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Very late recurrence of primary gastric diffuse large B-cell lymphoma followed by grade 3B follicular lymphoma: a case report

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Case Report

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Abstract

Background: Very late recurrence of diffuse large B-cell lymphoma (DLBCL) is uncommon and may reflect branching evolution from an early precursor or a clonally unrelated second lymphoma. Case presentation: A 62-year-old man was diagnosed with gastric DLBCL in 2007 and achieved complete remission after radical gastrectomy, six cycles of anthracycline-based chemotherapy, and radiotherapy. Fourteen years later, he developed stage III nodal DLBCL with a non-germinal-center B-cell-like phenotype. The 2021 tumor harbored an immunoglobulin heavy-chain-BCL6 fusion and mutations in MYD88, BRAF, NOTCH2, KMT2D, and TNFAIP3, whereas the archived gastric specimen had a distinct reported mutation profile. Rituximab-based chemoimmunotherapy produced a second complete remission. In February 2025, approximately 3 years later, an axillary lymph-node biopsy was diagnosed as grade 3B follicular lymphoma. After cytoreductive therapy and lymphodepletion, the patient received relmacabtagene autoleucel, a CD19-directed chimeric antigen receptor T-cell (CAR-T) product, on April 16, 2025. He developed grade 1 cytokine release syndrome and remained in complete remission after more than 6 months of follow-up. Conclusion: This prolonged course highlights the importance of repeat biopsy and clonal assessment when lymphoma recurs after a long remission or with discordant histology. CAR-T therapy was feasible in this selected older patient, although incomplete staging, absent formal clonal analysis, and short follow-up limit causal and efficacy conclusions.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive but potentially curable lymphoma, and most disease progression occurs within the first 2 years after treatment. Recurrence more than 5 years after diagnosis or complete remission is uncommon. Molecular studies of paired diagnostic and relapse specimens indicate that late recurrences often share few mutations with the dominant diagnostic clone and may arise through branching evolution from a common precursor; a subset are clonally unrelated second lymphomas [1, 2]. We describe an 18-year clinical course that included gastric DLBCL, a nodal DLBCL event 14 years later, a subsequent biopsy diagnosed as grade 3B follicular lymphoma (FL), and treatment with CD19-directed chimeric antigen receptor T-cell (CAR-T) therapy. The case illustrates both the therapeutic possibilities and the interpretive limitations created by discordant histology and incomplete clonal testing.

Case presentation

Initial presentation and treatment in 2007

A 62-year-old man presented with epigastric discomfort in June 2007. Gastroscopy showed a large irregular ulcer involving the greater and lesser curvatures of the gastric body, with impaired motility. Radical gastrectomy was performed. The resection specimen was diagnosed as infiltrative diffuse large B-cell lymphoma involving the gastric antrum. Immunohistochemistry showed CD20 and CD79a expression; CD10 was negative, BCL6 and MUM1 were positive, BCL2 was expressed in approximately

70% of cells, and the Ki-67 proliferation index was approximately 60%. MYC, cyclin D1, TdT, EBER, and cytokeratin were negative, supporting a non-germinal-center B-cell-like phenotype by immunohistochemistry. Single-photon emission computed tomography (SPECT) showed increased tracer uptake in the right upper mediastinum. Computed tomography demonstrated postoperative gastric changes and a lymph node near the celiac trunk; ultrasound also showed inguinal lymphadenopathy. Because the patient had chronic hepatitis B virus (HBV) infection with a markedly elevated HBV DNA level, rituximab was withheld. He received six cycles of CHOP-like chemotherapy (cyclophosphamide, epirubicin, vincristine, and prednisone) followed by radiotherapy to a total dose of 49.7 Gy in 31 fractions. Surveillance endoscopy from 2008 through 2020 showed only anastomotic or remnant gastritis, and serial imaging and hematologic assessments showed no evidence of lymphoma, consistent with a complete remission lasting 14 years.

Nodal DLBCL in 2021

In August 2021, the patient developed enlargement of the right tonsil. Biopsy showed DLBCL with a non-germinal-center B-cell-like phenotype (CD19+, CD20+, CD10-, BCL6+, MUM1+, BCL2 approximately 70%, Ki-67 approximately 80%, and EBER-). Tumor next-generation sequencing detected an IGH-BCL6 fusion (variant allele frequency, 26.3%) and mutations in MYD88, BRAF, NOTCH2, KMT2D, and TNFAIP3, a profile compatible with a BN2-like molecular subgroup [3]. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) showed FDG-avid disease in the right tonsil, lateral pharyngeal wall, and piriform sinus, together with widespread nodal involvement above and below the diaphragm. The gastric anastomosis was mildly thickened without abnormal FDG uptake. Bone-marrow flow cytometry did not identify an aberrant lymphoid population. The disease was classified as Ann Arbor stage III with an International Prognostic Index score of 3. Testing of the archived 2007 gastric specimen reported PC, KIT, STAT5B, and ABCB1 mutations, which did not overlap with the alterations reported in the 2021 specimen. The patient received six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) from August 2021 through February 2022 and achieved complete remission on restaging PET/CT. Orelabrutinib plus lenalidomide maintenance was started but discontinued because of treatment-related diarrhea.

Grade 3B follicular lymphoma and CAR-T therapy in 2025

In February 2025, the patient presented with left axillary pain and multiple enlarged lymph nodes on ultrasound. An excisional biopsy of a left axillary lymph node was diagnosed as grade 3B follicular lymphoma. The tumor expressed CD19, CD20, CD10, BCL6, BCL2, CD21, and CD79b; MUM1 and MYC were expressed in scattered cells; the Ki-67 index was approximately 70%; and EBER, cyclin D1, ALK, and SOX11 were negative. The patient declined PET/CT and bone-marrow biopsy, so complete restaging was not available. He received one cycle of rituximab, cyclophosphamide, vincristine, and prednisone (R-COP) for disease debulking, followed by lymphodepletion with fludarabine (42 mg on day 1 and 21 mg on days 2–3) and cyclophosphamide (350 mg on days 1–3). On April 16, 2025, he received CD19-directed CAR-T

cells (relmacabtagene autoleucel; relma-cel). Recurrent fever after infusion was assessed by the treating team as grade 1 cytokine release syndrome [4] and was managed with supportive therapy and nonsteroidal anti-inflammatory medication. The overall clinical course is summarized in Fig. 1. Peripheral-blood monitoring showed expansion of CAR-T cells after infusion (Fig. 2). At more than 6 months of follow-up, he remained in ongoing complete remission without reported disease progression.

Discussion

Late recurrence is clinically heterogeneous [5, 6]. Among patients who achieved event-free survival at 24 months after immunochemotherapy, Wang et al. reported cumulative incidences of late relapse of 6.9%, 9.3%, and 10.3% at 3, 5, and 8 years after that landmark, respectively [7]. Paired-tumor studies show that genetic divergence increases with time: late DLBCL recurrences may share only early precursor alterations with the diagnostic tumor, consistent with branching evolution, whereas some events are clonally unrelated [1, 2, 8–10]. In this patient, the distinct reported mutation profiles in 2007 and 2021 are compatible with biologic divergence but do not establish a clonal relationship. Without immunoglobulin-gene clonality testing, phylogenetic analysis, or confirmation that both specimens were tested with equivalent assays and coverage, the 2021 event could represent either a very late recurrence from a common precursor or a second primary DLBCL.

The 2025 biopsy adds a second interpretive challenge. DLBCL can be followed by a lymphoma with indolent histology, particularly when an occult follicular component was present initially; however, grade 3B FL differs biologically and clinically from classic low-grade FL and is generally managed as an aggressive large B-cell lymphoma [11, 12]. Therefore, describing the 2025 lesion as a definitive histologic transformation from DLBCL to FL would overstate the available evidence. Plausible explanations include an unrecognized follicular component, evolution from a shared precursor, a discordant lymphoma, or an independent second lymphoma. Direct comparison of the 2021 and 2025 specimens with morphology review, immunoglobulin clonality analysis, and harmonized sequencing would be needed to distinguish among these possibilities.

Treatment was shaped by age, prior anthracycline exposure, and lack of suitability for intensive salvage therapy and autologous transplantation. Real-world series indicate that CD19 CAR-T therapy can be feasible in carefully selected older patients with large B-cell lymphoma, although toxicity, frailty, and competing risks require individualized assessment [13–15]. In this case, R-COP was used for debulking before fludarabine-cyclophosphamide lymphodepletion and relma-cel infusion. The reported grade 1 cytokine release syndrome and early complete remission are encouraging, but a single case with limited follow-up cannot establish comparative efficacy or long-term disease control.

Strengths and limitations

The principal strength of this report is the longitudinal documentation of three pathologically sampled lymphoma episodes over 18 years, including molecular data from archived tissue. Important limitations

are the absence of formal clonal analysis; uncertainty about assay comparability and the reported PC gene symbol; incomplete staging in 2025 because PET/CT and bone-marrow biopsy were declined; limited detail on response-assessment modality, CAR-T quantification, and neurotoxicity surveillance; and follow-up of only slightly more than 6 months after CAR-T infusion.

Conclusion

Very late lymphoma events after DLBCL require renewed tissue diagnosis rather than an assumption of conventional relapse. Discordant histology and nonoverlapping targeted-sequencing results should prompt clonality-focused testing when material is available. CD19-directed CAR-T therapy was feasible in this selected older patient and produced an early complete remission, but longer follow-up and more complete molecular comparison are required before broader conclusions can be drawn.

Declarations

Patient perspective

A patient-authored perspective is not included in this report.

Competing Interests:

The authors declare no competing interests.

Ethics approval:

The requirement for ethical approval was waived by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine.

Consent to participate

and publish: Informed consent was obtained from the patient for participation and for publication of this case report and any accompanying images.

Use of artificial intelligence tools

An OpenAI large language model was used to assist with language editing.

Clinical trial number

Not applicable.

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Author Contribution

Jingwen Li drafted the manuscript. Jingwen Li, Xing Guo, and Fangshu Guan collected and analyzed the clinical data. Zhen Cai contributed to the interpretation of the findings and critically revised the manuscript. Yi Zhao supervised the work and critically reviewed the manuscript. All authors approved the final manuscript and agree to be accountable for all aspects of the work.

Acknowledgments

Not applicable

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

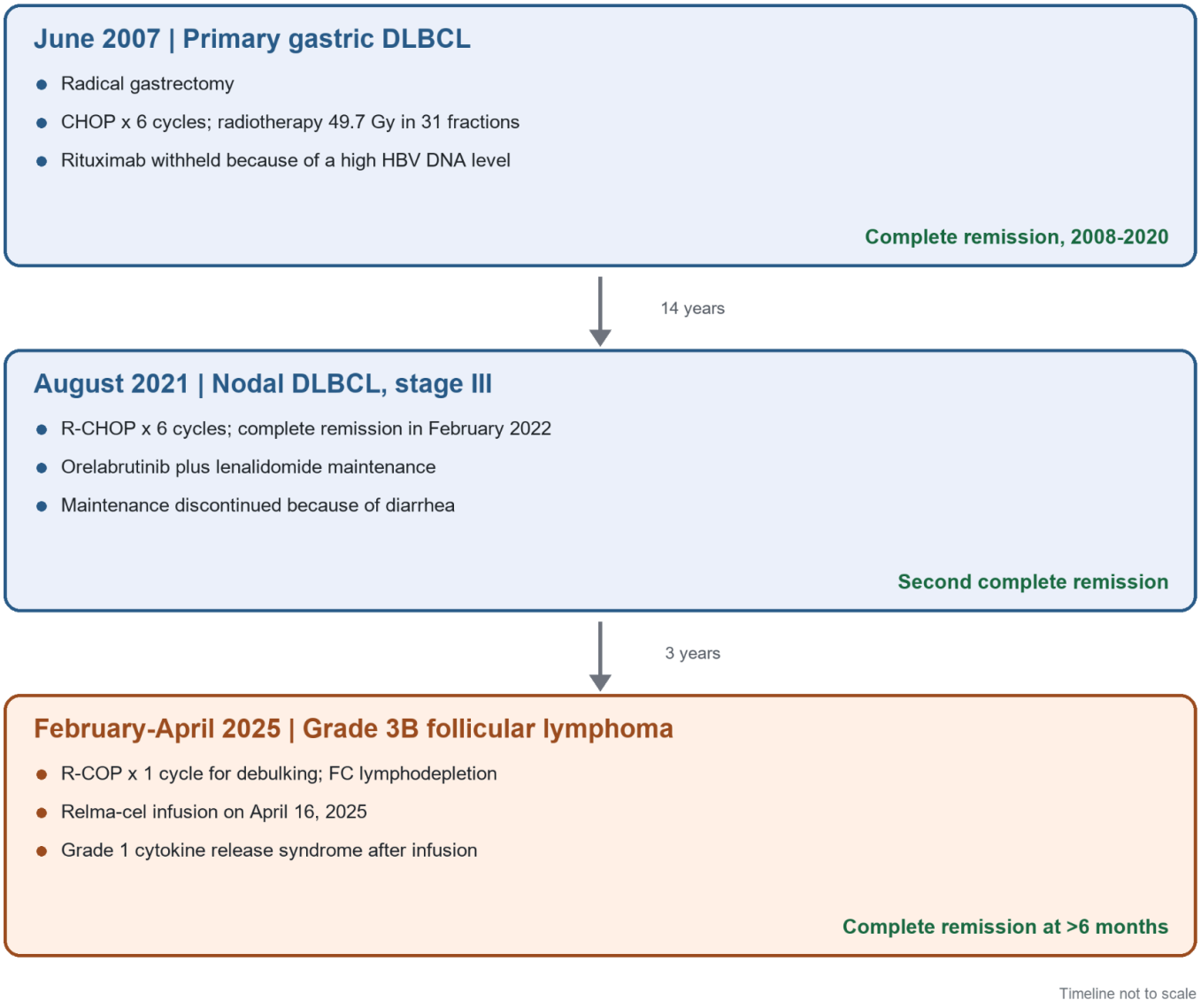


Figure 1

Clinical course and treatment timeline. CHOP, cyclophosphamide, an anthracycline, vincristine, and prednisone; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; FC, fludarabine and cyclophosphamide; FL, follicular lymphoma; R-CHOP, rituximab plus CHOP; R-COP, rituximab, cyclophosphamide, vincristine, and prednisone. Timeline intervals are summarized and not drawn to scale.

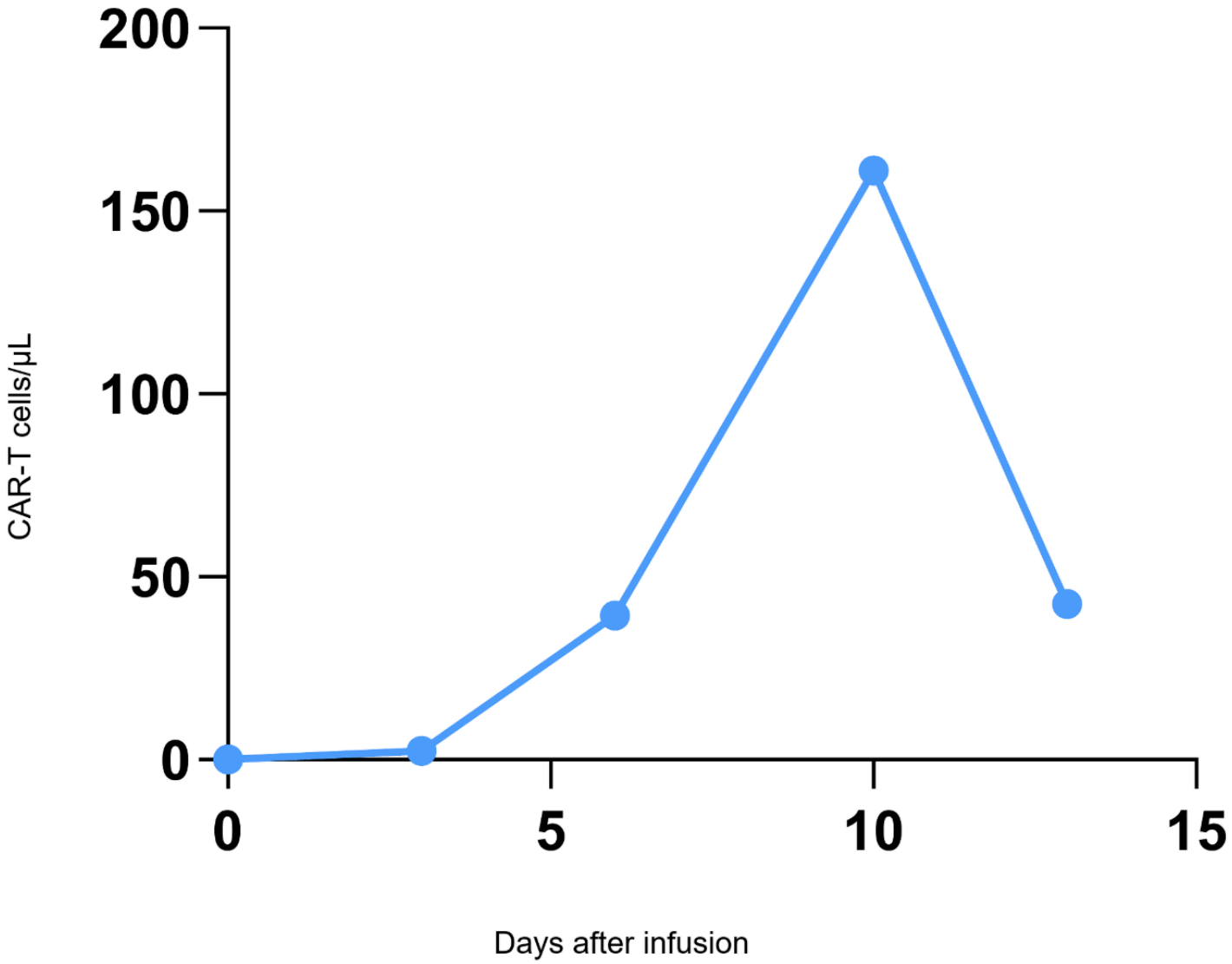


Figure 2

Peripheral-blood CAR-T cell expansion after relma-cel infusion. Values are presented as CAR-T cells per microliter at the recorded post-infusion time points.