

Isolated, Multiply Relapsing Secondary CNS Involvement in Triple Expressor Diffuse Large B-cell Lymphoma Despite Systemic Complete Remission: A 4-Year Case Report on Rare Disease Course and Barriers to Dual Chimeric Antigen Receptor Therapy Access

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common B-cell lymphoma globally. DLBCL with co-expression of MYC, BCL2 and BCL6, is an aggressive subtype with chemotherapy resistance and poor outcomes. Isolated secondary CNS relapse in the setting of sustained systemic remission is an exceptionally rare pattern with no established management algorithm.

OBJECTIVE

To report a rare case of triple-expressor Diffuse Large B-cell Lymphoma with recurrent isolated CNS relapse occurring despite complete systemic remission

To characterize the clinical, radiological, and histopathological course of this pattern in order to highlight gaps in management and the consequences of delayed Chimeric Antigen Receptor Therapy (CAR-T) access in a resource-limited setting

METHODS

Single-case retrospective report with nearly four years of follow-up.

It was reported for the first time in 2022.

Written informed consent for use and publication of the case details was obtained from the patient's family (specifically the patient's sister, who was his primary attendant) ensuring full patient data anonymization per institutional standards.

This report was part of routine clinical radiological (PET-CT, MRI), and histopathological data collected serially to document disease course, treatment response per Lugano criteria, and barriers to definitive therapy.

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CASE PRESENTATION

A 33-year-old man **presented with** submental swelling and was diagnosed with stage IVB, non-germinal center, DLBCL (Hans classifier), triple-expressor (MYC+/BCL2+/BCL6+) with extranodal involvement of kidneys, adrenals, peritoneum, and bone (CNS-IP1 3).

He achieved **complete systemic metabolic remission** after six cycles of R-CHOP with intrathecal methotrexate.

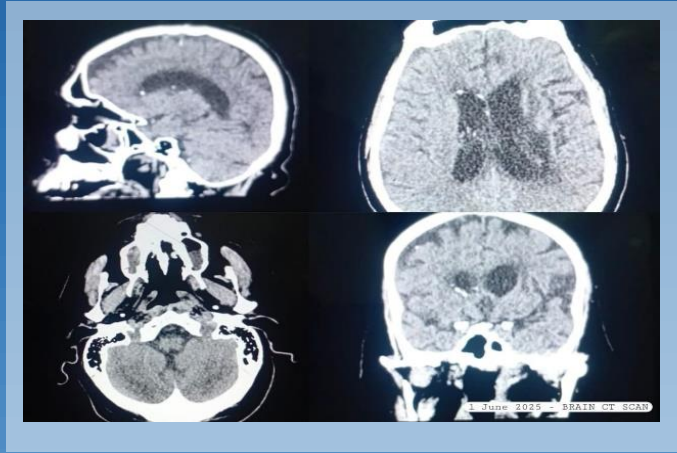
One month later, he developed isolated **CNS relapse** on MRI with systemically negative PET imaging. This pattern recurred three additional times over two years despite stereotactic radiosurgery, R-DHAP, R-DHAC, rituximab-temozolomide, and ibrutinib.

Autologous stem cell transplant and biopsy was **deferred** by the family at multiple time points.

He was referred for CD19/CD22 **dual-target CAR-T therapy** and travelled overseas to receive it. Upon arrival, he developed rapidly progressive cerebral edema, brain herniation, pneumonia, and seizures, becoming comatose.

He **died** in the intensive care unit before bridging chemotherapy or CAR-T could be administered.

Date	Event	Treatment	Result
2022	Submental swelling; antibiotics tried, no improvement. FNAC: atypical hyperplasia. SCF LN biopsy inconclusive. CT: abdominal LNs, omental/peritoneal nodules, splenomegaly	—	Lost to follow-up ~6 months (relocated)
2023 (early)	Re-presented with B-symptoms. PET-CT: widespread nodal disease + extranodal involvement (kidneys, adrenals, peritoneum, bones). Biopsy (porta hepatis LN, peritoneal deposits)	—	Diagnosis: DLBCL, stage IVB, Non-GCB, triple-expressor
2023	—	Started R-CHOP + IT MTX	Cycle 1: febrile neutropenia, hospitalized; subsequent cycles dose-reduced 20%
2023 (mid)	Interim PET-CT after cycle 4	—	Partial metabolic response (Deauville 4); CSF cytology negative
Late 2023	Completed 6 cycles; EOT PET-CT	—	Complete metabolic remission (Deauville 1) → surveillance
Dec 2023	Acute right weakness, slurred speech, facial deviation. MRI: lesion in left hemipons → midbrain/thalamus/internal capsule. Systemic PET & spine MRI negative	SRS — 5 gamma knife sessions (biopsy declined)	Symptoms initially resolved
Early 2024	Recurrent right weakness. MRI: new supra-/infratentorial lesions; PET systemically negative	R-DHAP + high-dose MTX	Cycle 1 → sepsis, AKI, hyperglycemia
2024	—	Cycle 2: rituximab + HD-MTX only	—
June 2024	—	Cycle 3: modified to R-DHAC (carboplatin for cisplatin, cytarabine ~30%)	Patient then non-compliant, lost to follow-up
Oct 2024	MRI: prior lesions regressed, new left thalamic lesion	2 more cycles HD-MTX + R-DHAC; ASCT discussed	ASCT declined (patient hesitant)
Dec 2024	—	DHAC → HD-MTX → dexamethasone + cytarabine + HD-MTX	—
~Early 2025	Repeat MRI: thalamic lesion extending into left caudate, internal capsule, lentiform nuclei. PET systemically negative	Rituximab + temozolomide x2 cycles	—
Through Mar 2025	Patient agreed to biopsy: confirmed DLBCL, CD20+, Ki-67 70%	—	—
~Post-Mar 2025	Repeat PET: increased size/activity of CNS lesions	Single-agent ibrutinib 560 mg/day; referred for CAR-T in China	—
On arrival in China	Evaluated for refractory DLBCL with secondary CNS involvement, pneumonia, epilepsy, cerebral edema, brain herniation, paroxysmal AF	—	Comatose, anisocoria (4:3 mm), no response to pain
July 2025	Repeat chest CT	—	Slight improvement in pulmonary infection
—	—	Chemotherapy initiated; CAR-T pending	Patient collapsed before chemotherapy/CAR-T could be administered



CONCLUSION

This case demonstrates an exceptional ly rare trajectory: extranodal triple-expressor DLBCL with recurrent isolated CNS relapse despite durable systemic remission.

The fatal outcome underscores how delayed access to CAR-T therapy can render an otherwise promising intervention ineffective.

This highlights the critical need for timely CAR-T access within Pakistan and supports early consideration of this modality in CNS-refractory DLBCL before disease progression becomes irreversible.

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