022 and 2024. A total of three PEL cases (PEL group) and seven FO-LBCL cases (FO-LBCL group) were included. Cases were selected if they presented with body cavity effusion without detectable solid masses and had sufficient cytologic or histologic material for immunophenotypic and molecular analyses. This study was approved by the Institutional Review Board of Korea University Hospital (approval no. 2024AN0166) and was conducted in accordance with the Declaration of Helsinki. The need for informed consent was waived due to the retrospective nature of the study. Clinical data were retrieved from electronic medical records, and pathological factors were reviewed independently by two pathologists (T. Jeon and Y. Kim). Cases of secondary lymphoma involvement of effusion were excluded based on clinical and imaging evaluations.

Immunohistochemistry and in situ hybridization (ISH)

Immunocytochemical studies were performed on cell block sections using the OptiView DAB IHC Detection Kit (Ventana Medical Systems, Arizona, United States), following the manufacturer's protocol. The primary antibodies used included CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD79a, PAX5, BOB1, OCT2, CD30, CD10, BCL6, BCL2, MYC, MUM-1, CD138, Ki-67, and HHV-8 (Table S1). Epstein-Barr virus-encoded RNA (EBER) and kappa and lambda light chains were assessed using ISH.

Immunoglobulin heavy chain (IGH) and T-cell receptor (TCR) clonality assay

Polymerase chain reaction assays were performed to detect IGH, TCR beta (*TRB*), and TCR gamma (*TRG*) gene rearrangements following the BIOMED-2 concerted action protocols, as described previously [11].

DNA extraction and next-generation sequencing

Targeted sequencing was performed using SolidAccu-Lymphoma Panel v.2.0. on the NextSeq platform (Illumina, San Diego, CA, USA), according to the manufacturer's protocol. DNA was extracted from the dissected cell block sections and assessed for quality. Following bioinformatics analysis, all detected variants were manually reviewed. All output files were integrated and visualized using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria). A list of the 432 genes included in the panel is presented in Table S2.

Data analysis

An oncoPrint of select genes known to be relevant to lymphoma and mutated in this cohort was created using the ComplexHeatmap R package (version 4.5.0; Gu, Z., The Comprehensive R Archive Network [CRAN], Vienna, Austria) [12].

Results

Clinical features

The major clinical features of the three PEL cases and seven FO-LBCL cases are summarized in Table 1. The study cohort predominantly consisted of male patients in both groups (3/3 patients in the PEL group and 5/7 patients in the FO-LBCL group). The median age of patients was 72 years (range, 69–81 years) in the PEL group and 83 years (range, 53–99 years) in the FO-LBCL group. In the PEL group, two patients presented with pleural effusion and one with ascites, whereas in the FO-LBCL group, four patients had pleural effusion and three had pericardial effusion. HIV positivity was observed in one PEL patient only.

Underlying conditions associated with fluid overload were absent in the PEL group, except in one patient with a history of kidney transplantation. In contrast, all seven patients with FO-LBCL had underlying medical conditions, including hypertension, diabetes mellitus, chronic kidney disease, prior hematologic or solid malignancies, or cerebrovascular disease. Two patients with PEL received CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone) or EPOCH (etoposide, prednisone, oncovin, cyclophosphamide, and hydroxydaunorubicin) chemotherapy, whereas one patient with a poor general condition did not. Among the FO-LBCL patients, four received R-CHOP, one received diethylcarbamazine and levatinib, and two were managed with observation. All patients with PEL died of the disease. In the FO-LBCL group, four patients remained alive at the last follow-up, whereas one patient died of an unrelated cause. Among the three patients who died of the disease, follow-up thoracentesis revealed no detectable malignant cells in two cases.

Histopathology with immunohistochemistry

In both the PEL and FO-LBCL groups, neoplastic cells exhibited immunoblastic, plasmablastic, or anaplastic morphological features, with overlapping characteristics observed between the two groups (Figs. 1–3). Immunophenotypic findings are summarized in Table 2, and representative images are shown in Figs. 2 and 3.

All PEL cases showed positive results for HHV-8 (3/3 patients) and Epstein-Barr virus (EBV) (3/3 patients), whereas all FO-LBCL cases showed negative results for HHV-8 (0/7), with only one case being EBV positive (1/7 patients, Case #8). PEL showed negative or weak expression of B-cell markers, including CD20 (0/3 patients), CD79a (1/3 patients), PAX5 (0/3 patients), BOB1 (0/3 patients), and OCT2 (1/3 patients). In contrast, all FO-LBCL cases showed diffuse positivity for CD20, CD79a, PAX5, BOB1, and OCT2 (7/7 patients).

T-cell marker expression, including CD2 (1/3), CD3 (2/3), CD4 (2/3), and CD8 (1/3), was more frequent in PEL cases, whereas FO-LBCL cases showed minimal T-cell marker expression (CD2 and CD8 in 1/7 patients). CD30 was diffusely positive in all PEL cases but was negative in six of seven FO-LBCL cases. CD10 was negative in all cases. BCL2 and BCL6 were negative in PEL cases but were positive in four FO-LBCL cases (4/7 patients). MUM1 was consistently positive and CD138 was negative in all cases.

Ki-67 proliferation indices showed no notable differences between the groups. Light chain restriction was observed in two PEL cases (lambda) and three FO-LBCL cases (two kappa and one lambda).

Table 1

Clinical features and outcome of patients with PEL and FO-LBCL.

Case #	Diagnosis	Age	Sex	Site	Underlying disease	Plasma HIV-RNA	LDH (IU/L)	First-line chemotherapy	Second cytology	Follow-up (month)	Outcome
1	PEL	72	M	Pleural	Type 2 DM	-	622	CHOP	Pos	14	DOD
2	PEL	81	M	Pleural	Type 2 DM, HTN, KT status	-	291	-	Pos	6	DOD
3	PEL	69	M	Ascitic	HIV (2019), Tb (1998), liver abscess (2004)	+	886	EPOCH	Pos	2	DOD
4	FO-LBCL	73	M	Pleural	HTN, DL	-	343	-	Neg	4	DOD
5	FO-LBCL	84	M	Pleural	AKI on CKD, Tb pleurisy	-	627	R-CHOP	Pos	38	Alive
6	FO-LBCL	84	M	Pericardial	Type 2 DM, HTN, MDS, DL, Acute ischemic stroke (2022), prostate cancer (2004)	-	271	DEC levatinib	Neg	18	Alive
7	FO-LBCL	99	F	Pleural	HTN, DM, bladder cancer	ND	294	-	Neg	23	Alive
8	FO-LBCL	53	M	Pericardial	CML (2020), HTN, Gout	-	421	R-CHOP	ND	23	Alive
9	FO-LBCL	83	M	Pleural	HTN, stable angina, acute ischemic stroke (2018)	-	1212	R-CHOP	Pos	1	DOD
10	FO-LBCL	81	F	Pericardial	Type 2 DM, HTN, DL	-	805	R-CHOP	Neg	26	DOO

PEL, primary effusion lymphoma; FO-LBCL, fluid overload-associated large B-cell lymphoma; F, female; M, male; DM, diabetes mellitus; HTN, hypertension; KT, kidney transplantation; DL, dyslipidemia; AKI, acute kidney injury; CKD, chronic kidney disease; Tb, tuberculosis; MDS, myelodysplastic syndrome; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; EPOCH, etoposide, prednisone, oncovin, cyclophosphamide, and hydroxydaunorubicin; DEC, diethylcarbamazine; ND, not done; DOD, died of disease; DOO, died of other causes.

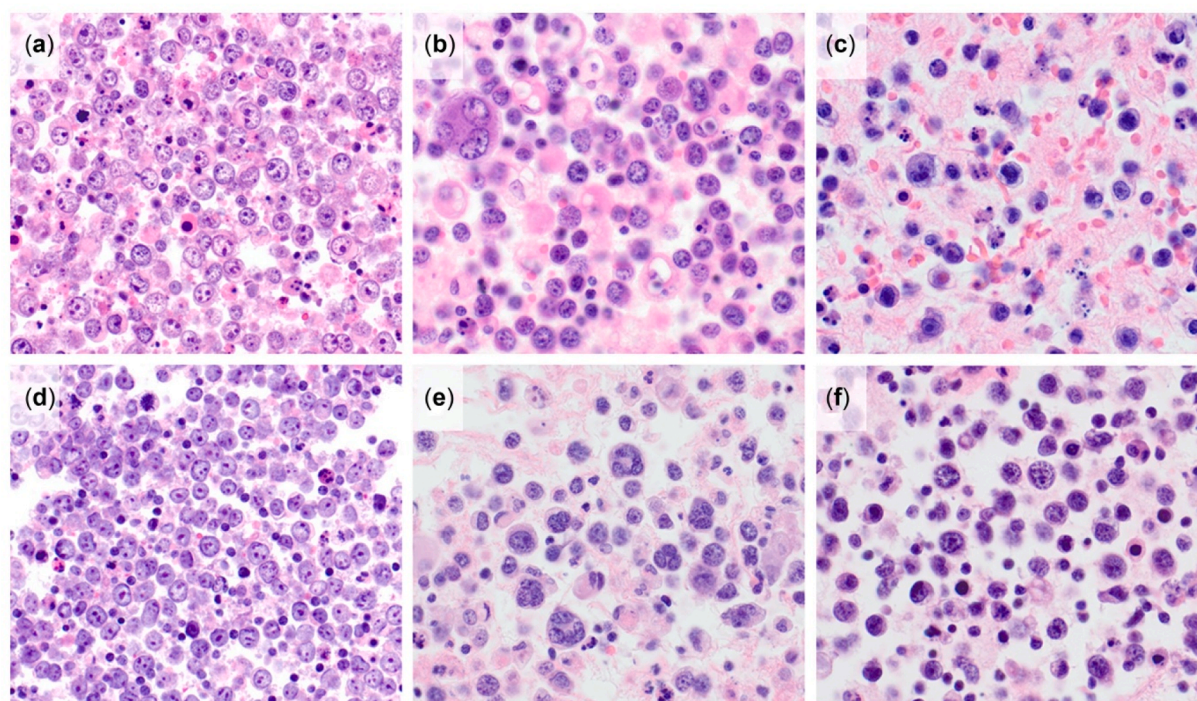


Fig. 1. Morphological features of primary effusion lymphoma (PEL) and fluid overload-associated large B-cell lymphoma (FO-LBCL). (A-C) PEL: (A) Centroblastic (Case #3), (B) Plasmablastic with Reed-Sternberg-like cell (Case #2), (C) Anaplastic (Case #1). (D-F) FO-LBCL: (D) Immunoblastic (Case #8), (E) Anaplastic (Case #6), (F) Anaplastic (Case #5).

T-cell and B-cell receptor clonality assay

Eight patients were evaluated for B-cell and T-cell clonality. Clonal *IGH* rearrangement was detected in all eight samples. Among the PEL cases, two showed monoclonal *TRB* gene rearrangements, whereas the remaining case showed a low signal peak. In the FO-LBCL group, low signal peaks in *TRB* were observed in two of five cases. A positive *TRG* gene rearrangement was identified in only one PEL case.

Next-generation sequencing (NGS)

NGS was performed in 5 of the 10 cases (Fig. 4). In the PEL group, *TJPI* mutations and copy number variations in *IKBKB*, *CTCF*, and *MDM2* were observed in both PEL cases. In contrast, the FO-LBCL group

demonstrated mutations in *CD79B* and *PIM1*, as well as mutations or copy number variations involving *POU2F2*; these were found in three FO-LBCL cases but were not detected in the PEL group. Additionally, two FO-LBCL cases harbored mutations in *CUX1*, *MYD88*, and *TRRAP* that were not observed in PEL, along with copy number variations in *CD37*, *CD79A*, *LILRB1*, *NKG7*, and *PTKD2*. Mutations in *ABCG2*, *KMT2D*, and *MUC2* were identified in one PEL case and two FO-LBCL cases (Fig. 4 and Table S3).

Discussion

PEL and FO-LBCL (also known as HHV-8-negative PEL or PEL-like effusion lymphoma) are rare lymphomas, with PEL exhibiting more aggressive behavior and poorer clinical outcomes than FO-LBCL [13,

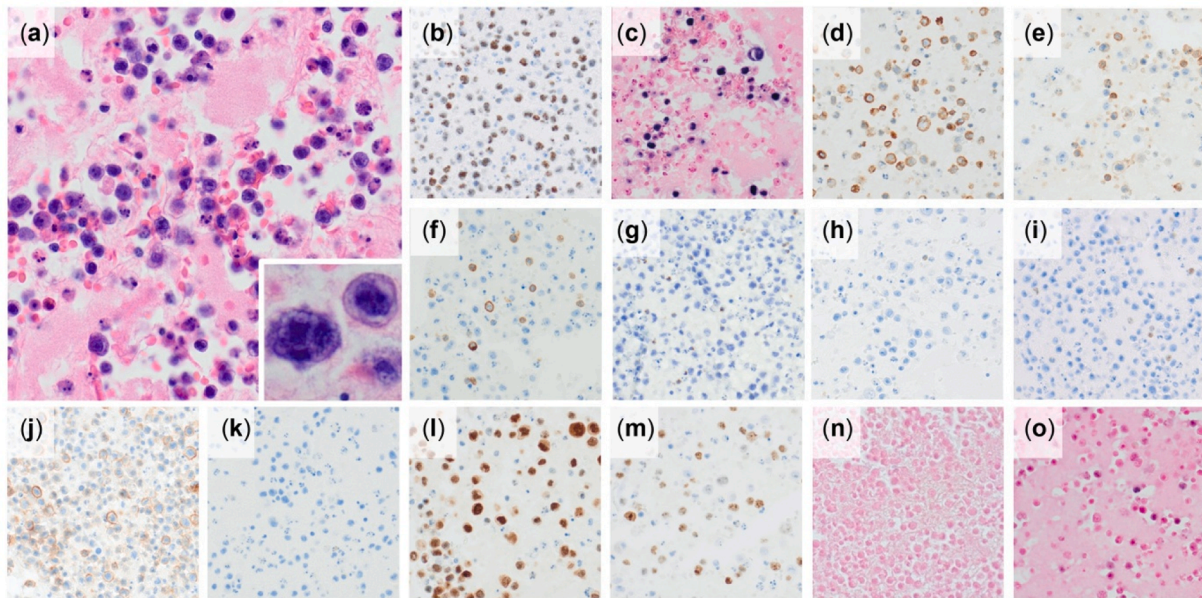


Fig. 2. Representative histopathologic and immunophenotypic features of primary effusion lymphoma (PEL). (A) Representative histopathology of PEL (Case #1), showing anaplastic, large, hyperchromatic lymphoid cells. (B) Tumor cells are positive for HHV-8 in all cases. (C) In situ hybridization showing EBER+ in all cases, with frequent aberrant expression of T-cell markers, particularly (D) CD3. In Case #1, (E) CD4 and (F) CD5 show focal positivity, whereas (G) CD2 show negative result. Similar positivity for CD2, CD3, CD4, and CD8 is observed in Case #2 (not shown). PELs generally lacked expression of pan-B-cell markers, such as (H) CD20 and (I) PAX5, except for Case #3 (not shown), which shows CD79a positivity. All PEL cases show (J) CD30 positivity, (K) CD138 negativity, and (L) MUM-1 positivity. (M) The Ki-67 labeling index in Case #1 is approximately 40 %–50 %. In situ hybridization for (N) kappa and (O) lambda shows lambda restriction.

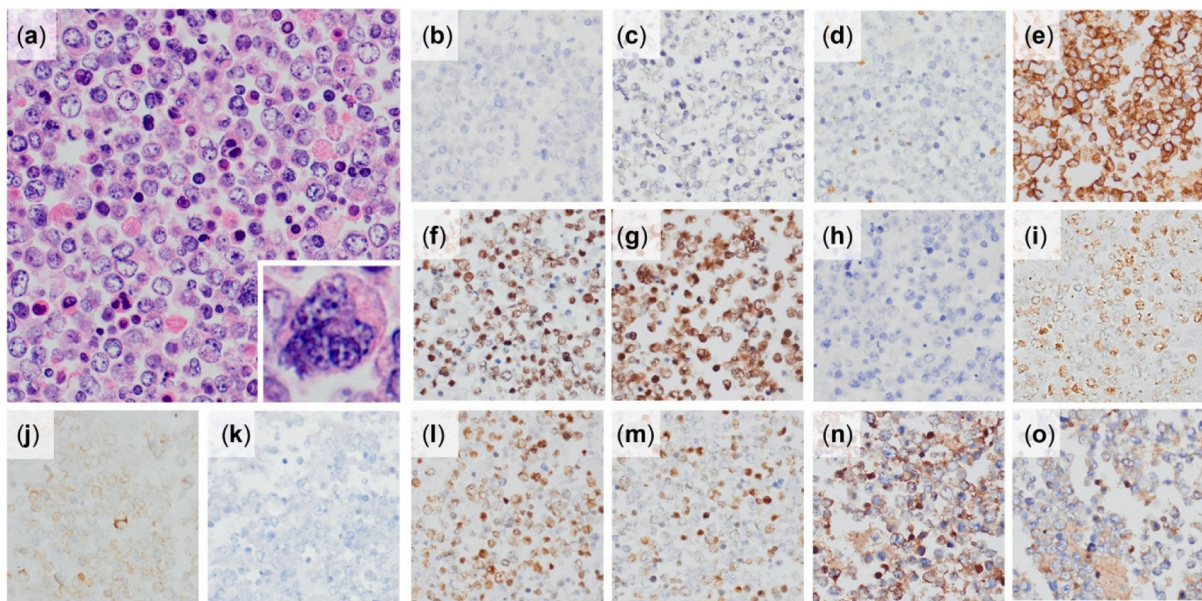


Fig. 3. Representative histopathologic and immunophenotypic features of fluid overload-associated large B-cell lymphoma (FO-LBCL). (A) Representative histopathology of FO-LBCL (Case #9), showing centroblastic, large lymphoid cells. Tumor cells showing negative result for (B) HHV-8 and (C) EBV in all cases. All FO-LBCL cases, except for Case #7, showing negative result for T-cell markers, including (D) CD3. All cases showing diffuse positivity for B-cell markers, including (E) CD20, (F) Pax5, and (G) OCT2. In FO-LBCL cases, (H) CD30 shows negative result in all cases. (I) BCL6 is positive in five of seven cases, and (J) BCL2 is positive in four of seven cases. (K) CD138 shows negative result in all cases, whereas (L) MUM-1 shows positive result in all cases. In this case, the (M) Ki-67 labeling index is approximately 50 %, and immunohistochemistry for (N) kappa and (O) lambda reveals kappa restriction.

14]. Despite their distinct clinical behavior, direct comparative studies of the clinicopathologic and molecular features of these two entities remain limited. In this preliminary retrospective case series, we compared the morphologic, immunophenotypic, and molecular features of PEL and FO-LBCL, with targeted sequencing performed in a subset of cases.

Although PEL and FO-LBCL showed no consistent morphologic differences, distinct differences were observed in their immunohistochemical features, with T-cell lineage infidelity being more frequently observed in PEL. Furthermore, FO-LBCL showed recurrent alterations involving CD79B, PIM1, and MYD88, suggesting partial molecular overlap with the MCD-like molecular pattern reported in subsets of

Table 2
Histological, immunophenotypical, and genotypical features of patients with PEL and FO-LBCL.

Pt #	Dx.	CD2	CD3	CD4	CD5	CD7	CD8	CD20	CD79a	PAX5	BOB1	OCT2	CD30	CD10	BCL6	BCL2	MYC	MUM-1	CD138	Ki-67 (%)	HHV-8	EBER	κ/λ	IGH	TRB	TRG
1	PEL	-	+	+10%	-	-	-	-	-	-	-	-	+	-	-	-	-	+	-	40-50	+	+	λ	+	Low	-
2	PEL	+	+	+	-	-	+10%	-	-	-	-	+	+	-	-	-	+5%	+	+	50-60	+	+	λ	+	+	+
3	PEL	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+40%	+	-	70-80	+	+	-	+	+	-
4	FO-LBCL	-	-	-	-	-	-	+	+	+	+	+	-	-	+90%	+30%	+50%	+	-	70-80	-	-	-	+	-	-
5	FO-LBCL	-	-	-	-	-	-	+	+	+80%	+	+	-	-	+80%	-	+30%	+	-	80	-	-	λ	+	Low	-
6	FO-LBCL	-	-	-	-	-	-	+	+	+	+	+	-	-	+80%	-	+30%	+	-	60-70	-	-	-	+	-	-
7	FO-LBCL	+	-	-	+	-	+10%	+	+	+	+	+	-	-	-	+	+	+	-	90	-	-	-	+	-	-
8	FO-LBCL	-	-	-	-	-	-	+	+	+	+50%	+	+80%	-	-	+	+40%	+	-	80	-	+	κ	+	Low	-
9	FO-LBCL	-	-	-	-	-	-	+	+	+	+	+	-	-	+	+	-	+30%	-	50	-	-	κ	NA	NA	NA
	FO-LBCL	-	-	-	-	-	-	+	+	+	+	+	-	-	+80%	+25%	-	+	-	70-80	-	-	-	NA	NA	NA

PEL, primary effusion lymphoma; FO-LBCL, fluid overload-associated large B-cell lymphoma; EBER, Epstein-Barr virus-encoded RNA; HHV-8, human herpes virus 8; TRB, T-cell receptor beta; TRG, T-cell receptor gamma; IGH, immunoglobulin heavy chain; ND, not done; NA, not available.

activated B-cell-like (ABC) DLBCL [7].

In our study, both PEL and FO-LBCL exhibited male predominance, with all three PEL cases occurring in male patients and a male-to-female ratio of 2.5:1 observed in the FO-LBCL group. The median age of patients in the FO-LBCL group (83 years) was higher than that in the PEL group (72 years). This age difference may reflect the distinct pathogenesis of the two entities: HHV-8-associated oncogenesis in PEL and fluid-overload-related malignant transformation in older individuals with FO-LBCL [2,15]. These findings were consistent with those of previous studies [16,17]. These distinct pathogenetic mechanisms may also contribute to differences in clinical outcomes. In our cohort, all patients with PEL died due to the disease within 2–14 months of diagnosis. In contrast, FO-LBCL appeared to have a comparatively more favorable clinical course in this cohort: 3 of 7 patients (43 %) remained alive, 3 of 7 patients (43 %) died due to the disease, and one patient (14 %) died due to an unrelated cause.

Interestingly, patients with FO-LBCL showing pericardial involvement (Cases #6, #8, and #10) appeared to have more favorable clinical outcomes than those with pleural involvement. This observation aligns with the findings of Kubota et al., who reported a significantly better overall survival in patients with pericardial effusion (P = 0.045) [17].

Another notable finding was that 67 % (4/6) of patients with FO-LBCL who had available follow-up cytology had negative results for subsequent cytologic specimens. Among these, half of them achieved spontaneous remission despite not receiving systemic treatment because of poor general condition or other factors. Except for one case in which IGH clonality testing failed owing to insufficient material, all spontaneously regressed cases were confirmed to be monoclonal. Moreover, two of these cases underwent targeted sequencing, revealing that CD79B and PIM1 mutations were commonly associated with DLBCL [7,18]. These findings further support the notion that, despite its relatively favorable clinical course, FO-LBCL is a true hematologic malignancy harboring known driver mutations.

Ashihara et al. previously suggested that external factors such as fluid overload may trigger malignant transformation within effusion cavities, a mechanism proposed in previous reports of HHV-8-negative effusion-based lymphoma [19]. However, as demonstrated in Cases #4 and #10, such lymphomas can also arise in the absence of any apparent fluid overload, suggesting that alternative mechanisms, such as immunosenescence, may contribute to their pathogenesis.

Molecular studies have suggested that PEL and FO-LBCL arise through partially distinct oncogenic mechanisms despite their shared presentation as cavity-based lymphomas. PEL is driven primarily by HHV-8-associated viral oncogenesis. HHV-8-encoded proteins promote constitutive activation of multiple prosurvival signaling pathways, including NF-κB, JAK/STAT, and PI3K/AKT, while viral-mediated dysregulation of p53 signaling further contributes to lymphomagenesis [20–25].

Within the limits of our cohort, IKBKB copy number amplification was identified in the PEL group. This alteration may be biologically relevant because HHV-8 promotes persistent NF-κB pathway activation via the viral FLICE inhibitory protein, a known viral oncoprotein [20, 21]. Functional dependence on MDM2 has also been reported in PEL, suggesting that suppression of p53 activity may contribute to tumor-cell survival [22,23]. HHV-8-mediated activation of NF-κB together with dysregulation of p53-related signaling has been implicated in the biology of PEL [20–23,25].

TJP1, a tight junction protein, is not widely recognized as a recurrently mutated gene in lymphoma. However, studies on leiomyosarcoma, lung cancer, and bladder cancer have shown that TJP1 overexpression promotes cell aggregation and tumor progression and is often associated with poor prognosis [26–28]. Our findings raise the possibility that alterations in adhesion-related genes such as TJP1 may contribute to the unique biology of PEL, including its effusion-based growth pattern.

In contrast, the limited molecular data available for FO-LBCL have

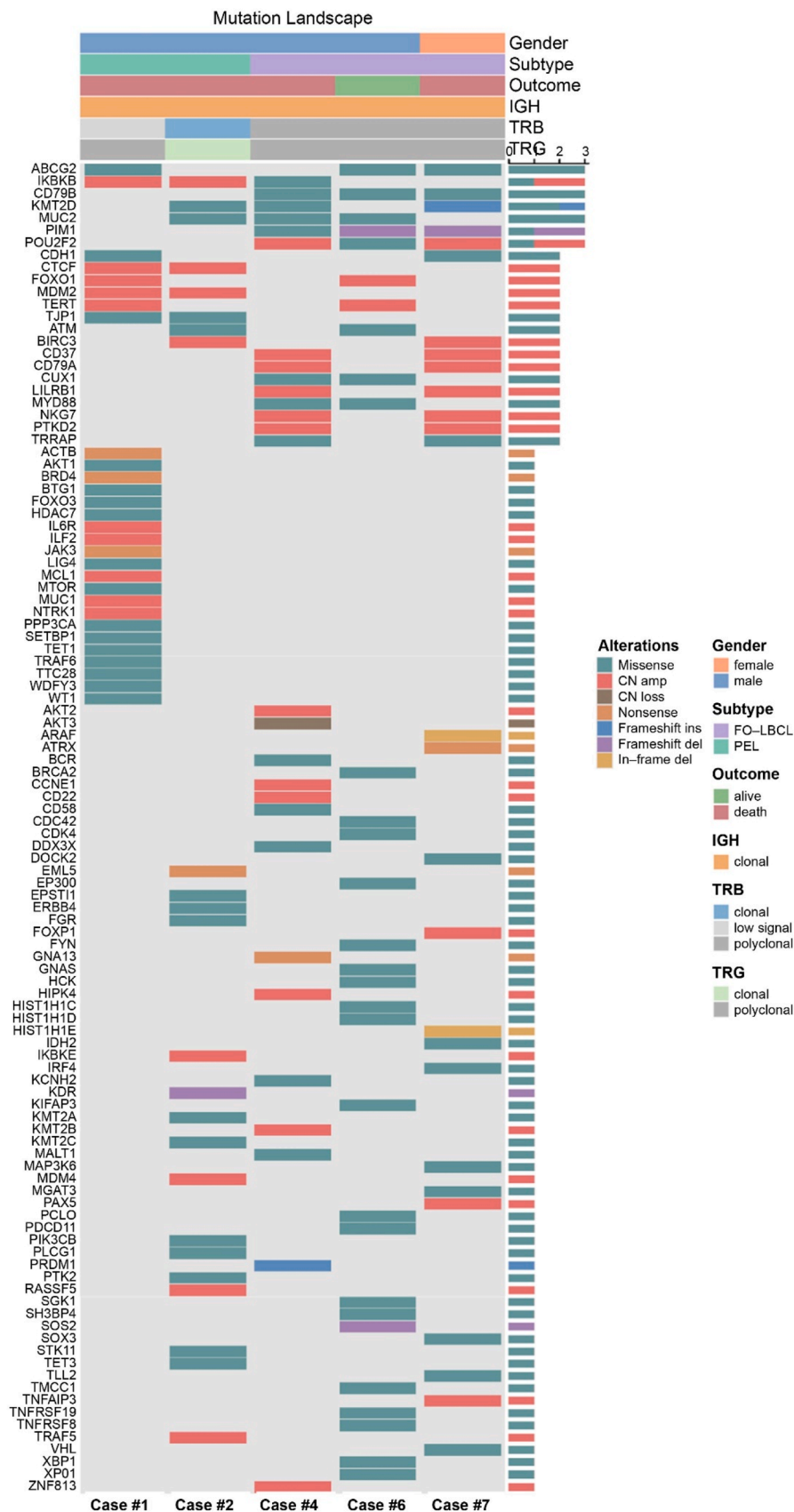


Fig. 4. Mutational landscape of alterations in two PEL cases and three FO-LBCL cases. The X-axis represents each case, and the mutated genes are shown along the Y-axis. The frequency of each mutation is indicated at the right side of the plot. Color coding in the oncoplot corresponds to the type of genetic alteration. Samples are annotated with additional clinical and molecular features, including gender, lymphoma subtype, clinical outcome, and immunoglobulin (IG) and T-cell receptor gene rearrangement status.

identified recurrent alterations involving genes implicated in B-cell receptor signaling and other lymphoma-associated pathways. Mendeveille et al. detected *MYD88* mutations in four of eight HHV-8-negative effusion-based lymphomas, including three cases with the canonical L265P variant, and identified a concurrent *CD79B* mutation in one case [9]. Subsequent reports have described recurrent alterations involving *MYD88* and *CD79B*, together with mutations in *PIM1* and other lymphoma-associated genes, although the number of molecularly characterized cases remains small [10,29–32]. In our cohort, *MYD88* mutations were detected in two of three FO-LBCL cases, although neither involved the L265P variant, and all three cases carried mutations in both *CD79B* and *PIM1*. Together, these recurrent alterations suggest partial molecular overlap between FO-LBCL and the molecular features characteristic of the MCD subtype of ABC-DLBCL, with involvement of chronic active B-cell receptor signaling and NF- κ B pathway activation [33,34].

Given these molecular features and their overlap with those reported previously, it is possible that FO-LBCL shares certain microenvironmental features with MCD-type DLBCLs that show a predilection for immune-privileged sites such as the central nervous system and testes [7,35]. Although FO-LBCL arises in serous cavities, such as the pleura or pericardium, these spaces may similarly support compartmentalized lymphoma growth in which local environmental factors contribute to tumor persistence. As anatomically confined spaces with potentially limited immune cell infiltration, serous cavities may permit malignant cells to proliferate under reduced immune pressure. Consistent with this concept, some FO-LBCL cases have shown tumor regression after simple fluid drainage, suggesting that the serous cavity milieu can play an important role in sustaining lymphoma growth [2,36,37]. Nevertheless, the mechanisms by which the effusion environment supports tumor cell survival and expansion remain to be clarified.

In the present study, *IGH* monoclonality was confirmed in all eight evaluable cases of PEL and FO-LBCL, excluding two FO-LBCL cases in which the analysis failed owing to insufficient specimen quantity. Interestingly, three cases of PEL demonstrated monoclonality or low signal intensity in the *TRB*, with one also showing *TRG* positivity. In contrast, among the FO-LBCL cases, only two showed low *TRB* signals. Two PEL cases expressed T-cell markers, namely, CD3 and CD4, exhibiting both dual genotypes and dual phenotypes of B-cell and T-cell lineages. These findings are occasionally observed in hematological malignancies and may arise because of lineage infidelity, particularly in the presence of EBV infection [38–40]. One hypothesis is that EBV proteins induce lineage infidelity during malignant transformation by interfering with the expression of certain host genes and activating others, such as those encoding T-cell antigens [39] while another suggests that transformation at the progenitor cell level, accompanied by the release of genetic repression, drives the neoplastic expansion of a subset of B-cell populations expressing T-cell antigens [38]. Notably, one EBER-positive FO-LBCL case also showed a low *TRB* signal was detected. All four PEL- and FO-LBCL cases with EBER infection demonstrated *TRB* rearrangement or a low *TRB* signal.

Few studies have directly compared the molecular genetic features of FO-LBCL and PEL, and our findings provide additional support for a partial molecular overlap between FO-LBCL and the MCD-like genetic pattern reported in subsets of DLBCL. However, this study has some limitations. First, the study cohort included only Korean patients, and the clinicopathological characteristics of PEL and FO-LBCL may vary across different ethnic backgrounds. Second, genomic profiling was performed in only five cases, limiting the statistical power of our findings. Larger-scale studies are warranted to validate these results. Finally, the retrospective design may have introduced a selection bias, particularly regarding treatment response and outcome data. Accordingly, the molecular observations presented here should be regarded as preliminary and hypothesis-generating pending validation in larger cohorts.

In conclusion, this preliminary retrospective case series

characterized the clinicopathological, immunophenotypic, and molecular features of PEL and FO-LBCL through direct comparison of their genetic profiles. Our findings suggest partial molecular overlap between FO-LBCL and the molecular features characteristic of the MCD subtype of DLBCL in a subset of cases. Although the two entities share similar morphological features that make histologic distinction challenging, they can be reliably differentiated using established immunohistochemical markers.

These findings enhance diagnostic precision and underscore the importance of integrating morphologic, immunophenotypic, and molecular data for accurate classification of effusion-based B-cell lymphomas. Clinically, the identification of recurrent alterations involving BCR/NF- κ B-related pathways in FO-LBCL may provide a basis for future studies exploring targeted therapeutic approaches such as BTK inhibitors.

The distinct genetic alterations observed in each group likely reflect differences in pathogenesis that contribute to their divergent clinical behavior. Future studies involving larger, multi-institutional cohorts with integrated molecular analyses are warranted to further clarify the biological relationships among PEL, FO-LBCL, and immune-privileged site DLBCL.

Data statement

All data supporting the findings of this study are available within the article and its supplementary information files.

CRediT authorship contribution statement

Taesung Jeon: Writing – review & editing, Formal analysis, Data curation. **Young-Hyeh Ko:** Writing – review & editing, Conceptualization. **You-Na Sung:** Conceptualization. **Harim Oh:** Conceptualization. **Hyunsung Kim:** Methodology, Data curation. **Seongsik Bang:** Data curation. **Ka-Won Kang:** Resources, Data curation. **Changgon Kim:** Data curation. **Kunye Kwak:** Data curation. **Yeseul Kim:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Sangjeong Ahn:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

I have nothing to declare. The authors declare no competing financial interests.

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Supplementary materials

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