EJCRIM
European Journal
of Case Reports
in Internal Medicine

# B-CELL LYMPHOMA FOLLOWING AN INDOLENT COURSE OVER 30 YEARS WITH IMMUNOPHENOTYPIC CHANGES AT EACH RECURRENCE

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**Received:** 17/01/2026
**Accepted:** 20/01/2026
**Published:** 03/02/2026

**Conflicts of Interests:** The Authors declare that there are no competing interests.
**Patient Consent:** As the patient is deceased and their next of kin could not be located, the Institutional Review Board (IRB) of Ehime University waived the requirement for written informed consent for publication.
**Acknowledgments:** We would like to express our sincere gratitude to the medical staff of the First Department of Internal Medicine, Ehime University Hospital, and the Department of Pathology of Fujisawa City Hospital for their invaluable contributions to the treatment of this patient.
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How to cite this article: Yamanaka S, Hasebe S, Fujii T, Gondo T, Kitazawa R, Kitazawa S, Yakushijin Y. B-cell lymphoma following an indolent course over 30 years with immunophenotypic changes at each recurrence. *EJCRIM* 2026;**13**:doi:10.12890/2026_006191

## ABSTRACT

*Introduction:* Diffuse large B-cell lymphoma (DLBCL) comprises biologically distinct subtypes, but whether cell-of-origin–related features remain stable over long disease courses is unclear.

*Case description:* A woman was initially diagnosed with CD20-positive B-cell lymphoma in 1988 and treated with cyclophosphamide, vincristine and prednisolone (COP) chemotherapy. She experienced a first relapse in 1998 and received cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) chemotherapy. The second relapse occurred in 2008 and was managed with rituximab. At the third relapse in 2011, rituximab plus bendamustine (RB) was administered. During the fourth relapse in 2015, R-pirarubicin (THP)-COP chemotherapy was given. At the fifth relapse in 2017, at 80 years of age, RB therapy was administered again. A sixth relapse occurred in 2019, and the patient died within the same year. Histopathological evaluation throughout the disease course consistently demonstrated DLBCL. Notably, the immunophenotype showed sequential changes from a germinal centre B-cell-like pattern to an activated B-cell-like pattern and ultimately to a CD30-positive anaplastic B-cell variant.

*Discussion:* This unusually long clinical course highlights stepwise immunophenotypic evolution during repeated relapses, suggesting that surrogate subtype profiles may change over time.

*Conclusion:* Repeat biopsies with comprehensive pathological (and, when available, molecular) re-evaluation are important to accurately characterize relapsed DLBCL and inform treatment selection.

## KEYWORDS

Diffuse large B-cell lymphoma (DLBCL), GCB type, ABC type, immunophenotype, gene expression profiling

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## LEARNING POINTS

- Diffuse large B-cell lymphoma (DLBCL) can undergo stepwise immunophenotypic and molecular evolution over decades, progressing from a germinal Center B-cell-like (GCB)-like phenotype to an activated B-cell -like/non-GCB pattern (MUM1+, CD30+) and ultimately to an aggressive anaplastic variant.
- The cell-of-origin profile and its associated molecular features are not necessarily static; thus, therapeutic strategies for relapsed DLBCL should be tailored to the current disease state rather than relying on the signature at initial diagnosis.
- Longitudinal re-evaluation through repeat biopsies is imperative to capture the evolving landscape of the malignancy, ensuring that treatment selection is guided by the most recent pathological and molecular findings.

## INTRODUCTION

Malignant lymphoma is regarded as a curable hematologic malignancy, and approximately 65% of patients with diffuse large B-cell lymphoma (DLBCL) are cured[1]. DLBCL can be classified into at least two major molecular subtypes based on gene expression profiling: germinal centre B-cell-like (GCB) subtype and activated B-cell-like (ABC) subtype[2]. These subtypes are biologically distinct and exhibit markedly different transcriptional programs that reflect their respective cells of origin. The GCB subtype is characterized by the expression of genes associated with normal germinal centre B cells, including BCL6, CD10, and LMO2, and is often linked to the activation of the PI3K/AKT/mTOR signalling pathway. Clinically, patients with the GCB subtype tend to have a relatively favourable prognosis. In contrast, the ABC subtype exhibits high expression of genes involved in plasmablastic differentiation, such as IRF4/MUM1 and BLIMP1 (PRDM1), and is driven by the constitutive activation of the NF-κB pathway. This molecular profile is frequently associated with BCL2 overexpression and correlates with significantly poorer clinical outcomes compared to the GCB subtype[3]. However, whether such differences in gene expression arise at the onset of tumorigenesis or during tumour progression remains unclear.

Our patient experienced six relapses over a period of 30 years, during which the subtype shifted from the GCB type to the ABC type and further progressed to anaplastic B-cell lymphoma. Based on this case, we discuss evolutionary changes in B-cell malignancies and their treatments based on gene expression profiling.

## CASE DESCRIPTION

An 80-year-old woman was referred to our institution with a diagnosis of the fifth relapse of DLBCL, GCB immunophenotype. She had initially been diagnosed with DLBCL of the diffuse mixed small and large cell type (Working Formulation) in 1988. Her first relapse occurred in 1998 *(Fig. 1A)* and was treated with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) chemotherapy. The second relapse occurred in 2008 *(Fig. 1B)* and was managed with rituximab (R)-CHOP. At the third relapse in 2011, the patient received rituximab in combination with bendamustine (RB). During the fourth relapse in 2015 *(Fig. 1C)*, R-pirarubicin [THP]) -COP chemotherapy was administered. At the fifth relapse in 2017, at the age of 80, RB therapy was administered again. Two years later (2019) *(Fig. 1D)*, her disease relapsed for the sixth time, at which point she was also diagnosed with dementia. The patient subsequently died after a month follow-up period and did not receive further chemotherapy. The chronological treatment course and accompanying immunophenotypic changes across relapses are summarized in *Table 1*.

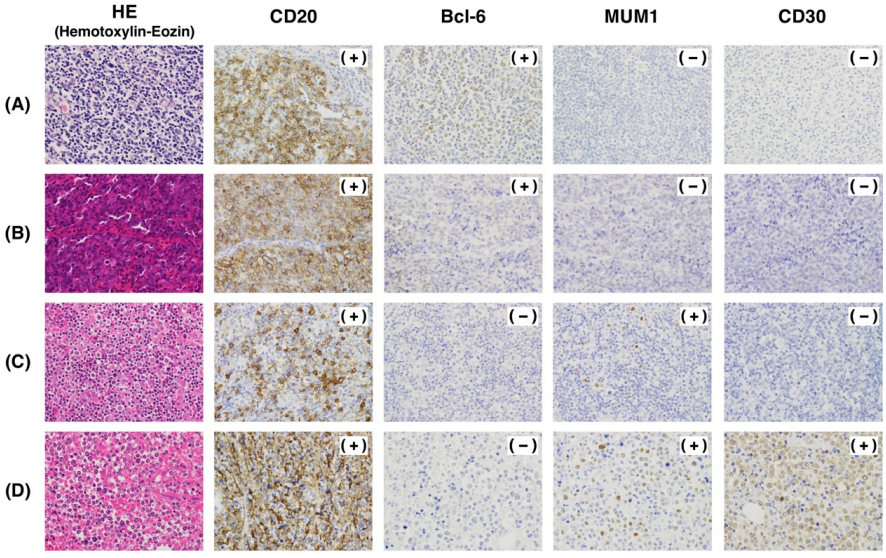



***Figure 1.*** *A) Pathological examination findings from 1998, B) 2008, C) 2015, D) 2019.*

| | CD5 | CD10 | CD20 | CD30 | Bcl-2 | Bcl-6 | MUM1 | Diagnosis | Treatment |
|---|---|---|---|---|---|---|---|---|---|
| 1988 | - | - | + | | | | | Diffuse mixed small- and large-cell lymphoma (working formulation) | COP |
| 1998 (first relapse) | - | - | + | - | + | + | - | Diffuse mixed small- and large-cell lymphoma (working formulation) | CHOP |
| 2008 (second relapse) | - | - | + | - | + | + | - | Diffuse large B-cell lymphoma (GCB type) | R-CHOP |
| 2011 (third relapse) | | | | | | | | | RB |
| 2015 (forth relapse) | - | - | + | - | + | - | + | Diffuse large B-cell lymphoma (ABC type) | R-THP-COP |
| 2017 (fifth relapse) | | | | | | | | | RB |
| 2019 (sixth relapse) | - | - | + | + | - | - | + | Diffuse large B-cell lymphoma (anaplastic variant) | (died) |

***Table 1.*** *Changes in treatment courses and the accompanying transitions in cellular phenotypes.*
*Abbreviations: COP, cyclophosphamide, vincristine, prednisolone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RB, rituximab, bendamustine; R-THP-COP, rituximab, pirarubicin, cyclophosphamide, vincristine, prednisolone.*

## DISCUSSION

We were able to follow this case of DLBCL for over 30 years and through 6 relapses, observing the detailed transition of its immunophenotypic profile from the GCB type to the ABC type and eventually to the anaplastic variant[2].

The cellular origin of DLBCL has traditionally been classified into GCB and ABC subtypes. Recent gene profiling data has further categorized DLBCL into four major groups: BN2, EZB, MCD, and N1[4]. These differences in gene expression are increasingly forming a conceptual basis for the development of precision therapies that can influence treatment selection. Among the four gene expression classifications of DLBCL, a high bcl-2 expression or translocation is a characteristic of the EZB subtype. A high bcl-6 expression is observed in both the EZB and BN2 subtypes, while MUM1 expression is characteristic of the MCD and N1 subtypes, and CD30 expression is frequently observed in the N1 subtype. The current case indicated that the tumour originally showed EZB and BN2 subtypes (bcl-2+ and bcl-6+), and the case was considered one of transformation, where the B cells evolved over a 30-year period, ultimately acquiring an aggressive gene expression profile (MUM1 and CD30 high), leading to the patient's death. The observed evolution of B cell gene expression in this case seems to present an intriguing and noteworthy pattern.

Recently, the treatment of DLBCL has shifted from R-CHOP therapy to a gene expression-guided approach[5-7]. Although the BN2 and EZB types still primarily rely on R-CHOP therapy, there is growing anticipation for targeted therapies in EZB types, such as EZH2 inhibitors and BCL2 inhibitors, as future treatment options. R-CHOP remains in use for the MCD subtype; however, BTK and PI3K inhibitors are currently under research as potential treatments. For the N1 subtype, R-CHOP was the first-line treatment. However, the development of drugs targeting NOTCH1 mutations, which could play a significant role in future treatment strategies, is underway. As cancer gene panel profiling analyses[8-10] are being applied increasingly frequently to hematologic malignancies, including lymphoid malignancies, therapeutic decision-making based on such genetic alterations is expected to progress, and the treatment of DLBCL is anticipated to change substantially in the future after R-CHOP.

In the current case, due to the patient's advanced age and cumulative toxicity of anthracyclines, which are key drugs in DLBCL therapy, adequate treatment intensity could not be maintained throughout the course. However, advances in therapies targeting the cell of origin and genetic alterations are expected to soon enable sufficient treatment, even in elderly patients or those with comorbidities.

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