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PLEURAL DISEASE

# Pleural Effusions in Diffuse Large B-Cell Lymphoma: Clinical and Prognostic Significance

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## Abstract

**Purpose** Pleural effusion (PEs) may complicate diffuse large B-cell lymphomas (DLBCL). However, their real prevalence and prognostic significance have seldom been approached systematically.

**Methods** Retrospective single-center evaluation of consecutive patients with DLBCL was conducted. Baseline characteristics, PEs on CT imaging, pleural fluid analyses, and outcome until death or censoring date were collected.

**Results** Of 185 DLBCL patients, 55 (30%) had PEs, of which 27 (49%) were analyzed. Most tapped PEs were malignant ($n=24$) and cytological and/or flow cytometric analyses provided the diagnosis in about 70% of the cases. Malignant PEs were exudates with adenosine deaminase levels > 35 U/L in 35% of the cases. More than one-third of lymphomatous PEs required definitive pleural procedures for symptomatic relief. PEs greater than 200 mL on CT scans were an independent predictor of poor survival in Cox regression modeling (hazard ratio 1.9).

**Conclusions** PEs are common in DLBCL and foreshadow a poor prognosis.

**Keywords** Pleural effusion · Diffuse large B-cell lymphoma · Survival · Indwelling pleural catheter · Pleurodesis · Adenosine deaminase · Chylothorax

## Introduction

Lymphoma is a relatively frequent etiology of malignant pleural effusions (PEs). It ranked fourth in one study of 840 tapped malignant PEs, after lung, breast, and unknown primaries [1]. However, the real prevalence of PEs in lymphoma patients is inconsistent and their prognostic significance conflicting, probably due to the heterogeneous grouping of lymphoma subtypes and populations studied [2, 3]. We undertook a retrospective study in a clinical cohort of diffuse large B-cell lymphomas (DLBCL), the most common histologic subtype of non-Hodgkin's lymphomas (NHL) [4], with the aims of describing the prevalence of PEs and their relationship with survival.

## Methods

The analysis included all consecutive adult patients with a histologically proven DLBCL who were newly diagnosed between January 2010 and December 2017 at the University Hospital Arnau de Vilanova (Lleida, Spain). The study protocol was approved by the local ethics committee (CEIC No. 1965).

The following variables were extracted from electronic medical charts: demographics, presence and characteristics of PEs on computed tomography (CT) scans at any time from the DLBCL diagnosis (side, volume according to a previously reported formula [5], loculations, pleural thickening ≥ 3 mm and/or nodularity, pleural-based masses ≥ 3 cm), presence of pericardial effusions or ascites on CT imaging, pleural fluid data when analyzed (biochemistries, cytological and flow cytometric studies), pleural interventional procedures (therapeutic thoracenteses, pleurodesis, indwelling pleural catheters), serum β-2 microglobulin and

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lactate dehydrogenase (LDH) levels, Ann Arbor staging, International Prognostic Index (IPI), LENT (pleural fluid LDH, Easter Cooperative Oncology Group performance score, serum neutrophil-to-lymphocyte ratio and tumor type) prognostic score [6] calculated at the time of presentation with malignant PEs, treatments received (curative-intent or palliative), complete remissions achieved after therapy, recurrences following complete remissions, overall survival (OS), and progression-free survival -PFS- (i.e., time from diagnosis to recurrence or death).

Malignant PEs were diagnosed when malignant cells were present in pleural fluid cytology (either smears or cell blocks), flow cytometry or pleural biopsy. A diagnosis of probable malignant PE was made on DLBCL patients with a cytology-negative exudate, after reasonably ruling out benign causes of fluid accumulation.

Continuous and categorical variables were expressed as medians (quartiles) and percentages, respectively. For comparisons between patients with and without PEs the Chi-square or Mann–Whitney *U* tests were used, whichever was appropriate. Survival time was calculated from the clinico-pathological diagnosis of DLBCL until death or censoring date (August 20, 2018). The effect of any individual variable or PE status on survival was estimated by using the Kaplan-Meyer method and log-rank testing. The Cox proportional hazards regression model was used to confirm the significance of each prognostic factor selected by bivariate analysis. Calculations were done using SPSS version 24.0 statistical software.

## Results

Of 185 DLBCL patients, 55 (30%; 95% CI 24–37%) had PEs, either at presentation ($n=41$) or following a median of 7 (1–12) months from tumor diagnosis ($n=14$). The median follow-up time of the study population was 21 (9–43) months. Table 1 reveals other patient characteristics. PEs were bilateral in 28 (51%) cases, loculated in 22 (40%), associated with pleural nodularity/mass and/or thickening in 15 (27%), and had a median volume of 150 mL (50–648 mL) on CT scans. Twenty-seven (49%) PEs were analyzed, the

**Table 1** Baseline characteristics of patients with diffuse large B-cell lymphoma

| Variable | All patients ($n=185$) | Patients with PE ($n=55$) | Patients without PE ($n=130$) | *P* value[a] |
|---|---|---|---|---|
| Age, years | 65 (52–76) | 68 (54–78) | 65 (51–76) | 0.74 |
| Male, sex | 105 (57) | 31 (56) | 74 (57) | 0.94 |
| HIV infection | 7/158 (4) | 3/48 (6) | 4/110 (4) | 0.46 |
| Serum β-2 microglobulin, mg/L | 2.9 (2.1–4.1) | 3.6 (2.7–5.3) | 2.6 (1.8–3.5) | < 0.001 |
| Serum LDH, U/L | 443 (330–795) | 701 (458–1120) | 391 (310–614) | < 0.001 |
| CT imaging | | | | |
| Ascites | 16 (9) | 14 (26) | 2 (2) | < 0.001 |
| Pericardial effusion | 19 (10) | 14 (26) | 5 (4) | |
| Ann Arbor stage | | | | |
| Stage I–II | 69 (37) | 12 (22) | 57 (44) | 0.005 |
| Stage III–IV | 116 (63) | 43 (78) | 73 (56) | |
| IPI | | | | |
| 0–2 | 93 (50) | 19 (35) | 74 (57) | 0.005 |
| 3–5 | 92 (50) | 36 (66) | 56 (43) | |
| Treatment | | | | |
| Curative-intent | 167 (90) | 48 (87) | 119 (91) | 0.55 |
| Palliative | 18 (10) | 7 (13) | 11 (9) | |
| Complete remission (if curative-intent therapy) | 126 (75) | 26 (54) | 110 (84) | < 0.001 |
| Recurrences following complete remission | 17 (14) | 4 (15) | 13 (13) | 0.75 |
| OS, months | NC[b] | 19 (0–60) | NC[b] | < 0.001 |
| PFS, months | NC[b] | 18 (6–30) | NC[b] | 0.001 |

Data are presented as median (interquartile range) or %

*CT* computed tomography, *HIV* human immunodeficiency virus, *IPI* International prognostic index, *LDH* lactate dehydrogenase, *NC* non-calculable, *OS* overall survival, *PE* pleural effusion, *PFS* progression-free survival

[a]For comparisons between patients with and without pleural effusions

[b]OS and PFS were not calculable because more than half the patients in the group were alive

etiology being definitely malignant in 19 (70%), probably malignant in 5 (18.5%) and benign in 3 (11%). Benign PEs were attributable to heart failure, hepatic hydrothorax, and pancreaticopleural fistula (1 case each). All malignant PEs ($n=24$) met Light's exudative criteria; only 4 (17%) had fewer than 50% lymphocytes in the differential leukocyte count, 6 (25%) exhibited glucose levels < 60 mg/dL, 2 (8%) a pH < 7.2, 15 (64%) an LDH level > 1000 U/L (i.e., 2.6 times the upper normal limit of serum LDH) and 8/23 (35%) adenosine deaminase (ADA) levels above 35 U/L. Two (8%) effusions had a milky appearance. The sensitivity of the cytologic diagnosis of malignant PEs was 71% (17/24) and that of flow cytometry 74% (14/19). Fifteen pleural procedures (6 therapeutic thoracenteses, 5 indwelling pleural catheters, 4 bedside pleurodesis) were required in 10 (42%) patients with malignant PEs.

The 1- and 2-year OS rates were 60% and 41% among patients with PEs, respectively, in contrast to 81% and 70% for those without PEs (respective p values of 0.005 and 0.001). Although there was a trend towards a better OS in subjects with PEs which coincided with the diagnosis of DLBCL as compared to those in which the PE followed the diagnosis (48 vs. 16 months), it did not reach statistical significance ($P=0.92$). The 26 (47%) patients with PEs greater than 200 mL on CT scans (a threshold reflecting a potential safe thoracentesis and for which there was roughly a similar proportion of patients above and below it) showed a worse OS than the 29 (53%) with a lesser fluid volume and those with no PE (14 months vs. non-calculable, $P<0.001$; hazard ratio -HR- 3.63 with 95% CI 2.05–6.43) (Fig. 1). In the Cox regression analysis, a PE > 200 mL remained an independent predictor of poor survival (HR 1.9, 95% CI 1.004–3.6), along with the application of supportive care (HR 8, 95% CI 4.2–15.2), the presence of ascites (HR 3.4, 95% CI 1.6–7) and an IPI ≥ 3 (HR 2.4, 95% CI 1.4–4.2). The Ann Arbor staging system was eliminated by the multivariate model, as was the effusion's timing (at diagnosis vs. during disease course), the performance of a diagnostic pleural tap, and certain CT features (laterality, loculations, pleural nodularity or thickening).

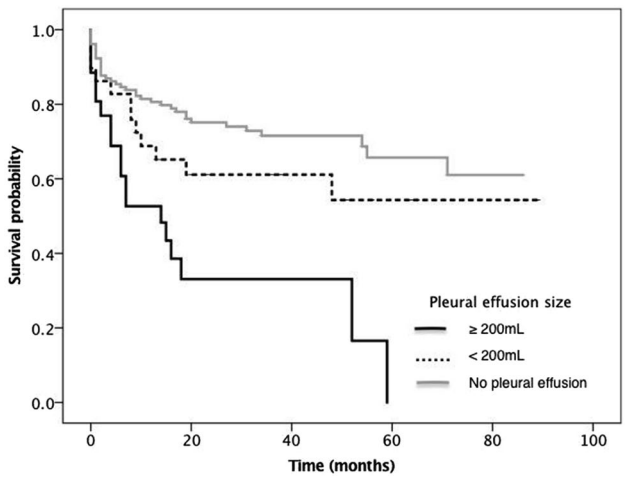


**Fig. 1** Kaplan–Meier estimates of survival according to the presence of pleural effusions and their volume in patients with diffuse large B-cell lymphoma

The LENT scoring system predicted survival in patients with malignant PEs, the only subgroup where it is applicable ($n=24$). There were 3 patients in the low-risk prognostic group (score 0–1), of whom 1 died 81 months after diagnosis and 2 were still alive at the 70- and 72-month follow-up. Of the 20 patients in the moderate-risk group (score 2–4), 18 died and had a median survival time of 18 months (95% CI 12–24 months). Finally, only 1 patient had a high-risk LENT score (score 5–7) and survived for only 20 days following diagnosis. Survival differences between groups achieved statistical significance ($P=0.003$).

## Discussion

This is the first study that simultaneously addresses prevalence (using CT as the reference imaging), clinical characteristics and prognosis of PEs in DLBCL. PEs occurred in 30% of patients with DLBCL. In literature, this percentage varied from 8 to 18% [3, 7–9], possibly because either only tapped effusions were included or radiological detection techniques were non-specified (presumably chest radiographs).

Most PEs in DLBCL were of malignant origin and could be indistinctly unilateral or bilateral [10]. In ours and a previous study [10] all lymphomatous effusions were exudates, though one series reported that 12% of 67 malignant PEs associated with a variety of NHL met Light's transudative criteria [11]. We found that cytology and flow cytometric analyses of the PE were positive in more than two-thirds of the patients. The cytologic tests with lymphomas in general (which also include less aggressive forms) identify less than half the cases [12], thus reinforcing the recommendation to perform flow cytometry when the condition is suspected. Less than 10% of the effusions were chylothoraces, which is in agreement with other series [10, 11]. However, chylothoraces have the classic milky appearance in only half the cases [13] and, therefore, their diagnosis may be underestimated if a systematic measurement of pleural fluid triglycerides is not performed. Moreover, pleural fluid ADA reached the diagnostic cutoff for tuberculosis in about one-third of patients, as observed in preceding reports [14, 15]. Finally, it should be highlighted that, despite it being a highly chemosensitive tumor, 37.5% (9/24) of patients with lymphomatous PEs required definitive pleural procedures (i.e.,

pleurodesis and/or indwelling pleural catheters); a figure only slightly lower than that reported for malignant PEs in general (e.g., 53.6% of 537 patients in one study) [16].

Notably, the presence of a PE large enough to be aspirated (> 200 mL) adversely affected complete remission, PFS and OS rates in DLBCL. A small number of studies with a focus on this issue have yielded differing conclusions. An earlier case-control study which only included 46 NHL patients, of whom 17 had PEs, reported that PEs at the time of presentation did not carry adverse prognostic implications [2]. However, no matched controls were used for the subgroup of patients with a high degree NHL. Subsequently, in two studies comprising 148 DLBCL [7] and 92 NHL [17], involvement of the pleura represented a poor prognostic factor; in the latter study 47% of patients who died within 4 months of the lymphoma diagnosis had serosal effusions [17]. Additionally, in a small study of 41 DLBCL patients with serosal involvement (mostly pleural), of whom 19 (46%) had cytologic confirmation of malignancy, a prognostic comparison with another cohort of 12 stage IV DLBCL was performed [3]. The median OS was 9.2 months for patients with malignant PEs in contrast with 18.8 months for those without; the presence of malignant PEs being a more powerful poor prognosticator than stage IV disease [3], as our investigation further supports. More recently, a study found that among 29 PE-associated DLBCL patients, those harboring the MYC proto-oncogene rearrangement had significantly shorter OS and PFS than those without dysregulation of MYC [9], which highlights the potential contribution of cancer genetic profiling. Overall, the behavior of DLBCL-associated PEs was similar to that reported for lung cancer, where PEs (including minimal effusions not amenable to tapping) confer a survival disadvantage [18]. In DLBCL cases, however, patients with small PEs (< 200 mL) showed a trend towards worse survival than those without PEs (Fig. 1), but it did not reach statistical significance, likely due to small sample size.

In conclusion, PEs are frequently encountered in DLBCL patients. In the majority of cases, thoracentesis established the diagnosis of malignancy through cytological and/or flow cytometric studies. More than one-third of lymphomatous effusions will require definitive pleural procedures for symptomatic control. The presence of PEs in the context of DLBCL portends a poor prognosis, worse than that of classical parameters such as advanced tumor stages. Although limited by its retrospective nature, moderate sample size, and lack of a longer term follow-up, this study represents a pragmatic assessment of the clinical and prognostic significance of PEs in the more aggressive lymphoma subtypes.

**Author Contributions** Conception and design: JMP and SB; Acquisition, analysis and interpretation of data: IC, TGC, MP, SB, and JMP; and drafting the manuscript: JMP All authors gave final approval.

## Compliance with Ethical Standards

**Conflict of interest** None of the authors has any conflicts of interest to declare in relation to this work.

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