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Primary Central Nervous System Lymphoma: A Case Series of Three Adults

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Abstract **Case Report**

Background: Primary central nervous system lymphoma (PCNSL) is a rare, aggressive diffuse large B-cell lymphoma confined to the CNS. Diagnosis is challenging due to non-specific presentations and imaging overlap with other brain tumors. ***Cases:*** We describe three immunocompetent adults: (1) a septuagenarian with a solitary parietal mass treated by resection and WBRT but who ultimately died; (2) a 75-year-old man with a large fronto-parietotemporal lesion managed with total excision followed by HD-MTX–based chemotherapy but who died before planned consolidation; and (3) a middle-aged woman with multifocal lesions treated with HD-MTX plus cytarabine and consolidative WBRT, achieving partial radiological response and sustained clinical improvement. ***Discussion:*** PCNSL typically manifests with subacute focal deficits or cognitive decline; seizures and systemic "B" symptoms are uncommon. MRI usually shows homogeneously enhancing deep or periventricular masses with restricted diffusion. Histology is most often an activated B-cell type DLBCL harboring MYD88^L265P and CD79B mutations. Standard therapy centers on HD-MTX–based induction, with consolidation chosen according to patient age and performance status. ***Conclusion:*** These cases underscore the diagnostic importance of early biopsy before steroid exposure and the central role of HD-MTX–based regimens. However, outcomes remain poor in older or frail patients, as illustrated by the two fatal courses despite aggressive management. WBRT or transplant-based consolidation should be tailored to fitness and neurotoxicity risk. Novel targeted and immune-based therapies are needed to improve survival and reduce long-term cognitive decline.

Keywords: Primary central nervous system lymphoma; PCNSL; Adult, Chemotherapy, Radiotherapy, Prognosis.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an uncommon, highly aggressive extranodal non-Hodgkin lymphoma that develops within the brain, leptomeninges, spinal cord, or eyes, without systemic involvement at diagnosis. Histologically, it is almost always a diffuse large B-cell lymphoma (DLBCL) with an activated B-cell immunophenotype. Although PCNSL accounts for only 3–5 % of primary brain tumors and 1–2 % of non-Hodgkin lymphomas, its incidence has been increasing among immunocompetent elderly individuals. The disease often presents with non-specific, subacute neurological symptoms such as cognitive or behavioral changes, focal deficits, and signs of raised intracranial pressure, while seizures and systemic "B symptoms" remain uncommon. Magnetic resonance imaging (MRI) typically demonstrates homogeneously enhancing parenchymal masses, frequently periventricular or deep hemispheric, with restricted diffusion and little necrosis or calcification in immunocompetent hosts. Definitive diagnosis requires histopathology and immunohistochemistry, as corticosteroid pre-treatment may obscure biopsy results. Therapeutically, high-dose methotrexate (HD-MTX)–based chemotherapy is the backbone of induction, often combined with agents such as cytarabine, thiotepa, or rituximab, followed by consolidation with either whole-brain radiotherapy (WBRT) or high-dose chemotherapy with autologous stem-cell transplant (HDC-ASCT) in selected patients. Despite therapeutic advances, relapse remains frequent and neurotoxicity is a key concern, particularly with WBRT in older patients.

We report three cases of PCNSL in immunocompetent adults, illustrating the clinical heterogeneity, imaging patterns, histopathology, and evolving therapeutic approaches treated at the Oncology-

Radiotherapy Department of the Mohammed VI University Hospital in Marrakech.

Case Presentation

Case 1

A 75-year-old man with no significant past medical history was admitted for evaluation of an intracranial mass. He denied vomiting, headache, visual disturbances, seizures, vertigo, and cognitive impairment; the only reported symptom was progressive weight loss with global health decline. Brain CT and MRI demonstrated a solitary supratentorial parietal lesion, non-cystic and non-calcified, associated with perilesional edema and moderate mass effect, without hemorrhage. Stereotactic biopsy confirmed a primary central nervous system lymphoma (PCNSL), WHO grade III, with positive immunohistochemistry (specific markers not documented). The patient underwent curative-intent total surgical excision followed by whole-brain radiotherapy (WBRT/EIT) delivering 40 Gy in 20 fractions with a 28 Gy boost in 14 fractions. Despite treatment, the clinical course was unfavorable and the patient ultimately died.

Case 2

A 75-year-old man without notable comorbidities presented with progressive headaches and general health deterioration. He denied vomiting, visual disturbances, vertigo, and seizures. Brain MRI revealed a large solitary supratentorial mass extending through the frontal, parietal, and temporal lobes; the lesion was non-cystic, with extensive perilesional edema and marked mass effect, and showed neither calcification nor hemorrhage. Histopathological evaluation confirmed primary central nervous system lymphoma (WHO grade not specified) with positive immunohistochemistry. The patient underwent curative-intent gross total resection, followed by high-dose methotrexate–based chemotherapy (six cycles over 16 weeks). Whole-brain radiotherapy had been planned but was not delivered because his clinical condition deteriorated rapidly, and he died before its initiation.

Case 3

A 52-year-old woman presented with a multifocal neurological syndrome consisting of headache, visual disturbances, vertigo, cognitive impairment, and partial motor and sensory deficits, without seizures. Brain MRI demonstrated multiple supratentorial frontal and parietal lesions, non-cystic, with surrounding edema and mass effect, without calcification or hemorrhage. Histopathology confirmed primary central nervous system lymphoma. Given the multifocal presentation, no surgery was performed. The patient received high-dose methotrexate combined with cytarabine (six cycles over 17 weeks), followed by whole-brain radiotherapy (WBRT/EIT) 40 Gy in 20 fractions with a 28 Gy boost in 14 fractions. Follow-up MRI demonstrated a partial radiological response, although persistent stable sequelae characterized by gliotic foci remained at the treated sites, with marked clinical improvement.

Discussion

Primary central nervous system lymphoma (PCNSL) is an aggressive extranodal non-Hodgkin lymphoma that arises exclusively in the central nervous system (CNS) – typically the brain parenchyma, but it can also involve the leptomeninges, spinal cord, or eyes [1]. Histologically, PCNSL is almost always a diffuse large B-cell lymphoma (DLBCL) confined to the CNS, distinguishing it from systemic lymphomas [1,2]. It accounts for only about 3–5% of all primary brain tumors and 1–2% of all non-Hodgkin lymphomas [3]. The incidence in the general population is low (on the order of 0.4–0.5 per 100,000 persons per year) [2,3], though it increases markedly in immunocompromised individuals. Congenital or acquired immunodeficiency is the strongest risk factor for PCNSL. In patients with AIDS, for example, PCNSL is considered an AIDS-defining illness with an incidence several thousand-fold higher than in immunocompetent people [1]. (Notably, virtually 100% of HIV-associated PCNSL are driven by Epstein-Barr virus (EBV) infection of B-cells [4]. With the advent of antiretroviral therapy, HIV-related cases have declined, and today most PCNSL cases occur in immunocompetent patients, typically older adults – the median age at diagnosis is around 60–70 years [1]. There is no known definitive predisposing exposure, and familial cases are exceedingly rare. The slight male predominance is inconsistent, with some series showing an approximately 1:1 male-to-female ratio [3]. Overall, PCNSL remains a rare but potentially curable CNS malignancy, and its incidence in immunocompetent populations has been gradually rising in the elderly.

Clinical manifestations of PCNSL are often variable and non-specific, which can make diagnosis challenging. Most patients present with focal neurological deficits (reflecting the lesion's location) or with neuropsychiatric symptoms and cognitive decline [2]. In a large series of immunocompetent PCNSL patients, the most common presenting features were behavioral or cognitive changes (seen in ~43% of cases), followed by signs of increased intracranial pressure such as headaches, nausea, and papilledema (~33%) [2]. Focal symptoms like hemiparesis, aphasia, or ataxia are also frequent, depending on tumor location [2,4]. Seizures are less common at presentation (occurring in roughly 10–15% of patients) compared to other cortical brain tumors. This is thought to be because PCNSL lesions often reside in deep or subcortical regions rather than the epileptogenic cortex [2]. Our cases reflect this trend: none of the three patients had seizures at onset, consistent with the lower seizure propensity in PCNSL. Likewise, symptoms of increased intracranial pressure (progressive headache in Case 2) and various focal deficits (Case 3) were noted, aligning with typical presentations.

Systemic or "B" symptoms (fever, night sweats, unintentional weight loss) are rare in PCNSL [2]. Unlike systemic lymphomas, PCNSL usually remains confined to the CNS and thus seldom produces febrile or cachectic syndromes. For example, one of our patients (Case 1) had weight loss and general decline, but this is an uncommon finding and can easily be attributed to the overall illness rather than true B symptoms. Ocular involvement (vitreoretinal lymphoma) is an important clinical consideration: up to 20–25% of patients have lymphoma in the eye, either at presentation or on eventual relapse [4]. Patients may report blurring of vision or floaters, though in many cases the ocular disease is asymptomatic. Routine ophthalmologic examination (including slit-lamp exam) is advised for suspected PCNSL patients, even without visual complaints [4]. None of our three cases had ocular symptoms; consistent with this, they were immunocompetent and had parenchymal brain lesions, as is most typical. Overall, the clinical picture of PCNSL can mimic other CNS diseases, and a high index of suspicion is required, especially in an older patient with unexplained focal deficits or cognitive changes progressing subacutely.

Neuroimaging is critical for the initial detection of PCNSL. Magnetic resonance imaging (MRI) with gadolinium contrast is the modality of choice for evaluation [2]. Characteristically, PCNSL appears as a solid, contrast-enhancing mass lesion (or lesions) in the brain. In immunocompetent patients, the lesions are usually solitary (in ~60–70% of cases) and demonstrate homogeneous enhancement on post-contrast MRI [5]. Multiple lesions are seen in a minority (~20–40%), and ring enhancement is uncommon (reported in only ~10% of cases in immunocompetent hosts) [5]. These classic imaging features were exemplified by our Cases 1 and 2, each of whom had a single, solidly enhancing tumor (in the parietal and fronto-parietal region, respectively) without ring-like features. Case 3, in contrast, had multiple enhancing lesions, reflecting the multifocal disease that can occur in a subset of patients despite an intact immune system.

On unenhanced scans, PCNSL lesions tend to be hyperdense on CT and hypo- to isointense on T1-weighted MRI, with iso- to hypointense signal on T2 (often appearing darker than gray matter) [5]. This pattern is due to the densely cellular nature of the lymphoma. Diffusion-weighted MRI typically shows restricted diffusion (high DWI signal with low ADC values) because of the high tumor cellularity [5]. Surrounding vasogenic edema is usually present, sometimes causing significant mass effect, although the edema is often less extensive than that seen with high-grade gliomas or metastases of similar size [4,5]. All of our cases demonstrated MRI evidence of perilesional edema and mass effect, though notably none had overt signs of intracranial hemorrhage.

The location of PCNSL within the brain is often central. Lesions have a predilection for the periventricular white matter, corpus callosum, and deep gray nuclei (basal ganglia/thalamus) [2,5]. In one series, 38% of lesions were in the cerebral hemispheric cortex or subcortical white matter, 16% in basal ganglia/thalamus, 14% in corpus callosum, and only ~9% in the cerebellum or brainstem [2]. Consistent with this, all lesions in our patients were supratentorial (frontal, parietal, temporal lobes). Infratentorial or spinal involvement is rare (spinal cord PCNSL occurs in <1% of cases) [1]. PCNSL lesions enhance uniformly with contrast in most immunocompetent patients [4]. They typically do not contain calcifications or macroscopic hemorrhage – these imaging features are distinctly uncommon and should prompt consideration of alternative diagnoses or an immunocompromised state [4,5]. Indeed, none of our cases showed calcification or hemorrhage on imaging, in line with expectations for PCNSL in immunocompetent individuals.

It is worth noting that imaging appearances can differ in immunosuppressed patients. In immunodeficient hosts (e.g. AIDS patients), PCNSL lesions are more often multiple, necrotic, and tend to exhibit ring-enhancement (mimicking toxoplasmosis) [4,5]. In AIDS-related PCNSL, up to 75% of lesions show ring-like enhancement and hemorrhagic foci are more frequent [5]. By contrast, our patients were HIV-negative and had the solid enhancement pattern. Advanced imaging techniques can aid in differentiation: for example, PET scans typically show intense FDG uptake in PCNSL (hypermetabolic lesion) compared to lower uptake in infections like toxoplasmosis [4]. MR spectroscopy often reveals elevated choline and lipid peaks with decreased N-acetylaspartate, a profile that can help distinguish PCNSL from other entities [4]. Nonetheless, imaging alone cannot conclusively diagnose PCNSL, as other brain tumors (high-grade gliomas, metastases) or inflammatory lesions can appear similar [5]. Definitive diagnosis requires pathologic confirmation.

On microscopic examination, PCNSL appears as a diffuse infiltrate of atypical lymphoid cells that invade the CNS parenchyma. In ~95% of cases, these cells are large B-lymphocytes, classifying the tumor as a DLBCL [4]. (Rare non-DLBCL variants of PCNSL include T-cell lymphomas, Burkitt lymphoma, or low-grade lymphomas, but these collectively account for <5% [3,4].) The lymphoma cells characteristically congregate around and within blood vessel walls – a phenomenon known as perivascular "hooping" or angiotropism [2]. This leads to an image of lymphoid cells tracking along small cerebral vessels on histology. Tumor cells often destroy normal brain structures, creating an angiocentric pattern with central necrosis less common (in immunocompetent patients). A dense reactive gliosis and infiltrating reactive T-cells may be present at the tumor margins; interestingly, the presence

of such reactive T-cells has been correlated with better outcomes, although it is observed less frequently in PCNSL than in systemic DLBCL [4].

Immunohistochemistry (IHC) confirms the tumor's B-cell lineage in virtually all cases. The neoplastic cells typically express pan B-cell antigens including CD20, CD19, CD22, CD79a, and surface or cytoplasmic immunoglobulin light chains (showing clonal restriction) [3]. Nearly all PCNSL-DLBCL are of the non-germinal center B-cell subtype by cell-of-origin – immunophenotypically, CD10 (a germinal center marker) is expressed in <10% of cases, whereas BCL6 is positive in about 60–80% and MUM1 (IRF4) is positive in ~90%. Co-expression of BCL6 and MUM1 is common, reflecting an "activated B-cell" (ABC) phenotype in which the lymphoma cells are in a late germinal center or post-germinal center stage of differentiation [3,4]. High proliferation indices are the norm – Ki-67 labeling is usually very high, often >90%, consistent with the aggressive nature of the disease. Other markers variably seen include BCL2 (frequently positive) and MYC (positive in a subset); however, the prognostic significance of dual BCL2/MYC expression in PCNSL is not clearly established, unlike in systemic DLBCL [4].

IHC (along with flow cytometry or PCR on CSF/vitreous fluid) is also useful to exclude other possibilities like reactive conditions or to distinguish PCNSL from secondary CNS involvement by a systemic lymphoma. By definition, a diagnosis of PCNSL requires that there is no systemic lymphoma at the time of CNS presentation. Hence, staging workup (body CT/PET scans, bone marrow biopsy) should be negative in true PCNSL [2]. In our series, thorough systemic investigations were done to rule out occult systemic lymphoma, and no evidence of extracranial disease was found, confirming the "primary" nature of the CNS lymphoma.

Molecular studies have revealed that PCNSL has a distinct genetic profile, despite its morphologic overlap with peripheral DLBCL. Recurrent mutations in the NF-κB pathway are a hallmark of PCNSL. The most common is a gain-of-function mutation in MYD88 (typically the MYD88^L265P variant), which is reported in approximately two-thirds to three-quarters of immunocompetent PCNSL cases. Often accompanying it are mutations in the B-cell receptor signaling component CD79B (mutated in ~50–65% of cases) [3]. These two mutations frequently co-occur and define a genetic subtype often referred to as the "MCD" cluster (MYD88^L265P + CD79B^mut) seen in PCNSL and related extranodal lymphomas [1]. Functionally, MYD88 L265P activates IRAK and NF-κB signaling, while CD79B mutations amplify B-cell receptor signaling; together they drive chronic NF-κB activation, promote B-cell survival, and block differentiation [3]. Other recurrent alterations in PCNSL include mutations in PIM1 (a kinase implicated in lymphomagenesis), CARD11 (activator of NF-κB), IRF4 (encoding MUM1), and deletions of tumor suppressors like CDKN2A (found in nearly half of cases). Many PCNSL also have losses of HLA class I/II locus (6p21), which is thought to be a mechanism of immune evasion [3]. Notably, the molecular profile of PCNSL in immunocompetent patients (rich in MYD88 and BCR pathway mutations) contrasts with EBV-positive PCNSL in AIDS patients, which usually lack those mutations and instead rely on viral oncogenesis [1]. This underlines that PCNSL arising in the context of profound immunosuppression (e.g. HIV, post-transplant) is biologically distinct – often an EBV-driven immunoblastic lymphoma – whereas PCNSL in immunocompetent hosts follows an ABC-type DLBCL genetic program.

Increasingly, these molecular insights have diagnostic and therapeutic implications. For instance, detecting the MYD88 L265P mutation in CSF or vitreous fluid by PCR can help confirm a PCNSL diagnosis in patients where brain biopsy is risky or nondiagnostic [1]. This mutation has a very high specificity for PCNSL in the appropriate context. Therapeutically, the prominence of NF-κB signaling has spurred trials of Bruton tyrosine kinase (BTK) inhibitors (like ibrutinib) and other targeted agents in relapsed PCNSL, as discussed below. Ongoing research into the PCNSL genome may yield further targets and biomarkers, but at present, high-dose chemotherapy remains the cornerstone of treatment despite the genomic advances. Beyond tumor-intrinsic genomics, the PCNSL microenvironment — comprising T cells, tumor-associated macrophages/microglia, astrocytes and endothelial cells — shapes immune evasion and treatment response (**Figure 1**)

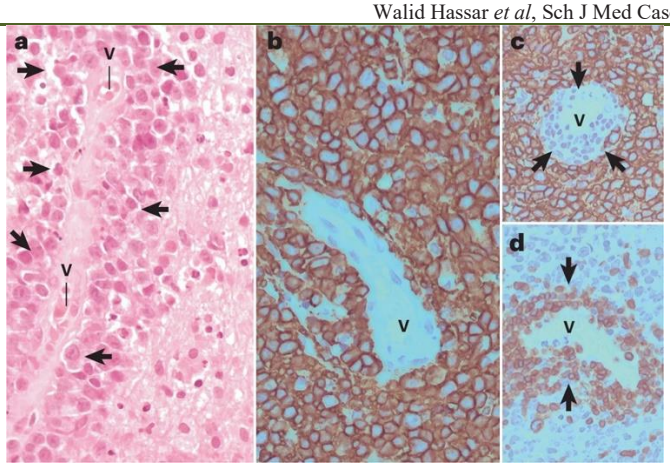

Figure 1 : Biological and molecular properties of microenvironment in PCNSL (1)

The management of PCNSL requires a multidisciplinary approach, but systemic high-dose chemotherapy is the foundation of initial therapy in virtually all eligible patients. Surgery has a limited role in PCNSL. Unlike many solid tumors, gross resection of PCNSL is usually not feasible nor beneficial: the lymphoma is often diffuse, infiltrative and frequently multifocal, and it invades vital deep structures [1,4]. No improvement in survival has been demonstrated with aggressive resection, so stereotactic biopsy is the standard for obtaining tissue diagnosis [4]. Surgical resection is reserved only for rare cases of life-threatening mass effect or diagnostic uncertainty [1]. In our series, two patients (Cases 1 and 2) underwent an initial craniotomy and tumor resection due to the large, localized nature of their lesions and significant edema. While this approach provided immediate relief of intracranial pressure and yielded ample tissue for diagnosis, it is not considered a curative measure by itself – indeed, median survival with surgery alone is only ~1–4 months [2]. Thus, definitive therapy relies on chemo- and radiotherapy after surgery (or after biopsy in unresectable cases).

Corticosteroids merit special mention: dexamethasone can dramatically reduce tumor edema and even transiently shrink PCNSL lesions (due to the lymphoma's exquisite sensitivity to steroids). However, steroids also induce rapid apoptotic cell death that can obscure the diagnosis. It is well documented that administering steroids before the biopsy can lead to "vanishing" lymphomas and nondiagnostic samples. Therefore, unless clinically necessary to reduce acutely raised intracranial pressure, steroids are best avoided until after a diagnostic biopsy is obtained [4]. All three of our cases had diagnostic biopsies or resection without steroid pretreatment, or with minimal steroids, to ensure accurate histopathology.

For initial therapy, high-dose methotrexate (HD-MTX)-based chemotherapy is the cornerstone of treatment for PCNSL. HD-MTX has the ability to penetrate the blood-brain barrier at high doses and has demonstrable activity against lymphoma cells in the CNS. Typically, HD-MTX (doses ≥3–3.5 g/m^2) is given intravenously with leucovorin rescue, in combination with other chemotherapeutic agents. A variety of multi-agent regimens have been developed, and there is no single superior regimen established by randomized trials [4,5]. Common induction regimens include: HD-MTX combined with high-dose cytarabine (Ara-C) (e.g. the regimen "MA" or "AraC-MTX"), HD-MTX with rituximab, vincristine, and procarbazine (the older "R-MPV" regimen), or more intensive protocols like MATRix (HD-MTX + HD-AraC + thiotepa + rituximab) [1]. The addition of cytarabine to methotrexate has been shown to improve response rates and survival: in a randomized trial, HD-MTX plus Ara-C nearly doubled the complete response rate and prolonged survival compared to HD-MTX alone [1]. Likewise, the inclusion of the anti-CD20 monoclonal antibody rituximab may improve outcomes. While one phase III study (RTOG 1114/HOVON 105) did not show a significant survival benefit for adding rituximab to an HD-MTX regimen, another (IELSG32) suggested rituximab and thiotepa contributed to better 5-year survival. A meta-analysis of these trials indicated a progression-free survival benefit with rituximab [1], so most modern regimens incorporate rituximab given its relatively low toxicity. In summary, combination chemoimmunotherapy with HD-MTX is the standard induction therapy, aiming to achieve complete remission of all CNS lesions.

After induction chemotherapy, consolidation therapy is typically recommended to sustain remission. For "fit" patients (generally ≤~60–65 years old, good performance status), two main consolidation approaches exist: whole-brain radiotherapy (WBRT) or high-dose chemotherapy with autologous stem-cell transplant (HDC-ASCT) [1]. Historically, WBRT at doses of ~36–45 Gy was used after chemotherapy to consolidate responses, and it is very effective at controlling residual disease. However, WBRT carries a significant risk of delayed neurotoxicity, especially in older patients (age >60) [2]. Survivors who receive full-dose WBRT often develop cognitive decline, leukoencephalopathy, and other neurologic deficits months to years later. Because

of this, there has been a move to limit or avoid upfront WBRT in PCNSL, particularly for older patients [1,2]. In younger patients, some protocols still include reduced-dose or targeted-field WBRT (e.g. 23.4 Gy in CR patients) in an attempt to minimize neurotoxicity while providing CNS disease control [2]. For example, Case 3 (in her 50s) received WBRT after chemotherapy as consolidation, but in a reduced fractionated dose of 40 Gy + boost. She experienced significant clinical improvement with an ongoing partial radiologic response, suggesting the benefit of consolidative radiation in achieving durable control in multifocal disease. In contrast, Case 2 (age 75) did not receive WBRT … although he initially responded radiologically to HD-MTX, his condition deteriorated and he died before consolidation, underscoring the frailty and poor tolerance of intensive therapy in elderly patients

The alternative consolidation approach, increasingly favored for younger patients, is myeloablative chemotherapy followed by autologous stem cell transplant. High-dose regimens (such as thiotepa-based combinations like BEAM-Thiotepa or TBC [thiotepa, busulfan, cyclophosphamide]) are used to purge residual lymphoma, and the patient's own stem cells (harvested earlier) are reinfused to rescue the bone marrow [1]. Recent studies have shown very promising results with HDC-ASCT consolidation. For instance, one multicenter trial reported 5-year overall survival ~79% in patients who received R-MTX-based induction followed by thiotepa-conditioned ASCT. This suggests a substantial subset of patients can achieve long-term remission or cure with this intensive approach. Accordingly, current guidelines often recommend ASCT consolidation for transplant-eligible patients (generally up to age ~70) who attain at least a partial remission after induction [1]. Case 1 in our series (age ~70) was treated with surgery and WBRT alone, but despite this aggressive local therapy his course was ultimately fatal, illustrating the poor long-term control with surgery + WBRT alone.

For patients who cannot tolerate intensive therapy – e.g. frail or very elderly patients – reduced-intensity regimens or palliative approaches are considered. Strategies like HD-MTX monotherapy or combination chemotherapy without transplant or radiation have been studied in the elderly. Even in patients ≥ 70 years, HD-MTX-based chemo can induce remissions, though with shorter durations (the PRIMAIN study showed feasibility of HD-MTX ± rituximab in elderly, with median survival ~7–18 months) [1]. In those who are too ill for systemic chemo, corticosteroids or palliative WBRT can temporarily improve symptoms, but typically with limited survival.

Intrathecal chemotherapy (e.g. methotrexate or cytarabine delivered via lumbar puncture or Ommaya reservoir) has not shown clear benefit in PCNSL when adequate systemic HD-MTX is given [2]. It is generally reserved for patients with overt leptomeningeal lymphoma or ocular lymphoma that is unresponsive to systemic therapy. Similarly, intravitreal chemotherapy (methotrexate injections into the vitreous) can be used as adjunctive therapy for vitreoretinal lymphoma, but only in select cases [1].

Relapse and prognosis of PCNSL deserve discussion as part of treatment considerations. Unfortunately, PCNSL has a high relapse rate. More than half of patients will experience recurrence of lymphoma in the brain or eye, even after achieving an initial complete remission. Relapses most often occur in the first 2–3 years but can be seen even a decade after therapy [4]. There is no standardized salvage regimen, but options include repeating HD-MTX if it worked initially, using non–cross-resistant chemotherapy combinations (e.g. ICE regimen – ifosfamide, carboplatin, etoposide), or delivering WBRT in those who did not receive it upfront. WBRT is an effective salvage modality, often yielding a median survival around 1 year when used at relapse [4]. For fit patients at relapse, high-dose chemotherapy with ASCT is also utilized as a salvage strategy if not done initially [4]. Newer targeted agents are actively being explored in recurrent PCNSL. These include Bruton tyrosine kinase inhibitors (ibrutinib, tirabrutinib) which target the BCR pathway, immune checkpoint inhibitors (nivolumab, pembrolizumab) targeting PD-1, pomalidomide/lenalidomide (immunomodulatory drugs), and even CAR T-cell therapy directed at CD19 [1,4]. Early-phase trials of these agents have shown some promise, but their use is not yet standard. As of now, methotrexate-based combination chemotherapy remains the gold-standard first-line therapy, with consolidative transplant or radiation improving durability of remission in many cases.

PCNSL is a potentially curable malignancy, but overall outcomes vary widely based on patient factors and treatment approach. Without treatment, PCNSL is rapidly fatal (survival measured in just 1–3 months). With older therapies like radiotherapy alone, outcomes were poor: median survival was only about 12–18 months with WBRT alone, and virtually all patients relapsed [4]. The addition of chemotherapy in the 1980s–90s improved survival significantly. In the modern era of HD-MTX-based therapy, median overall survival has extended to 3–4 years or more in many series [2]. Population-based analyses indicate that around 30% of patients survive 5 years or longer [3], although this statistic encompasses a wide age range and treatment heterogeneity. Long-term cures are most commonly seen in younger patients who receive intensive combined-modality therapy. For instance, prospective studies in transplant-eligible patients have reported 2-year survival rates of 70–80% and 5-year survival exceeding 50–60% in some cohorts. In contrast, elderly patients (who often cannot tolerate intensive regimens) have worse outcomes – median survival in patients over 70 is on the order of

1–2 years even with therapy, and neurotoxicity from treatment remains a concern [2].

Prognostic factors in PCNSL have been studied to guide risk stratification. The two most important adverse factors are age > 60 years and poor performance status at diagnosis. These were the basis of the MSKCC and International Extranodal Lymphoma Study Group (IELSG) prognostic scoring systems, along with elevated serum LDH, high CSF protein, and deep brain involvement in some models. Patients younger than 50 have the best prognosis, with five-year survival rates well above 50% in modern series [2]. In contrast, patients over 75 have a much more guarded outlook. Our cases mirror this trend: the two septuagenarian patients initially responded radiologically but both ultimately died despite aggressive management, highlighting the poor prognosis in older or frail patients. The middle-aged patient (Case 3) also improved greatly (partial response) but still has residual disease under surveillance, illustrating that some patients may have an indolent or chemo-refractory component requiring ongoing management.

Close clinical and radiologic follow-up is essential for PCNSL. Imaging (MRI) every 3 months in the first 2 years, then at increasing intervals, is often recommended to catch early relapses [4]. Surveillance neurologic exams and ophthalmologic exams (for ocular relapse) are also important. If relapse is detected, further treatment (as discussed above) can sometimes salvage the patient – durable second remissions are achievable in a minority, especially if novel agents or transplant can be employed.

In summary, PCNSL is an aggressive but treatment-sensitive brain tumor. The outcomes have improved substantially with the use of high-dose methotrexate-based chemotherapy, such that a meaningful proportion of patients now enjoy long-term remission or cure [3]. Nonetheless, management is complex due to the risk of neurotoxicity and frequent relapses. Future advances, including molecular-targeted therapies and personalized approaches, hold hope for increasing the cure rate while reducing treatment-related toxicity [4]. The cases presented in our series underscore key points of PCNSL management: the importance of tissue diagnosis (and avoiding steroids prematurely), the efficacy of high-dose methotrexate chemotherapy, the judicious use of radiotherapy and surgery. Long-term prognostic vigilance remains warranted, but with appropriate therapy, PCNSL can be controlled in a significant fraction of patients – a fact that marks a dramatic improvement from the dismal outcomes of past decades.

Conclusion

PCNSL remains a rare but highly treatment-sensitive primary brain lymphoma. The presented cases illustrate several contemporary management themes: the limited role of extensive surgical resection beyond diagnosis or decompression; the central importance of HD-MTX–based chemotherapy; and the tailored use of consolidation (WBRT versus HDC-ASCT) according to age and fitness. Modern regimens have transformed outcomes from uniformly fatal disease to one with meaningful long-term remission in a subset of patients, particularly younger or fit individuals. Nevertheless, high relapse rates and delayed neurotoxicity after WBRT continue to challenge durable disease control. Integration of molecular diagnostics (e.g., MYD88/CD79B mutation testing) and novel targeted or immune-based therapies (BTK inhibitors, checkpoint inhibitors, CAR-T) holds promise for improving survival while minimizing cognitive sequelae. Long-term surveillance remains critical given the potential for late recurrences and treatment-related neurocognitive decline.

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