Received: 28 July 2023 | Revised: 9 December 2023 | Accepted: 18 December 2023

DOI: 10.1002/ccr3.8409

CASE REPORT

Clinical Case Reports Open Access WILEY

Relapsed isolated CNS lymphoma treated with radiotherapy and intrathecal methotrexate followed by high-dose intravenous methotrexate, rituximab, and temozolomide: A case report

Ikhwan Rinaldi[1,2] | **Abdul Muthalib**[1,2] | **Soehartati Gondhowiardjo**[3] | **Tjondro Setiawan**[2] | **Andhika Gunawan**[4] | **Nelly Susanto**[3] | **Lingga Magdalena**[3] | **Kevin Winston**[5] | **Ashila Disamantiji**[6] | **Bintang Wirawan**[6]

[1]Division of Hematology and Medical Oncology, Department of Internal Medicine, Cipto Mangunkusumo National General Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

[2]Department of Internal Medicine, Gading Pluit Hospital, Jakarta, Indonesia

[3]Department of Radiology, Gading Pluit Hospital, Jakarta, Indonesia

[4]Department of Nuclear Medicine, Gading Pluit Hospital, Jakarta, Indonesia

[5]Hospital Medicine, Bhakti Medicare Hospital, Cicurug, Indonesia

[6]Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Correspondence
Ikhwan Rinaldi, Division of Hematology and Medical Oncology, Department of Internal Medicine, Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia.
Email: ikhwanrinaldi@gmail.com

Key Clinical Message

Optimized treatments for relapsed isolated CNS lymphoma (RI-SCNSL) remains under investigation. Temozolomide combination-based therapy, which is often used in glioblastoma may be used as potential treatment in RI-SCNSL.

Abstract

One of the most common types of non-Hodgkin lymphoma (NHL) is diffuse large B-cell lymphoma (DLBCL). Despite advances in treatment, relapsed isolated CNS lymphoma (RI-SCNSL) from DLBCL remains an issue. The optimal approach in RI-SCNSL remains an area of active investigation as currently there is no high level of evidence for the treatments due to lack of randomized studies. In this case report, we present a DLBCL patient with CNS recurrence treated radiotherapy and intrathecal methotrexate (MTX) followed by intravenous high-dose MTX, rituximab, and temozolomide. To the best of our knowledge, this is the first case report describing RI-SCNSL treated with the regiments above which also include temozolomide which is used for glioblastoma.

KEYWORDS

CNS, DLBCL, MTX, radiation, rituximab, temozolomide

1 | INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is one of the most common types of non-Hodgkin lymphoma (NHL), representing up to around 40% cases of NHL.[1–4] DLBCL can occur at any age, but it is more common in older adults. The incidence of DLBCL increases with age, with the highest incidence in individuals over the age of 60. It is slightly more common in men than in women. Geographically, the incidence of DLBCL varies across different regions

and populations.[5] Studies have shown that DLBCL incidence is higher in developed countries compared to developing countries.[3,4,6]

With current treatment of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP), a significant proportion of DLBCL patients can achieve remission. However, approximately 10% of patients are not responsive to treatment and may progress to extranodal sites such as gastrointestinal tract, skin, and central nervous system (CNS).[7,8] Importantly, some patients undergo relapse after treatment and the relapse may present with CNS involvement only. These secondary CNS lymphoma patients are classified as relapsed isolated CNS lymphoma (RI-SCNSL) based on British Society for Haematology (BSH) good practice paper.[9] Other terminologies from BSH include synchronous CNS and systemic lymphoma at initial presentation (treatment-naïve; TN-SCNSL) and relapsed concomitant systemic and CNS disease following treatment for systemic lymphoma (RC-SCNSL). Based on literatures, CNS recurrence of DLBCL is a rare with its incidence ranges from approximately 1% to 35%.[10–14]

For management of RI-SCNSL, there is currently no high level of evidence for the treatments due to lack of randomized studies.[9,15,16] In this case report, we present a case of RI-SCNSL that was successfully treated with radiotherapy and intrathecal methotrexate (MTX) followed by intravenous high-dose MTX, rituximab, and temozolomide.

The highlight of our case report is that RI-SCNSL can be treated with combination of radiotherapy intrathecal MTX, intravenous MTX, and temozolomide. To the best of our knowledge, this is the first case report describing RI-SCNSL treated with the regiments above which also include temozolomide which is used for glioblastoma. Currently, there is no standardized treatment for RI-SCNSL and there is a wide variability in the treatments used in clinical practice.[9,17–19] As a matter of fact, even for primary CNS lymphoma, there is also limited evidences.

2 | CASE REPORT

A male patient aged 53-year-old on 1 May 2020 came due to chief complaint of rapidly enlarging and painless mass on left shoulder, right shoulder, left neck, and region near left ear. The patient stated that he first felt the mass on left shoulder, but subsequently, the mass appeared on right shoulder, left neck, and left ear. Other symptoms include losing around 5 kg of weight in less than 6 months and chronic low-grade fever. Medical history was also significant for asymptomatic gall stone diagnosed in 2005.

The patient denied any previous exposure to chemotherapy agents or a history of cancer within their family. Furthermore, there was no known history of autoimmune diseases. The patient also denied exposure to pesticides and fertilizers, but reported being a long-term smoker.

Physical examination showed normal mental status. Anthropometry showed obesity with BMI of 26.4 kg (weight 82 kg; height 176 cm). Blood pressure was 120/80 mmHg, respiratory rate 18× per minute, heart rate 76 beats per minute, and temperature of 36.3°C. Additionally, peripheral oxygen saturation was 99%. Other components of physical examinations were within normal limits.

TABLE 1 Laboratory examinations on 1 May 2020.

Lab	Values	Reference
Hemoglobin (g/dL)	11.9	13.2–17.3
Hematocrit (%)	35	40–52
Leukocyte (10^3/μL)	8.3	4.5–11
Basophil (%)	0	0–1
Eosinophile (%)	0	2–4
Band neutrophil (%)	0	3–5
Segmented neutrophil (%)	62	50–70
Lymphocyte (%)	18	25–40
Monocyte (%)	19	2–8
ESR (mm)	63	0–10
Thrombocyte (10^3/μL)	151	150–440
Total protein (g/dL)	7.4	6.0–8.8
Urine color	Yellow	Yellow
Turbidity	Clear	Clear
Urine		
Specific gravity	1.020	1.003–1.030
pH	5.5	4.6–8.5
Protein	Trace	Negative
Glucose	Negative	Negative
Ketone	Trace	Negative
Bilirubin	Negative	Negative
Occult blood	Negative	Negative
Nitrite	Negative	Negative
Urobilinogen	Normal	
Leukocyte esterase	Negative	Negative
Sediment		
Leukocytes (/HPF)	4	0–6
Erythrocytes (/HPF)	6	0–7
Cast	Negative	Negative
Epithelial cells	Positive	Positive
Crystal	Calcium oxalate	Negative

Initial lab examination showed elevated ESR, elevated monocyte, and mildly reduced hemoglobin (Table 1). Meanwhile, urinalysis only showed trace protein.

On 4 May 2020, a biopsy was conducted using tissue sample from left neck mass. Microscopic examination showed high cellularity with diffuse spread from cells nuclei that are large, pleomorphic, vesicular, and some cells were multinucleated. Cytoplasm of the cells were eosinophilic. Mitosis was prominent. Analysis by pathologist showed NHL with morphology of DLBCL.

Immunohistochemistry was then conducted to confirm diagnosis. Immunohistochemistry showed diffuse positive for LCA, CD20; negative for AE1/3, CD10, and CD30; negative CD3; positive BCL2; positive Ki-67 on 80% of cells. Thus, the pattern of immunohistochemistry correlated with DLBCL with high proliferation. Genetic mutations of DLBCL were not performed as there is lack of equipment availability for mutation testing in DLBCL.

Echocardiograph on 14 May 2020 showed normal heart dimension, no presence of hypertrophy, normal systolic function, mild diastolic relaxation dysfunction, normal heart valves, ejection fraction 75%, and TAPSE 2.5 cm.

On 14 May 2020, a PET-CT scan revealed multiple hypermetabolic lymph node enlargements in various regions, including bilateral parotid gland, bilateral nuchal lymph nodes, level 1A cervical lymph nodes, bilateral level 1B cervical lymph nodes, bilateral level 2 cervical lymph nodes, bilateral level 3 cervical lymph nodes, bilateral level 4 cervical lymph nodes, left level 5 cervical lymph nodes, bilateral axilla lymph nodes, left lower paratracheal lymph nodes, paraesophageal lymph nodes, bilateral common iliac lymph nodes, bilateral internal and external iliac lymph nodes, and bilateral inguinal lymph nodes. In addition, there were multiple hypermetabolic nodules detected in the left adrenal gland and right triceps brachii muscle. Splenomegaly was observed, which indicated the presence of splenic lymphoma. The PET-CT scan also showed hepatomegaly with diffuse fatty liver and small cysts located in the right liver lobe.

Based on the findings above, a diagnosis of DLBCL with Ann Arbor Stage 4, Lugano advanced Stage 4, was made. Treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) 21 for 6 cycles was planned from May 2020 to September 2020. Additional treatment using involved field radiation therapy for 18 cycles from 26 October to 20 November 2020 was also conducted.

PET-CT scan on 6 August 2020 after showed chemosensitivity and good response. The patient was declared to achieve complete response during after finishing the six cycles of R-CHOP on 28 September 2020 based on PET-CT scan showing no nodules. Laboratory examinations on 28 September 2020 is presented on Table 2.

TABLE 2 Laboratory examinations on 28 September 2020.

Lab	Values	Reference
Hemoglobin (g/dL)	12.3	13.2–17.3
Hematocrit (%)	36	40–52
Erythrocyte (10^6/μL)	3.96	4.4–5.9
Reticulocyte (%)	2.3	0.5–1.5
Leukocyte (10^3/μL)	4.4	4.5–11
Basophil (%)	1	0–1
Eosinophile (%)	0	2–4
Band neutrophil (%)	0	3–5
Segmented neutrophil (%)	73	50–70
Lymphocyte (%)	13	25–40
Monocyte (%)	13	2–8
ESR (mm)	64	0–10
Thrombocyte (10^3/μL)	240	150–440
Total protein (g/dL)	7.7	606–8.8
Albumin (g/dL)	4.3	3.5–5.2
Globulin (g/dL)	3.4	2.3–3.5
SGOT (U/L)	21	<35
SGPT (U/L)	24	<41
Gamma GT (U/L)	52	<49
Alkaline phosphatase (U/L)	64	53–128
Lactate dehydrogenase (U/L)	482	<480
Ureum (mg/dL)	20	18–55
Creatinine (mg/dL)	0.6	0.9–1.3
eGFR (mL/min/1.73 m^2)	140.9	
HbA1c (%)	8.8	
Calcium (mg/dL)	9.5	8.6–10.3

Follow-up until end of year 2021, the patient was stable with no lymphoma relapse observed based on PET-CT scan. However, on 24 April 2022, the patient came with chief complain of headache and diplopia. The patient denied other symptoms such as seizure, confusion, nausea, vomiting, extremity weakness, and sensory changes. Due to the symptoms and history of DLBCL, suspicion of CNS involvement of DLBCL was made.

On 25 April 2022, PET-CT scan was conducted that showed new enhancing hypermetabolic nodule on anterior horn of left ventricle with vasogenic oedema around the lesion when compared with PET CT on 21 October 2021 (Figure 1). The size of the nodule was approximately 15.3 × 13.5 mm (AP × transversal) with avid F-18 fluorodeoxyglucose (FDG) activity (SUV max 16.4). No abnormality was observed on upper and lower diaphragm lymph nodes. Thus, based on the PET-CT scan results, DLBCL with CNS involvement was very likely.

To confirm presence of DLBCL on CNS, spinal fluid analysis was conducted on 1 May 2022, which is shown

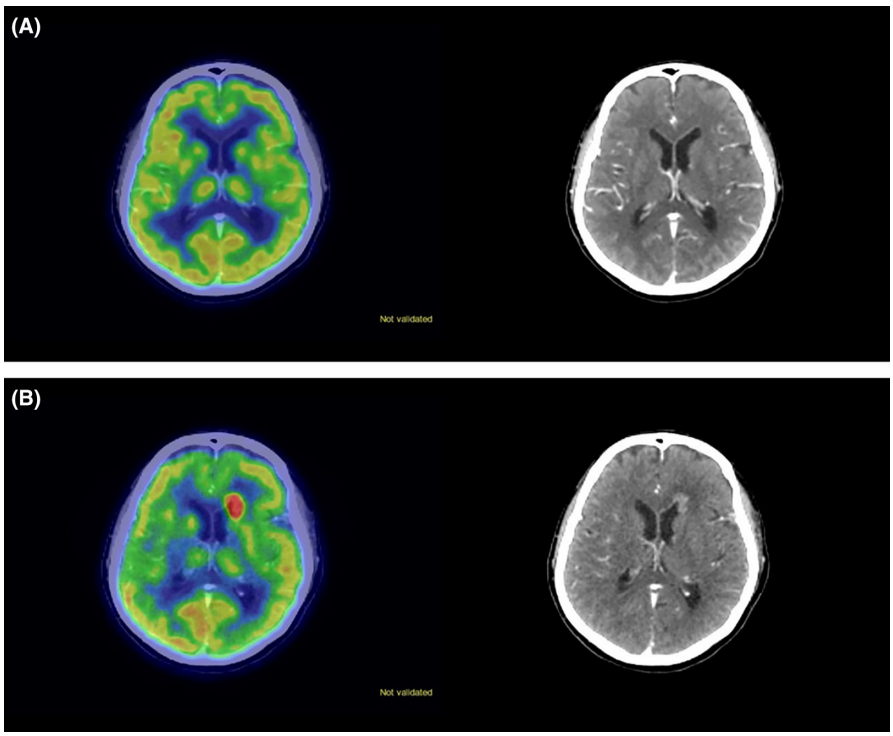

FIGURE 1 (A) PET CT scan and CT scan on 21 October 2021 showing no nodule; (B) PET CT scan and CT scan on 25 April 2022 showing nodule on left anterior horn.

TABLE 3 CNS Examination on 1 May 2022.

Lab	Values	Normal range
Color	Clear	Clear
Total cell (/μL)	7	0–5
Polymorphonuclear leukocytes (%)	30	20–60
Mononuclear leukocytes (%)	70	40–80
Protein (mg/dL)	65	15–45
Glucose (mg/dL)	193	32–82
Chloride (mmol/L)	118	115–130

on Table 3. Analysis of spinal fluid cells showed cell with large size (five to seven times of erythrocyte), blue cytoplasm, irregular cell nucleus, multinucleated, and coarse chromatin core which indicated lymphoma cells.

The patient was diagnosed with DLBCL CNS involvement and received a therapy consisting of whole brain radiation therapy 25 sessions and one intrathecal MTX injection. The radiation therapy was administered from 13 May 2022 to 30 June 2022, and the patient only experienced Grade 1 skin toxicity and Grade 1 hematological toxicity during the treatment. No other toxicity was observed from the patient.

On 10 June 2022, a brain MRI showed a reduction in the size of the CNS lymphoma located on the anterior horn of the left ventricle (Figure 2). Subsequently, rituximab 750 mg, and MTX 7 g/m^2 intravenously were given. Additionally, the patient was given temozolomide 300 mg and leucovorin. However, the size of the nodule remained unchanged as of 3 September 2022 based on MRI. Thus, temozolomide was continued for another 3 weeks.

A whole-body PET CT scan conducted on 1 October 2022 indicated that there was no longer any presence of lymphoma nodules in the brain parenchyma, and there was no presence of lymph nodes in the upper and lower diaphragm, when compared with the PET CT scan conducted on 25 April 2022.

On 12 December 2022, an MRI showed complete response posttreatment with no residual lymphoma present on the left lateral ventricle (Figure 2). Another PET CT scan conducted on 19 January 2023 showed stable findings, with no evidence of lymphoma nodules or extranodal involvement in the upper and lower diaphragm. The patient is still alive with no relapse during follow-up on May 2023.

3 | DISCUSSION

Up to 80% of CNS recurrences occur in brain parenchyma with concomitant systemic relapse occurring in almost half of patients.[20,21] Treatment modalities available for CNS recurrence of DLBCL include chemotherapy, radiation therapy, autologous stem cell transplantation (ASCT), and surgery.[17,18] MTX is a chemotherapy drug that is often used in the treatment of CNS lymphomas and other CNS malignancies. It is able to cross the blood–brain barrier, although the extent of penetration can vary among individuals. MTX is commonly used for CNS prophylaxis in

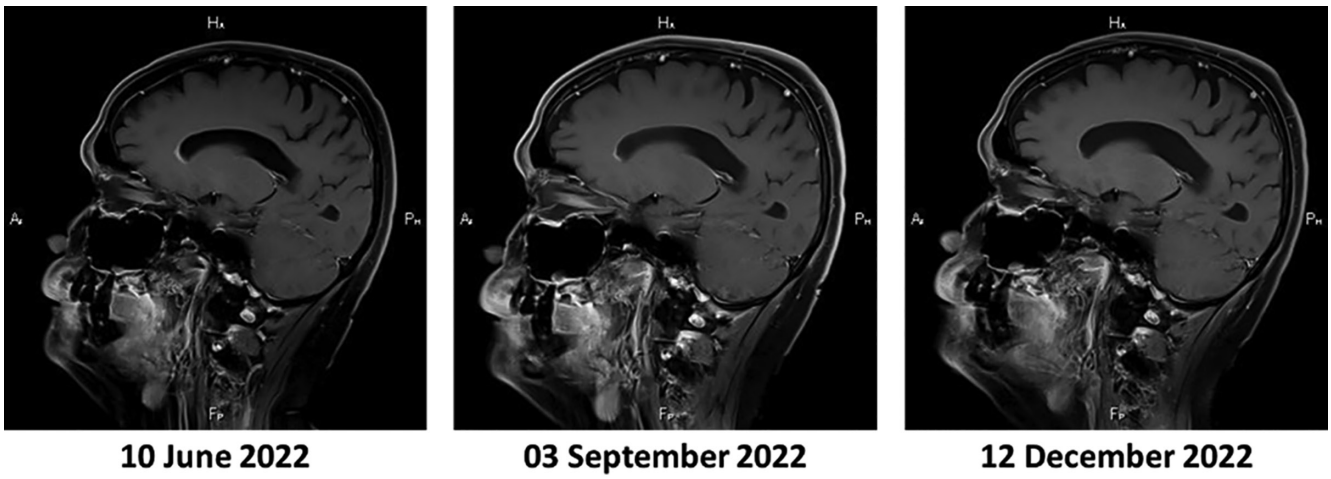

FIGURE 2 Brain MRI of patient and reduction of in size of nodule on MRI on 12 December 2022.

high risk DLBCL patients, however, study by Wilso et al. showed that both intrathecal and intravenous MTX is not adequate for CNS prophylaxis.[22]

Currently, there is a lack randomized studies specifically focusing on treatments for secondary CNS lymphoma, especially in RI-SCNSL for the last 20 years. In the recent multicentre Phase 2 trial called the MARIETTA study, conducted by Ferreri et al., it was demonstrated that a sequential combination of rituximab, MTX, cytarabine, and thiotepa (known as MATRix regiment), followed by rituximab, ifosfamide, etoposide, and carboplatin (RICE), along with subsequent autologous hematopoietic stem cell transplantation (HSCT), shows promise as a feasible treatment option.[23] However, it is worth noting that only 15 patients with RI-SCNSL were included in this study.

Study by Korfel et al. evaluated high-dose chemotherapy followed by stem-cell transplantation (HD-ASCT) in 24 patients with secondary CNS lymphoma.[24] Result showed that 63% of the patients achieved complete remission with acceptable toxicity.[24] Another clinical trial showed that high-doses of MTX and cytarabine, followed by R-HDS (rituximab, cyclophosphamide, cytarabine, and etoposide) and autologous stem-cell transplantation (ASCT) is effective for secondary CNS lymphoma.[25] Finally, a clinical trial by Doorduijn et al. showed that R-DHAP alternating with high-dose MTX and intrathecal rituximab did not improve outcome in secondary CNS lymphoma.[26]

One of the currently ongoing Phase 1b/2 study aims to evaluate a brain penetrant BTK inhibitor called as GB5121.[27] It would very interesting to see the result of the study as BTK inhibitor has been shown to improve outcomes in systemic lymphoma and there may be benefit in CNS lymphoma.[28]

Based on the aforementioned data, there is limited evidence available to determine the optimal treatment approach for RI-SCNSL in order to achieve the best outcomes. In fact, the BSH good practice paper recommends that patients with RI-SCNSL should be considered for enrolment in clinical trials, if such trials are available.[9] In cases where clinical trials are not accessible, it is advised to assess whether patients are suitable candidates for MATRix and ASCT treatments.[9] On the other hand, ESMO guidelines and guideline from combined three major national cancer societies in Pakistan (Society of Medical Oncology Pakistan, Pakistan Society of Haematology, and Pakistan Society of Clinical Oncology) do not mention treatments for secondary lymphoma.[17,29,30] European Association for Neuro-Oncology currently only has published a guideline for primary CNS lymphoma.[31] There is often a debate about whether clinicians can extrapolate data from studies on primary CNS lymphoma to secondary CNS lymphoma. However, this approach may not be appropriate due to potential differences in the mutational profile and clonal diversification between the two types of lymphoma, which can impact treatment strategies.[32] Then again, we don't have a choice currently.

Temozolomide is an alkylating agent which means that it damages DNA by adding methyl groups to it. This can lead to cell death, especially in cancer cells. Temozolomide is often used for gliomas due to its ability to cross blood–brain barrier.[33,34] Temozolomide is a prodrug, which means that it is converted into its active form inside the body. This conversion is spontaneous and occurs at physiological pH. The active form of temozolomide is called 5-(3-methyl-1-triazen-1-yl) imidazole-4-carboxamide (MTIC). MTIC methylates DNA at the N7 and O6 positions of guanine residues. This methylation can lead to DNA damage, including mispairing and breaks. Cancer cells are often less able to repair this damage than normal cells, which leads to their death.

Temozolomide is considered a radiosensitizer, meaning it enhances the effects of radiation therapy, resulting in a synergistic effect.[35] Additionally, rituximab has been shown to sensitize lymphoma cells to temozolomide.[36] Moreover, the combination of radiation therapy and temozolomide is considered the gold standard in the treatment of glioblastoma which should be explored further for CNS lymphoma as temozolomide based regimen has a possibility in improving patient's outcomes.

Studies on temozolomide in lymphoma is scarce, especially in RI-SCNSL. A letter to Editor by Renaud et al. described temozolomide and ibrutinib use in Primary (PCNSL) and Secondary Central Nervous System Lymphoma (SCNSL) provided better PFS compared with Ibrutinib only.[37] A retrospective study by Laucis et al. analyzed 45 patients of either primary or secondary CNS lymphoma with 20 patients receiving temozolomide.[38] According to the study, concurrent temozolomide provided better OS and PFS when compared with those not receiving temozolomide.[38] The multivariate analysis by the study showed a welcoming hazard ratio (HR) with HR of 0.2 and p: 0.02 in group receiving temozolomide. A recently published Phase III study in Japan in contrast did not find benefit of concomitant and maintenance temozolomide in primary CNS lymphoma.[39] However, it should be noted that the study did not include secondary CNS lymphoma as there may be different mutational profile and epigenetics. The authors mentioned that high proportion of lymphopenia in patients receiving temozolomide may be a potential cause of the lack of benefit.[39]

A retrospective cohort study Nagle et al. analyzed 46 patients with primary CNS lymphoma or secondary CNS involvement of DLBCL receiving rituximab with HD-MTX and temozolomide 150 mg/m^2.[40] Median OS was 41.8 months. The authors observed that patients with primary CNS lymphoma had higher response rates and OS than patients with secondary CNS involvement of DLBCL.[40] A smaller retrospective study by Gerstner et al. showed that there may benefit in adding temozolomide to primary CNS lymphoma patients.[41]

Based on the lack of evidence for secondary lymphoma, further studies are needed to determine the optimal treatment for secondary CNS lymphoma. Temozolomide as one of the candidates need to be researcher further, given some studies showing its efficacy CNS lymphoma.

In this case report, the patient had RI-SCNSL based on definitions by BSH good practice paper.[9] The paper recommended use of MATRix regimen; however, no mention of temozolomide based combination therapy was made on the paper. Indeed, as described above, data on the efficacy of temozolomide based combination therapy is very scarce. Thus, we believe that this case report and the small retrospective study by Laucis et al. can be used as an argument for further studies to analyze efficacy of temozolomide based combination therapy for RI-SCNSL patients.[38]

4 | CASE REPORT LIMITATION

Limitation of this case report is that no biopsy of the lesion was performed during relapse and thus no genetic mutation analysis was able to be conducted. Furthermore, evidence has showed that adrenal involvement in DLBCL is a risk factor for CNS involvement and patients with adrenal involvement should be given prophylaxis to prevent CNS recurrence. However, in our case, the patients refused this treatment due to fear of side effects.

5 | CONCLUSION

Close monitoring of patients with DLBCL for signs of recurrence, including CNS involvement, is of utmost importance, even after successful treatment of the primary tumor. This proactive approach ensures early detection and timely treatment of any recurrence, thereby increasing the likelihood of a positive outcome. The risk of RI-SCNSL remains a concern for DLBCL patients who have achieved remission. One potential treatment approach for RI-SCNSL involves a combination of radiotherapy and intrathecal MTX, followed by high-dose intravenous MTX, rituximab, and temozolomide. However, it is crucial to conduct large-scale observational studies and clinical trials to further assess the feasibility and effectiveness of this treatment regimen.

AUTHOR CONTRIBUTIONS

Ikhwan Rinaldi: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; visualization; writing – original draft; writing – review and editing. **Abdul Muthalib:** Conceptualization; methodology; supervision; writing – review and editing. **Soehartati Argadikoesoema:** Conceptualization; investigation. **Tjondro Setiawan:** Conceptualization; data curation; investigation; visualization. **Andhika Gunawan:** Conceptualization; investigation. **Nelly Susanto:** Conceptualization; investigation. **Lingga Magdalena:** Conceptualization; data curation; investigation; visualization. **Kevin Winston:** Conceptualization; data curation; formal analysis; investigation; methodology; supervision; writing – original draft; writing – review and editing. **Ashila Disamantiji:** Conceptualization; data curation; investigation; writing – original draft. **Bintang Wirawan:** Conceptualization; data curation; investigation; writing – original draft.

ACKNOWLEDGMENTS

The Authors would like to thank all staffs of Gading Pluit Hospital for their helps in care of the patient.

FUNDING INFORMATION

No funding was received for this case report.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Ikhwan Rinaldi https://orcid.org/0000-0002-6872-8802
Soehartati Gondhowiardjo https://orcid.org/0000-0002-9446-4361
Kevin Winston https://orcid.org/0000-0003-2667-1999

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:7-30.
2. Rodriguez-Abreu D, Bordoni A, Zucca E. Epidemiology of hematological malignancies. *Ann Oncol*. 2007;18(Suppl 1):i3-i8.
3. Thandra KC, Barsouk A, Saginala K, Padala SA, Barsouk A, Rawla P. Epidemiology of non-Hodgkin's lymphoma. *Med Sci*. 2021;9:5.
4. Kanas G, Ge W, Quek RGW, Keeven K, Nersesyan K, Arnason E. Epidemiology of diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) in the United States and Western Europe: population-level projections for 2020-2025. *Leuk Lymphoma*. 2022;63:54-63.
5. Garg M, Takyar J, Dhawan A, et al. Diffuse large B-cell lymphoma (DLBCL): a structured literature review of the epidemiology, treatment guidelines, and real-world treatment patterns. *Blood*. 2022;140:12106-12107.
6. Kim JS, Liu Y, Ha KH, Qiu H, Rothwell LA, Kim HC. Increasing incidence of B-cell non-Hodgkin lymphoma and occurrence of second primary malignancies in South Korea: 10-year follow-up using the Korean National Health Information Database. *Cancer Res Treat*. 2020;52:1262-1272.
7. Roschewski M. Preventing central nervous system spread in diffuse large B-cell lymphoma–novel approaches needed. *Haematologica*. 2021;106:2298-2300.
8. Almansour MA, Saif S, Alhrbi Z, et al. The outcome of diffuse large B-cell lymphoma with CNS involvement at diagnosis, single-center experience. *Blood*. 2020;136:29.
9. Cwynarski K, Cummin T, Osborne W, et al. Management of secondary central nervous system lymphoma. *Br J Haematol*. 2023;200:160-169.
10. Bernard S, Ghesquieres H, Casasnovas R-O, et al. Incidence of central nervous system relapses in patients with DLBCL treated with lenalidomide as maintenance after R-CHOP. *Blood Adv*. 2021;5:2965-2968.
11. Savage KJ. Secondary CNS relapse in diffuse large B-cell lymphoma: defining high-risk patients and optimization of prophylaxis strategies. *Hematol Am Soc Hematol Educ Program*. 2017;2017:578-586.
12. Illerhaus G. CNS relapse in DLBCL: a calculable risk? *Blood*. 2021;137:1011-1012.
13. Steffanoni S, Doorduijin JK. Narrative review: secondary central nervous system lymphoma. *Ann Lymphoma*. 2021;5:1. doi:10.21037/aol-20-39
14. Schmitz N, Zeynalova S, Nickelsen M, et al. CNS international prognostic index: a risk model for CNS relapse in patients with diffuse large B-cell lymphoma treated with R-CHOP. *J Clin Oncol*. 2016;34:3150-3156.
15. Graber JJ, Omuro A. Primary central nervous system lymphoma: is there still a role for radiotherapy? *Curr Opin Neurol*. 2011;24:633-640.
16. Orellana-Noia V, Abousaud A. Secondary central nervous system lymphoma: updates in treatment and prophylaxis strategies. *Curr Treat Options Oncol*. 2022;23:1443-1456.
17. Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2015;26:v116-v125.
18. Peñalver F-J, Sancho J-M, de la Fuente A, et al. Guidelines for diagnosis, prevention and management of central nervous system involvement in diffuse large B-cell lymphoma patients by the Spanish lymphoma group (GELTAMO). *Haematologica*. 2017;102:235-245.
19. Bobillo S, Khwaja J, Ferreri AJM, Cwynarski K. Prevention and management of secondary central nervous system lymphoma. *Haematologica*. 2023;108:673-689.
20. Kansara R, Villa D, Gerrie AS, et al. Site of central nervous system (CNS) relapse in patients with diffuse large B-cell lymphoma (DLBCL) by the CNS-IPI risk model. *Br J Haematol*. 2017;179:508-510.
21. McKay P, Wilson MR, Chaganti S, et al. The prevention of central nervous system relapse in diffuse large B-cell lymphoma: a British Society for Haematology good practice paper. *Br J Haematol*. 2020;190:708-714.
22. Wilson MR, Eyre TA, Kirkwood AA, et al. Timing of high-dose methotrexate CNS prophylaxis in DLBCL: a multicenter international analysis of 1384 patients. *Blood*. 2022;139:2499-2511.
23. Ferreri AJM, Doorduijn JK, Re A, et al. MATRix-RICE therapy and autologous haematopoietic stem-cell transplantation in diffuse large B-cell lymphoma with secondary CNS involvement (MARIETTA): an international, single-arm, phase 2 trial. *Lancet Haematol*. 2021;8:e110-e121.
24. Korfel A, Elter T, Thiel E, et al. Phase II study of central nervous system (CNS)-directed chemotherapy including high-dose chemotherapy with autologous stem cell transplantation for CNS relapse of aggressive lymphomas. *Haematologica*. 2013;98:364-370.
25. Ferreri AJM, Donadoni G, Cabras MG, et al. High doses of antimetabolites followed by high-dose sequential chemoimmunotherapy and autologous stem-cell transplantation in patients

with systemic B-cell lymphoma and secondary CNS involvement: final results of a multicenter phase II trial. *J Clin Oncol*. 2015;33:3903-3910.
26. Doorduijn JK, van Imhoff GW, van der Holt B, et al. Treatment of secondary central nervous system lymphoma with intrathecal rituximab, high-dose methotrexate, and R-DHAP followed by autologous stem cell transplantation: results of the HOVON 80 phase 2 study. *Hematol Oncol*. 2017;35:497-503.
27. Soussain C, Issa S, Lewis KL, et al. Trial in Progress: a phase 1b/2 study of GB5121, a brain-penetrant, potent, highly selective, and irreversible BTK inhibitor for relapsed/refractory primary/secondary CNS lymphoma and primary vitreoretinal lymphoma. *Blood*. 2022;140:12068-12069.
28. Nepal G, Khurana M, Bucheli DH, et al. Ibrutinib in refractory or relapsing primary central nervous system lymphoma: a systematic review. *Neurol Int*. 2022;14:99-108.
29. Ghielmini M, Vitolo U, Kimby E, et al. ESMO guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). *Ann Oncol*. 2013;24:561-576.
30. Iftikhar R, Mir MA, Moosajee M, et al. Diagnosis and management of diffuse large B-cell lymphoma: society of medical oncology, Pakistan society of hematology, and Pakistan society of clinical oncology joint clinical practice guideline. *JCO Glob Oncol*. 2021;7:1647-1658.
31. Hoang-Xuan K, Deckert M, Ferreri AJM, et al. European Association of Neuro-Oncology (EANO) guidelines for treatment of primary central nervous system lymphoma (PCNSL). *Neuro Oncol*. 2023;25:37-53.
32. Magnes T, Wagner S, Thorner AR, et al. Clonal evolution in diffuse large B-cell lymphoma with central nervous system recurrence. *ESMO Open*. 2021;6:100012.
33. Ortiz R, Perazzoli G, Cabeza L, et al. Temozolomide: an updated overview of resistance mechanisms, nanotechnology advances and clinical applications. *Curr Neuropharmacol*. 2021;19:513-537.
34. Role of temozolomide in the treatment of cancers involving the central nervous system. *Cancer Network*. 2018. https://www.cancernetwork.com/view/role-temozolomide-cns (2018, accessed 16 May 2023).
35. Kaina B, Beltzig L, Strik H. Temozolomide–Just a radiosensitizer? *Front Oncol*. 2022;12:912821. doi:10.3389/fonc.2022.912821
36. Wong ET, Tishler R, Barron L, Wu JK. Immunochemotherapy with rituximab and temozolomide for central nervous system lymphomas. *Cancer*. 2004;101:139-145.
37. Renaud L, Bossard JB, Carpentier B, et al. Treatment with temozolomide and ibrutinib in recurrent/refractory primary (PCNSL) and secondary CNS lymphoma (SCNSL). *Eur J Haematol*. 2021;107:370-373.
38. Laucis AM, Selwa K, Sun Y, et al. Efficacy and toxicity with radiation field designs and concurrent temozolomide for CNS lymphoma. *Neuro Oncol Pract*. 2022;9:536-544.
39. Mishima K, Nishikawa R, Narita Y, et al. Randomized phase III study of high-dose methotrexate and whole-brain radiotherapy with/without temozolomide for newly diagnosed primary CNS lymphoma: JCOG1114C. *Neuro Oncol*. 2022;25:687-698.
40. Nagle SJ, Shah NN, Ganetsky A, et al. Long-term outcomes of rituximab, temozolomide and high-dose methotrexate without consolidation therapy for lymphoma involving the CNS. *Int J Hematol Oncol*. 2017;6:113-121.
41. Gerstner ER, Hochberg FH, Plotkin SR, Eichler AF, Batchelor TT. High-dose methotrexate, rituximab, and Temozolomide (MRT) for patients with primary CNS lymphoma (PCNSL). *Blood*. 2009;114:1672.

How to cite this article: Rinaldi I, Muthalib A, Gondhowiardjo S, et al. Relapsed isolated CNS lymphoma treated with radiotherapy and intrathecal methotrexate followed by high-dose intravenous methotrexate, rituximab, and temozolomide: A case report. *Clin Case Rep*. 2024;12:e8409. doi:10.1002/ccr3.8409