





# Multiply Relapsed Secondary CNS Non-Germinal Center Diffuse Large B-Cell Lymphoma Successfully Treated with CNS-Centric Therapy

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**Abstract:** Secondary central nervous system involvement by systemic diffuse large B-cell lymphoma (DLBCL) carries a very poor prognosis. We present a female patient who had two episodes of intracerebral central nervous system (CNS)-only relapse of systemic non-germinal center diffuse large B-cell lymphoma (NGC-DLBCL). Her treatment at initial diagnosis consisted of induction with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and intrathecal (IT) - methotrexate (MTX) followed by consolidation with autologous stem cell transplant (ASCT) after high-dose carmustine, etoposide, cytarabine, and melphalan (BEAM) chemotherapy. She had the first CNS-only relapse 1.5 years post-ASCT and received whole brain radiation therapy (WBRT). She developed the second intracerebral CNS-only relapse 2 years post-WBRT. A CNS-centric therapeutic approach with salvage chemoimmunotherapy incorporating rituximab, high-dose methotrexate (HD-MTX), high-dose cytarabine (HiDAC), and ibrutinib was utilized for her second CNS-only relapse. She underwent consolidation with a second ASCT following high-dose carmustine (BCNU) and thiotepa chemotherapy. Given her high risk of CNS recurrence, she was started on maintenance ibrutinib. To date, she has remained in complete remission for 3 years. In our experience, multiply relapsed secondary CNS lymphoma (SCNSL) with this response is very rare. We suggest one CNS-centric therapeutic approach that can potentially salvage patients with SCNSL who have not had prior exposure to adequate CNS-directed therapies but acknowledge that additional research is necessary to validate our findings.

**Keywords:** SCNSL, relapsed CNS lymphoma, CNS lymphoma, secondary CNS DLBCL

## Introduction

Secondary central nervous system diffuse large B-cell lymphoma (SCNS-DLBCL) represents central nervous system (CNS) dissemination and involvement by a systemic DLBCL at the time of initial diagnosis (de novo SCNSL; DN-SCNSL) or relapse (R-SCNSL).<sup>1-6</sup> R-SCNSL include CNS-only or concomitant CNS-systemic relapse. R-SCNSL develops early in the disease course with a median time to relapse of 5.4 months from diagnosis. Approximately 80% of patients relapse while receiving chemotherapy or within 6 months of completion of therapy.<sup>1</sup>

Among the seventy-five patients enrolled in the largest clinical trial of secondary CNS DLBCL (MARIETTA trial), DN-SCNSL represented 43% of cases, while CNS-only R-SCNSL accounted for 20%, and CNS-systemic R-SCNSL 37% of cases.<sup>5</sup> The neuroanatomical localization of SCNSL included intracerebral (45%), leptomeningeal (11%), intracerebral/leptomeningeal (17%), intracerebral/ocular (13%), intracerebral/leptomeningeal/ocular (8%), ocular (3%), or spinal cord (3%) disease.<sup>5</sup> Based on Han's criteria for cell of origin, 59% of the evaluable patients had non-germinal center (NGC)-DLBCL.<sup>5</sup> The neurological manifestations of SCNSL included motor impairment (49%), sensory impairment (33%), cognitive impairment (20%), sensorial impairment (16%), and language impairment (9%).<sup>5</sup>

SCNSL is extremely uncommon, and there is limited data available regarding optimal treatment. Two of the largest studies reported an incidence of 1.05% for DN-SCNSL and 2.2–2.8% for relapse central nervous system lymphoma (R-SCNSL).<sup>1,7</sup> While others have suggested that CNS relapse of DLBCL occurs in 3% to 5% of patients with a median overall survival (mOS) of less than 7 months.<sup>6,8–10</sup> In the studies in which the treatment consisted of intensive CNS-directed therapy and consolidation with autologous stem cell transplant (ASCT), the mOS was less than 10 months with a 3-year overall survival (OS) of 22% for the population as a whole and 42% for patients who underwent consolidation with ASCT has been reported.<sup>2,11,12</sup> The survival outcome for multiply relapsed SCNSL is not known but likely very poor.

We report a case of multiply relapsed intracerebral SCNSL associated with systemic NGC-DLBCL who was successfully salvaged with CNS-centric therapy with a sustained complete remission (CR) for 3 years to date.

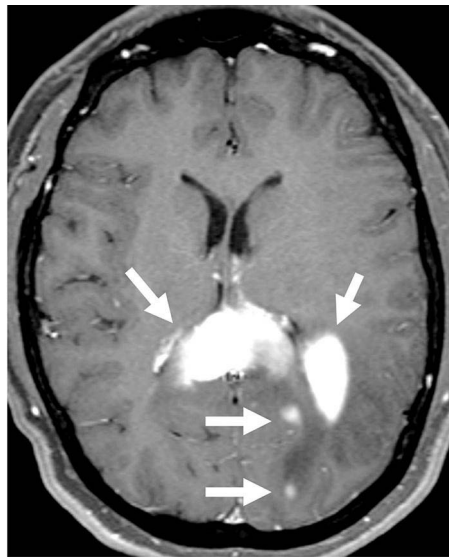
## Case

A 38-year-old Asian female presented with a 6-week history of progressive abdominal discomfort and distention, fatigue, 10-pound weight loss, and night sweats. Computed tomography (CT) of the abdomen and pelvis showed extensive soft tissue masses throughout the peritoneal cavity and retroperitoneum. Positron emission tomography-computed tomography (PET-CT) demonstrated generalized hypermetabolic bulky nodal masses including an 8.5 × 6.9 centimeter (cm) peritoneal mass, a 7.5 × 6.4 cm pelvic mass, and a 6.3 × 1.7 cm anterior mediastinal mass. CT guided biopsy of an abdominal mass was performed and demonstrated lambda light chain restricted monoclonal B-cells expressing CD19, CD20, CD45, BCL2, and MUM1. The Ki67 proliferation rate was greater than 90%. Fluorescence in situ hybridization (FISH) showed the *MYC* gene region was within normal limits. The peripheral blood lactate dehydrogenase (LDH) was reportedly elevated at an outside facility. Bone marrow biopsy and cerebrospinal fluid (CSF) evaluations were negative. She was diagnosed with stage IV NGC-DLBCL with a high-intermediate risk age-adjusted international prognostic index (IPI) score given stage IV disease and an elevated LDH at diagnosis. She received 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with 4 doses of intrathecal (IT) -methotrexate (MTX) with resolution of her symptoms. Restaging evaluation was consistent with complete remission (CR). After completion of induction therapy, there were concerns among the care team members at the time regarding the high risk of rapid relapse based on aggressiveness of the disease on presentation. The decision was made to proceed with ASCT. She underwent consolidation with high-dose carmustine, etoposide, cytarabine, and melphalan (BEAM) followed by ASCT.

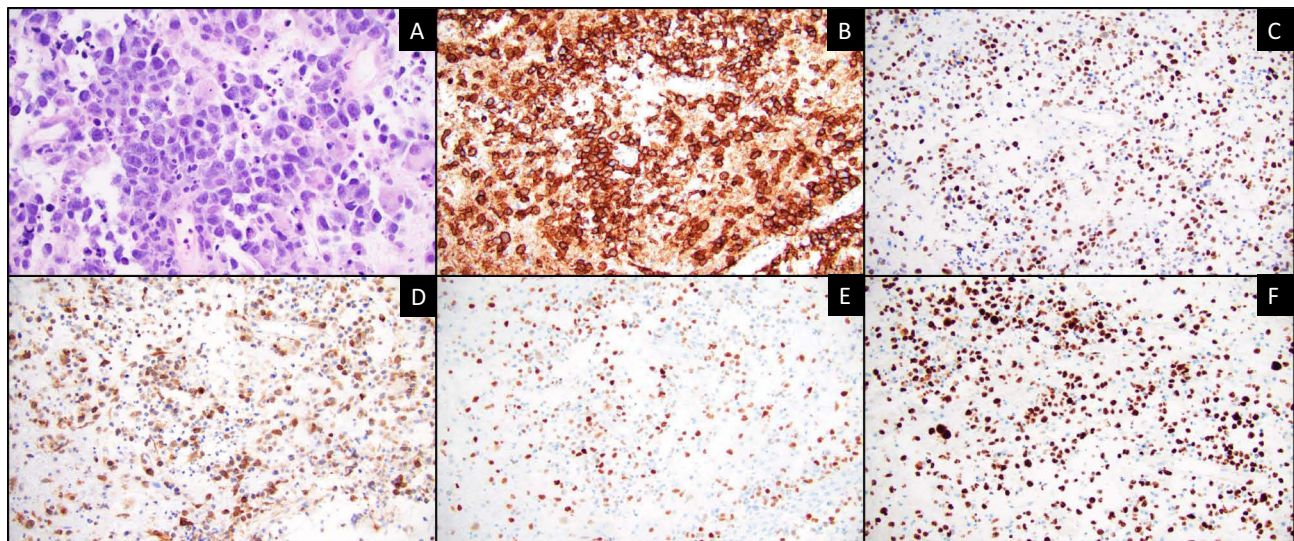
Unfortunately, she developed blurred vision and gait imbalance and was found to have an intracerebral CNS-only relapse 1.5 years following ASCT. Magnetic resonance imaging (MRI) brain showed a 1.7 cm mass in the right foramen of Luschka invading the medulla and right cerebellar tonsil. MRI brain was negative for leptomeningeal enhancement and CSF cytology was negative for lymphoma. CT soft tissue neck, chest, abdomen, and pelvis with contrast showed no evidence of systemic disease. She received whole brain radiation therapy (WBRT) for a total of 2340 cGy with a brain stem boost of 2340 cGy local radiation to the tumor. One month following WBRT, a repeat MRI brain showed a CR.

Two years following WBRT, she presented to our institution with word finding difficulty and mental status changes. MRI of the brain revealed intracerebral, multifocal, enhancing mass lesions with one of the larger components centered within the splenium of the corpus callosum, measuring 1.8 × 3.5 × 1.6 cm (Figure 1). A PET-CT demonstrated a hypermetabolic focus in the left parieto-occipital region suggesting recurrent lymphoma. An excisional biopsy of the left parietal tumor showed large lymphoma cells (Figure 2A). The lymphoma cells were positive for CD20, BCL6, BCL2, and MUM1 by immunohistochemistry (IHC) (Figure 2B–E). They were negative for CD10, CD30, and TdT. Epstein-Barr encoding region (EBER) ish was negative. The Ki67 proliferation index was 90% (Figure 2F). The CSF cytology was negative. These findings were consistent with relapsed CNS NGC-DLBCL according to Hans' algorithm.<sup>13</sup> Unfortunately, additional testing could not be performed due to the small biopsy.

Salvage chemotherapy with rituximab, high-dose methotrexate (HD-MTX), and high-dose cytarabine (HiDAC) was initiated with improvement in her neurologic symptoms. She developed severe dermatitis which was thought to be secondary to HiDAC. She was transitioned to rituximab, HD-MTX, and Ibrutinib for cycles 2–4 of treatment. Ultimately, the rash was due to acyclovir, and she completed cycles 5–6 with a combination of rituximab, HD-MTX and HiDAC. Subsequent MRI demonstrated a near CR (Figure 3A and B).



**Figure 1** MRI Imaging at Second Relapse. Contrast enhanced axial MRI showing infiltrative, multifocal, enhancing mass lesions with one of the larger components centered within the splenium of the corpus callosum.



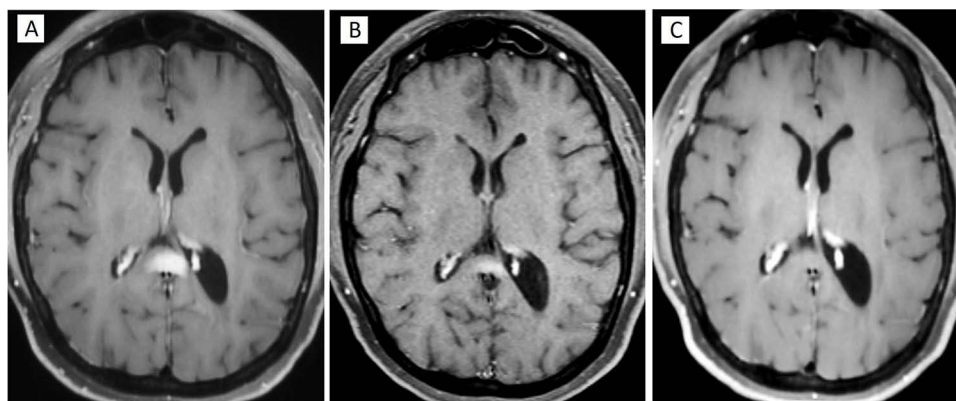
**Figure 2** Pathologic Evaluation of the Left Parietal Tumor. H&E x40 magnification shows large B cells (A). IHC x20 magnification shows that the neoplastic B-cells stained positive for CD20 (B), BCL6 (C), BCL2 (D), MUM1 (E) with a high MIB1 proliferation rate (F).

**Abbreviations:** H&E, haematoxylin and eosin; IHC, immunohistochemistry.

She was consolidated with a second ASCT following high-dose carmustine (BCNU) and thiotepa. Her day 100 work-up including a PET scan, MRI brain and bone marrow biopsy showed a CR (Figure 3C). She was started on maintenance Ibrutinib 560 mg daily due to her high risk of relapse. She has remained in CR for 3 years. She currently enjoys excellent quality of life with full-time employment. A summary of her treatment is provided in Table 1.

## Discussion

This case highlights the importance of utilizing CNS-penetrating agents for SCNSL. The patient developed her first CNS-only relapse despite R-CHOP, IT-MTX, and consolidation with ASCT following high dose BEAM chemotherapy. This suggests that the regimen was adequate for her systemic disease but insufficient for the CNS disease. Her second CNS-only relapse occurred after WBRT. This suggests that WBRT alone without systemic CNS-directed therapy is also inadequate. She was successfully



**Figure 3** MRI Imaging Post-Treatment. (A and B) MRI after salvage therapy with near complete remission. (C) Repeat contrast enhanced MRI following day 100 work-up status post second ASCT shows complete remission.

**Abbreviations:** ASCT, autologous stem cell transplant; MRI, magnetic resonance imaging.

salvaged with a combination of CNS-penetrating therapy followed by consolidation with ASCT following CNS-penetrating high dose conditioning chemotherapy. She was then placed on maintenance ibrutinib due to her high risk of CNS relapse. She has been in CR for 3 years to date. The findings in our case indicate that CNS-centric therapy can potentially salvage multiply relapsed SCNSL if the prior systemic treatments do not adequately penetrate the CNS.

Our patient received CNS-directed therapy without systemic disease-directed therapy as she had late-onset CNS-only SCNSL. Most commonly patients with R-SCNSL have early relapse; however, our patient's relapse was more atypical and presented late.<sup>1</sup> Her treatment resembled regimens commonly used for primary CNS lymphoma (PCNSL). In a Phase II clinical trial evaluating patients with SCNSL, induction regimens consisted of CNS-directed as well as systemic disease-directed therapies.<sup>4,5,14,15</sup> This approach is well suited if the SCNSL has both a CNS and systemic components or if the patient has an early CNS relapse. Therapy directed at systemic disease may not be necessary for CNS-only SCNSL with late relapse. In addition, CNS-directed therapy also impacts systemic disease. Further research is necessary to determine the optimal therapeutic approach for CNS-only SCNSL with late relapse.

**Table 1** Case Presentation Treatment Summary

Symptoms	Diagnosis	Induction Regimen	Consolidation Regimen	Maintenance
Presented to outside institution with abdominal pain/distension, fatigue, weight loss, night sweats	Stage IV NGC – DLBCL without BM or CNS involvement	6 cycles R-CHOP 4 doses of IT MTX	Autologous SCT with BEAM conditioning	None
Presented to outside institution with gait imbalance and blurred vision 1.5 years after autologous SCT	First CNS-only relapse of DLBCL	WBRT	None	None
Presented to our hospital with word finding difficulty and mental status changes 2 years post-WBRT	Second CNS- only relapse	Cycle 1: rituximab, HD-MTX, HiDAC. Cycles 2–4: rituximab plus HD-MTX and ibrutinib given rash thought to be due to HiDAC. Rash later determined due to acyclovir. Cycles 5–6: rituximab, HD-MTX, and HiDAC.	Second autologous SCT after conditioning with BCNU plus thiotepa	Ibrutinib

**Abbreviations:** BEAM, carmustine, etoposide, cytarabine, melphalan; BCNU, carmustine; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; HD-MTX, high-dose methotrexate; HiDAC, high-dose cytarabine; IT MTX, intrathecal methotrexate; NGC, non-germinal center; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; SCT, stem cell transplant; WBRT, whole brain radiotherapy.

There have been four phase II clinical trials for SCNSL.<sup>4,5,14,15</sup> These trials incorporated CNS and systemic disease directed induction followed by consolidation with ASCT/CNS-penetrating high-dose chemotherapy with promising survival outcomes.<sup>4,5,14,15</sup> The 5-year OS was 41% in the entire study group and 68% in patients who received ASCT.<sup>4</sup> This strategy was not as effective for R-SCNSL. These patients had a 2-year progression free survival (PFS) of 28% compared to 71% for DN-SCNSL.<sup>5</sup> Maintenance therapy following ASCT has not been evaluated. A summary of key clinical trials in SCNSL and associated outcomes are included in Table 2.

In regard to WBRT, a retrospective study evaluated response in 25 SCNSL patients who received consolidative versus palliative WBRT. Thirteen patients received consolidative WBRT with a mOS of 24 months and 2-year OS of 64%. The 12 patients who received palliative WBRT had a mOS of 3 months and 2-year OS of 8%. The results of this small study sample suggest that consolidative WBRT may improve long-term survival in SCNSL and could be a potential option for transplant ineligible patients or patients with CNS-only relapse.<sup>16</sup> Additionally, WBRT has been used as the stand-alone treatment in PCNSL with ORR of 90% and median OS of 11.6 months.<sup>17</sup>

At the time of first CNS-only relapse, our patient was treated at an outside institution and underwent WBRT. It would have been reasonable to consider treating with CNS-directed systemic therapy instead of WBRT. This is especially true when taking into consideration the neurotoxicity that can result from WBRT including decreased attentiveness and executive function.<sup>18</sup>

Our patient has been maintained on continuous ibrutinib therapy due to high risk of relapse. Ibrutinib has been shown to be efficacious in systemic NGC-DLBCL and provides excellent CNS penetration.<sup>19,20</sup> It has been used successfully in newly diagnosed and relapsed PCNSL.<sup>21–23</sup> In a Phase I clinical trial, seven patients with R-SCNSL were treated with ibrutinib with an overall response rate of 71%. Approximately 57% of patients experienced a CR, and the median PFS was 7.4 months.<sup>21</sup> Our patient has been tolerating maintenance ibrutinib quite well.

There is limited data regarding the optimal treatment of multiply relapsed CNS-only SCNSL. This represents just one case and potential treatment strategy. We acknowledge that additional research is necessary to determine the optimal treatment regimen and to assess the role of maintenance therapy.

**Table 2** Summary of Clinical Trials in SCNSL and Reported Outcomes

Clinical Trial	Phase	Type of SCNSL	Histology	Treatment	Total Accrual	CR	Survival
Ferreri AJM et al <sup>5</sup>	2	Initial diagnosis and relapsed	DLBCL	Initial treatment (MATRIX x 3 cycles → RICE x 3 cycles) followed by HD BCNU/TT and ASCT	79	55%	2Y PFS- 46%, 2Y OS- 46%
Ferreri AJM et al <sup>4</sup>	2	Initial diagnosis and relapsed	DLBCL Blastoid MCL FL (Grade-3)	Initial treatment (R + HDMTX + HiDAC → R-HD sequential chemotherapy with cyclophosphamide, Ara-C, and VP-16) followed by HD BCNU/TT and ASCT	38	63%	2Y EFS- 50%, 5Y OS- 41%
Korfel A et al <sup>15</sup>	2	Relapsed	Aggressive lymphoma (Burkitt lymphoma and lymphoblastic lymphoma excluded)	Initial treatment (MTX/IFO/DEP → Ara-C/TT/DEP) followed by HD BCNU/TT/VP-16 and ASCT	38	63%	2Y TTF- 49%

**Abbreviations:** DLBCL, diffuse large b cell lymphoma; MCL, mantle cell lymphoma; FL, follicular lymphoma; MATRIX, High-dose methotrexate + high-dose Ara-C + thiotepa + Rituximab; RICE, Rituximab + ifosfamide + carboplatin + etoposide; BCNU, carmustine; TT, thiotepa; ASCT, autologous stem cell transplant; R, Rituximab; HDMTX, high-dose methotrexate; HiDAC, high-dose ara-c; VP-16, etoposide; MTX, methotrexate; IFO, ifosfamide; DEP, liposomal ara-c; CR, complete response; PFS, progression free survival; OS, overall survival; EFS, event free survival; TTF, time to treatment failure.

## Conclusion

CNS-directed therapy is critical in the management of SCNSL. Our patient achieved a long-term CR after salvage CNS-directed treatment for multiply relapsed intracerebral CNS-only SCNSL. The therapeutic success in our patient is likely due to high-dose BCNU/Thiotepa chemotherapy with ASCT and maintenance ibrutinib. This case demonstrates the benefit of CNS-centric salvage therapy in multiply relapsed SCNSL when the patient has previously received inadequate systemic CNS-directed therapy. For eligible SCNSL patients, induction therapy and high-dose chemotherapy consisting of CNS-penetrating agents should be considered. Current therapies for R-SCNSL are limited and are often ineffective. Novel therapies are urgently needed for elderly and unfit patients who are not eligible for currently available intensive therapies. In addition, the role of maintenance therapy needs to be further explored. Additional research is necessary to assess the therapeutic approach which was undertaken in our patient with multiply relapsed SCNSL.

## Abbreviations

ASCT, autologous stem cell transplant; BCNU, carmustine; BEAM, carmustine, etoposide, cytarabine, melphalan; cm, centimeter; CNS, central nervous system; CR, complete remission; CSF, cerebrospinal fluid; CT, computed tomography; DN-SCNSL, de novo secondary CNS lymphoma; DLBCL, diffuse large b-cell lymphoma; EBER, Epstein-Barr encoding region; FISH, fluorescence in situ hybridization; HiDAC, high-dose cytarabine; HD-MTX, high-dose methotrexate; IHC, immunohistochemistry; IPI, international prognostic index; IT, intrathecal; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; MTX, methotrexate; mOS, median overall survival; NGC, non-germinal center; NGC-DLBCL, non-germinal center DLBCL; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PCNSL, primary CNS lymphoma; PFS, progression free survival; R-CNSL, relapse central nervous system lymphoma; R-SCNSL, relapse secondary CNS lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; SCNSL, secondary CNS lymphoma; SCNS-DLBCL, secondary CNS diffuse large B-cell lymphoma; WBRT, whole brain radiation therapy.

## Consent for Publication

The study participant has given written informed consent to participate as well as written informed consent to publish the case details and accompanying images. Institutional approval was not required to publish the case details.

## Disclosure

The authors report no conflicts of interest in this work.

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