

# Isolated Recurrence of Secondary CNS Lymphoma: Case Report and Literature Review

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## Abstract

### Keywords

- ▶ secondary central nervous system lymphoma
- ▶ isolated
- ▶ relapse
- ▶ recurrence
- ▶ aggressive treatment regimen

Isolated secondary central nervous system lymphoma (SCNSL) relapse is a rare disease. Consequently, standardized treatment regimens have yet to be developed. We present an interesting case of isolated SCNSL presenting with altered mental status and panhypopituitarism in a patient at low risk of developing the disease. We also review the related literature and discuss newer, more aggressive treatments for primary CNS lymphoma and SCNSL.

## Introduction

Central nervous system (CNS) lymphoma can present as either secondary, representing 1 to 7% of lymphomas, or primary, representing 0.2 to 2% of lymphomas.<sup>1</sup> Secondary CNS lymphoma (SCNSL) is currently defined as lymphoma not originating from within the CNS, and may be an isolated recurrence within the CNS or may be part of the systemic progressive disease.<sup>2</sup> Additionally, SCNSL may be further categorized as leptomeningeal, parenchymal, or as a combination of the two.<sup>3</sup> In particular, an isolated relapse within the CNS is rare, with retrospective cohorts typically numbering between 10 and 30 patients.<sup>4–7</sup> Furthermore, due to a lack of clinical data on isolated SCNSL recurrence, features of the disease, a standard treatment regimen, and overall prognosis have yet to be elucidated.<sup>4,8</sup>

### Current Treatment of Primary and Secondary Central Nervous System Lymphoma

Once the diagnosis has been established, treatment options for CNS lymphoma can be broadly divided into chemotherapy, radiation, and surgery. Surgery in CNS lymphoma has been reserved for diagnostic biopsy. Surgical resection of CNS

lymphoma is generally a last resort and only offered in cases when the lesion is causing extreme mass effect and herniation syndromes. The mainstays of primary and secondary CNS lymphoma treatment are chemotherapy and radiation. Unfortunately, the standard chemotherapy regimens used in the treatment of systemic lymphomas have shown only little effect in prophylaxis or direct treatment of CNS lymphomas.<sup>9</sup> These drugs (anthracyclines, vinca alkaloids, and some alkylating agents) have poor blood brain penetration, and their toxicity profiles limit the dose at which they can be delivered to overcome this. Methotrexate and cytarabine, in contrast, have poor blood brain barrier penetration but can be delivered at sufficient concentrations to overcome this and provide adequate concentration to the CNS.<sup>10</sup> Initial studies showed improved overall survival from treatment with high-dose methotrexate and radiation at time of diagnosis, with response rates of up to 80 to 90% and 5-year median survival times in primary CNS lymphoma.<sup>11</sup> Subsequent studies comparing high-dose methotrexate alone and combination high-dose methotrexate and radiation failed to prove robust survival benefit with combination therapy, especially in patients > 60 years of age, a growing segment of the disease.<sup>11–13</sup>

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In addition, responses to radiation treatment have been found to be short lived and have failed to increase overall survival.<sup>14</sup> The role of radiation therapy for CNS lymphoma has shifted from initial treatment to salvage therapy over the past several decades.<sup>9,15</sup> Treatment paradigms established for primary CNS lymphoma have been used in the treatment of SCNSL; however, the failure rate remains high, with overall survival typically on the order of 2 months.<sup>16</sup>

More recently, more aggressive regimens have been suggested. These include surgical resection that has been shown to provide survival benefit in a single trial within a subset of patients who had a single CNS lesion in a noneloquent, surgically accessible region.<sup>17</sup> Although there is no standard dosing for methotrexate, CNS concentration and response rates have been shown to be related to infusion rate.<sup>18</sup> More specifically, methotrexate area under the curve has been shown to be an independent predictor of clinical outcome.<sup>19</sup> Personalized dosing based on age, gender, and creatinine clearance has been proposed.<sup>10</sup> Blood brain barrier disruption methods in combination with chemotherapeutic agents that have been used successfully in systemic lymphomas has shown promise in early pilot studies and are currently being tested in larger centers.<sup>20,21</sup> Similarly, intrathecal administration of methotrexate, cytarabine, or rituximab has shown some early promise, but further data are still required. Administration of intrathecal chemotherapy is generally reserved for patients with leptomeningeal disease and positivity on cerebrospinal fluid (CSF) testing, although large retrospective series have been equivocal on this topic.<sup>22,23</sup>

## Illustrative Case

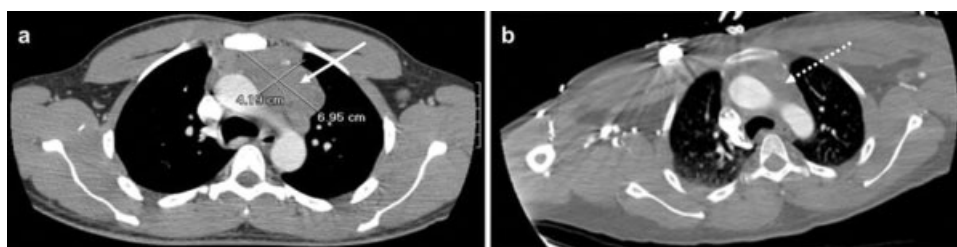
A 36-year-old man presented to his primary care physician with complaint of a soft nontender mass on the left side of his neck. The patient reported that he noticed this mass enlarging for the past year but had attributed it to an infectious process. An initial chest X-ray identified a left supraclavicular mass compressing the trachea and causing a rightward deviation. Additionally, a computed tomography (CT) scan of the chest and neck, with and without contrast, was performed for follow-up, with evidence of diffuse lymphadenopathy (►Fig. 1A), specifically, the supraclavicular, paratracheal, prevascular, lesser sac, left axilla, parasternal, and mesenteric chain nodes. A head CT scan with contrast performed at the same time was negative for any intracranial involvement. The

patient also tested negative for human immunodeficiency virus.

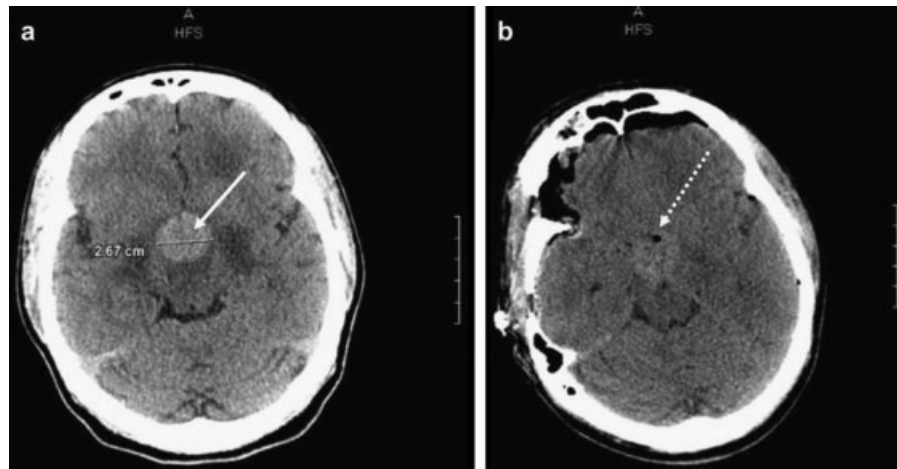
The patient was subsequently scheduled for a CT-guided biopsy of the supraclavicular lesion. The results of the biopsy were consistent with B cell lymphoma. Following the biopsy confirmation, the patient completed six cycles of outpatient rituximab, cyclophosphamide, hydroxydaunorubicin, Oncovin, and prednisone therapy. At his last outpatient oncology visit, the patient was considered to be in remission. The patient did not experience any cognitive symptoms, and he had no extranodal involvement at diagnosis or follow-up. The patient's lactate dehydrogenase level was not measured as a part of his follow-up. This would place the patient at a low risk for developing a secondary CNS lymphoma relapse.<sup>8,24</sup>

Approximately 7 months posttreatment, the patient was hospitalized at an outside medical center following a 1-week period of worsening mental status. On admission, the patient was found to have elevated serum sodium levels in the 160s, and further work-up revealed a suprasellar mass on head CT (►Fig. 2A). Upon arrival to our institution, the patient was found to have diabetes insipidus. With a known history of systemic lymphoma, the patient underwent a lumbar puncture for flow cytometry. The differential diagnoses also included germinoma, craniopharyngioma, and astrocytoma. A skull X-ray showed no calcifications. CT scan of the chest, abdomen, and pelvis displayed marked interval improvement in the degree of lymphadenopathy with near-complete resolution of the previous mediastinal lymphadenopathy (►Fig. 1B). CSF flow cytometry was negative for tumor cells. A brain magnetic resonance imaging (MRI) revealed a homogeneously enhancing suprasellar mass with surrounding edema (►Fig. 3A, B).

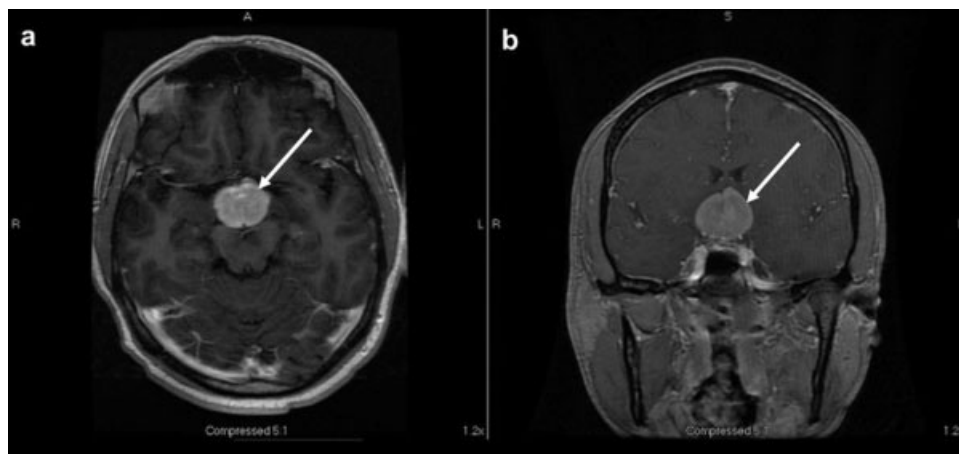
The patient was taken for a right fronto-orbital craniotomy and translamina terminalis approach for biopsy of the lesion (►Fig. 2B). Pathology was consistent with B cell lymphoma. Histologically, the samples showed highly cellular clumps of lymphocytes on hematoxylin and eosin staining (►Fig. 4A–C), and immunohistochemical studies were positive for Bcl2, Bcl6, CD10, CD20, and CD79a (►Fig. 5A–E). Additionally, Ki-67 staining (►Fig. 5F) highlighted the proliferation of ~5 to 10% of the neoplastic cells present in the biopsy. The patient was placed on high-dose methotrexate, and his mental status improved. Unfortunately, the patient's condition progressed and he succumbed to his illness.



**Fig. 1** (A) Pretreatment axial chest computed tomography (CT) with contrast revealing a prevascular lymph node mass (solid arrow) during the initial diagnosis of B-cell lymphoma. (B) Postchemotherapy axial chest CT with contrast illustrating near-complete resolution of the previously seen prevascular lymph node mass (dotted arrow).



**Fig. 2** (A) Preoperative axial head computed tomography (CT) without contrast from an outside institution revealing a 2.6-cm suprasellar mass (solid arrow). (B) Postoperative axial head CT without contrast illustrating the results of the right frontal orbital craniotomy for debulking and biopsy (dotted arrow).



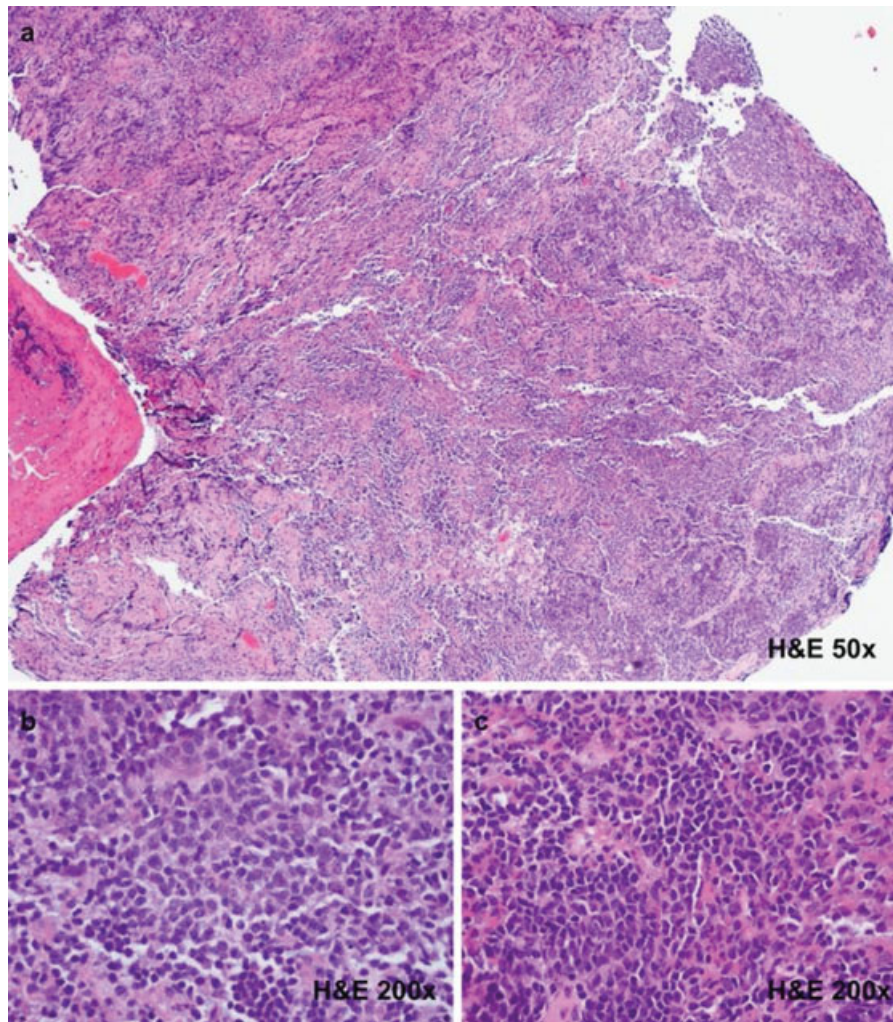
**Fig. 3** Preoperative (A) axial and (B) coronal T1-weighted cranial magnetic resonance imaging with contrast, revealing a 3-cm suprasellar mass with surrounding edema (solid arrows).

## Discussion

The incidence of SCNSL in the general population ranges from 4 to 23%.<sup>2,25–27</sup> The factors that most significantly influence the incidence rate of SCNSL include the variant of primary lymphoma, involvement of more than one extranodal site, a serum lactate dehydrogenase level greater than three times the normal limit, an advanced stage of the systemic disease, and a high International Prognostic Index.<sup>2,3,28,29</sup> Other studies have found that no one indicator of SCNSL is reliable on its own, but that the combination of several factors can help elucidate the risk of developing SCNSL and the need for possible prophylaxis. In particular, initial involvement of the breast, testis, and bone marrow with primary disease are heavily associated with an increased risk of developing SCNSL.<sup>30</sup> Populations with the highest risk are those with immune deficiencies, either innate or acquired. In the 1980s, a steep increase in the incidence of SCNSL paralleled the increase in incidence of human immunodeficiency virus and autoimmune deficiency syndrome. However, with the advent

of highly active antiretroviral therapy in the mid-1990s, the incidence has decreased and remained fairly steady since that time. The age of diagnosis of both primary and secondary CNS lymphoma has been steadily increasing, focusing more studies on treatment of an elderly population.<sup>31–35</sup>

As previously mentioned, the histologic grade of the primary lymphoma differentially influences the risk of developing SCNSL. Depending on whether the primary lymphoma is classified as indolent, aggressive, or highly aggressive, there is a 3%, 9%, and 27% risk, respectively, of developing SCNSL.<sup>36</sup> With specific regard to diffuse large B-cell lymphoma (DLBCL), the incidence has been reported as 5%, but interestingly, when the primary lymphoma is of the mediastinal large B-cell variant, the risk of SCNSL climbs to 19%, as in this case. Although most SCNSLs present with leptomeningeal disease, DLBCL most often presents with parenchymal disease.<sup>3</sup> Indolent lymphomas usually carry a low risk of recurrence, but when CNS disease has been found, it is usually after the histologic transformation to a more aggressive variant.<sup>27,37,38</sup> Furthermore, presence of at least two of these: bone marrow,



**Fig. 4** Histopathology of the biopsied suprasellar mass under (A) low magnification ( $\times 50$ ) and (B, C) high magnification ( $\times 200$ ) revealing highly cellular clumps of lymphocytes consistent with diffuse large B-cell lymphoma (hematoxylin and eosin).

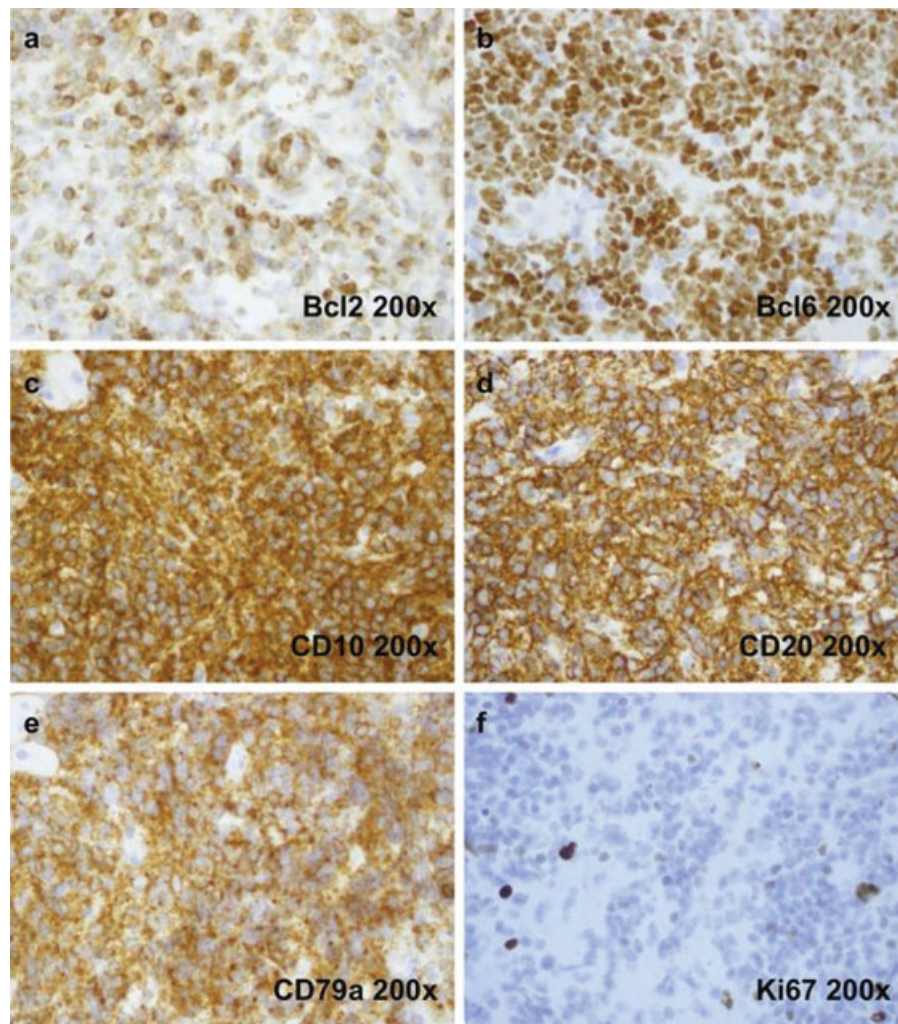
skin involvement, and B symptoms, increases the risk of SCNL in indolent primary lymphomas to 7%.<sup>8,24,28</sup>

The characteristic clinical presentation of SCNSL is a new-onset headache (50%), palsies of cranial nerves III, IV, VI, and VII, changes in mental status (29%), and even coma and seizures (23–29%).<sup>39</sup> It typically presents within 6 months of diagnosis of the primary lymphoma, which is typically confirmed with CSF studies and imaging.<sup>25,26</sup> Flow cytometry, however, is more sensitive than CSF cytology, and polymerase chain reaction studies can be used for further confirmation.<sup>37,40</sup> MRI is the current gold standard for localizing the recurrence because it has superior sensitivity compared with CT. Parenchymal lesions usually present with homogeneously enhancing superficial or periventricular lesions, but ring enhancement patterns can also be seen, especially in the population with acquired immunodeficiency syndrome.

SCNSL is characterized as an isolated recurrence  $\sim 50\%$  of the time; although most of these patients go on to develop systemic recurrences within several months. Isolated CNS recurrence has a worse prognosis than CNS disease at the time of diagnosis, suggesting an alternative disease mecha-

nism.<sup>41</sup> Survival is slightly better in isolated CNS recurrence when compared with systemic recurrence, which is the major cause of death in secondary CNS lymphoma. Unfortunately, the median survival time is  $< 6$  months when no treatment has been administered.

Treatment and CNS prophylaxis after the discovery of primary lymphoma is an area of active investigation. Based on the results of the large retrospective RICOVER-60 trial, intravenous (IV) rituximab is added to cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) therapy because it has shown a decreased incidence of SCNSL from 6.9 to 4.1%.<sup>24–26,39–43</sup> Another study found that a regimen of ACVBP with IV methotrexate (MTX) may also be superior to standard CHOP therapy.<sup>30</sup> The use of IV MTX has been shown to increase survival times for isolated SCNSL, especially for parenchymal SCNSL.<sup>44</sup> Despite these results, a strong consensus has yet to be reached on the indications for, efficacy of, and means of CNS prophylaxis. This is partially due to the retrospective nature of the studies to date and the variance in treatment regimens among the different studies. Also, the histopathology of the primary lymphoma is a determining



**Fig. 5** Immunohistochemistry of the biopsied suprasellar mass stained positive for (A) Bcl2, (B) Bcl6, (C) CD10, (D) CD20, (E) CD79a, and (F) Ki-67, all consistent with diffuse large B-cell lymphoma ( $\times 200$ ).

factor in the efficacy of treatment. For example, although IV rituximab decreased the incidence of SCNSL overall, it does not seem to influence the incidence of SCNSL in DLBCL (30%).

Interestingly, the patient in this case did not meet the criteria for increased risk of developing SCNSL, yet he still developed the disease. This leads us to believe that indeed no one factor is a definitive indicator that a patient will progress to a SCNSL. The classification of mediastinal DLBCL may have elevated the patient's risk of progression to SCNSL; however, his lack of other indicative risk factors made this an uncommon occurrence in an already uncommon condition. Despite the unusual presentation in this case (panhypopituitarism), the patient did have an isolated CNS relapse within 6 months, and the mental status change resolved in response to MTX treatment.

## Conclusions

Isolated SCNSL is a rare disease in which standardized treatment guidelines have yet to be developed. This case is one particular example where a patient designated as low risk for developing SCNSL did progress to an isolated occurrence of the disease. Additionally, although treatment extended the

patient's survival time and resolved the change in mental status, the disease continued to progress and the patient succumbed to his illness.

## Conflict of Interest

The author has nothing to disclose.

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