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Multimodal Treatment and Sustained Rehabilitation in Primary CNS Diffuse Large B-cell Lymphoma: A Five-Year Survivor With Long-Term Remission

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Abstract

Primary central nervous system lymphoma (PCNSL) is an aggressive extranodal non-Hodgkin lymphoma confined to the central nervous system and is most commonly associated with immunosuppression, although it may also occur in immunocompetent individuals. We report a case of a 51-year-old immunocompetent female who presented with a two-week history of slurred speech and right-sided facial weakness, initially managed as Bell's palsy. Neuroimaging revealed a solitary left parietal lesion. She underwent craniotomy, and histopathological examination confirmed high-grade B-cell lymphoma. The postoperative course was complicated within 24 hours by intracranial haemorrhage requiring re-exploration, followed by multifocal ischaemic infarcts.

Subsequently, she received high-dose methotrexate-based chemotherapy with rituximab, followed by whole-brain radiotherapy. Over the ensuing months, the patient demonstrated gradual neurological improvement with rehabilitation. At five-year follow-up, she remains in remission with stable neurological status.

This case highlights the occurrence of PCNSL in an immunocompetent patient, the potential for severe treatment-related complications, and the possibility of meaningful neurological recovery following sequential oncologic and haemorrhagic brain injury.

Categories: Neurosurgery

Keywords: brain neoplasms, intracranial hemorrhages, methotrexate, primary central nervous system lymphoma, rehabilitation

Introduction

Primary central nervous system lymphoma (PCNSL) is an aggressive form of non-Hodgkin lymphoma that arises within the central nervous system rather than in lymph nodes, a characteristic referred to as extranodal involvement. It primarily affects the brain, spinal cord, leptomeninges, or eyes and accounts for a small proportion of primary brain tumours and extranodal lymphomas [1,2]. Although PCNSL is associated with immunosuppression, particularly human immunodeficiency virus infection, it can also occur in immunocompetent individuals [3]. Most cases are classified as diffuse large B-cell lymphoma (DLBCL), a malignancy characterised by the uncontrolled proliferation of large, abnormal B lymphocytes, which are immune cells responsible for producing antibodies. Patients typically present with focal neurological deficits or neurocognitive disturbances [3,4].

Magnetic resonance imaging (MRI) is the modality of choice for detection, but definitive diagnosis requires histopathological confirmation [4]. High-dose methotrexate-based chemotherapy, often in combination with rituximab, remains the cornerstone of treatment, with radiotherapy used in selected cases [2,3]. Despite advances in therapy, the disease is associated with significant morbidity, and complications related to both the tumour and its management may adversely affect outcomes [5].

We report the clinical course of an immunocompetent patient with PCNSL who developed acute postoperative intracranial haemorrhage followed by multifocal ischaemic infarcts, resulting in severe neurological and functional impairment. The objective of this case report was to describe the diagnostic evaluation, multimodal oncologic treatment, major postoperative complications, and longitudinal neurological recovery over a five-year period. The case addresses a relatively uncommon clinical sequence in PCNSL, in which postoperative haemorrhagic and ischaemic brain injuries were followed by substantial functional recovery with disease-directed therapy and sustained multidisciplinary rehabilitation. By presenting this prolonged clinical course, we aim to highlight the importance of coordinated oncologic,

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neurosurgical, and rehabilitative management even in the setting of severe neurological injury.

Case Presentation

A 51-year-old woman presented to the Punjab Institute of Neurosciences, Lahore, Pakistan, in June 2021 with a two-week history of slurred speech and difficulty in word retrieval. She had no significant past medical history. Clinical examination revealed a Glasgow Coma Scale (GCS) score of 15 [6], right-sided facial weakness, and an initial diagnosis of Bell's palsy was made. She was prescribed a seven-day course of oral steroids. One week later, she returned with progressive facial weakness, deviation of the mouth, and new right upper-limb weakness, prompting further neurological evaluation and neuroimaging. At this stage, her motor power in accordance with the Medical Research Council (MRC) muscle power grading system [7] was 5/5 in both the right upper and right lower limbs, and her Karnofsky Performance Status (KPS) score [8] was 90.

One week later, she returned with worsening symptoms, including progression of facial weakness, deviation of the mouth, and right upper-limb weakness. MRI subsequently revealed a vividly enhancing solitary lesion at the grey-white matter interface in the left parietal lobe (Figure 1A), measuring approximately $19.6 \times 12.8 \times 20$ mm. Magnetic resonance spectroscopy suggested a neoplastic process, with differential diagnoses including high-grade glioma and metastatic disease. Initial laboratory values are documented in Table 1, which were mostly within the physiological range.

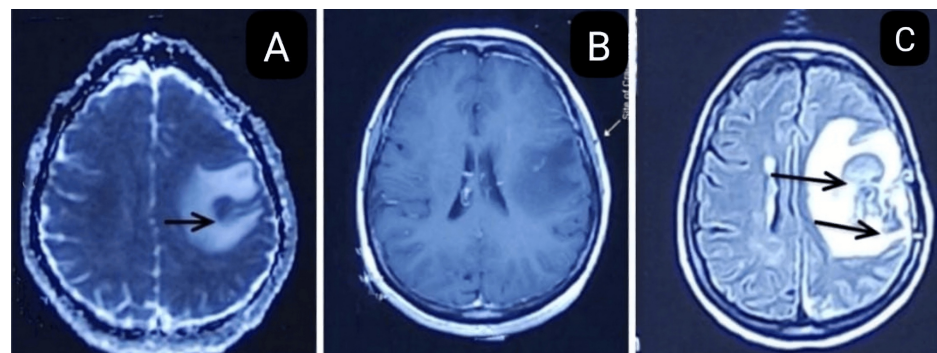


FIGURE 1: (A) Contrast-enhanced magnetic resonance imaging (MRI) brain showing a left parietal lesion at the grey–white matter interface (black arrow); (B) post-surgical changes at the site of craniotomy (white arrow on the right); and (C) follow-up imaging showing recurrent lesion (black arrows).

Test	Unit	Patient's Results	Reference Range
Haemoglobin (HGB)	g/dL	14.1	11.0–15.5
Red Blood Cell Count (RBC)	×10 ⁶ /μL	4.6	3.8–5.2
Total Leukocyte Count (WBC)	×10 ³ /μL	10.2	4.0–11.0
Platelet Count	×10 ³ /μL	320	150–450
Erythrocyte Sedimentation Rate (ESR)	mm/hr	20	0–15
Serum Creatinine	mg/dL	1.0	0.4–1.3
Serum Urea	mg/dL	36	15–40
Sodium	mmol/L	136	135–154
Potassium	mmol/L	4.1	3.5–5.4
Chloride	mmol/L	103	98–107
Alanine Aminotransferase (ALT)	U/L	55	7–56
Aspartate Aminotransferase (AST)	U/L	28	8–33
Alkaline Phosphatase (ALP)	U/L	227	42–306
Total Bilirubin	mg/dL	0.9	0.2–1.1
Prothrombin Time (PT)	sec	12	11–14
Activated Partial Thromboplastin Time (APTT)	sec	26	26–32
International Normalised Ratio (INR)	-	1.0	1.0–1.3

TABLE 1: Summary of laboratory investigations at initial presentation.

Abbreviations: WBC, white blood cell count; RBC, red blood cell count; HGB, haemoglobin; ESR, erythrocyte sedimentation rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; PT, prothrombin time; INR, international normalised ratio; APTT, activated partial thromboplastin time.

A multidisciplinary evaluation was conducted to exclude extracranial involvement. Preoperative HIV testing was negative, and there was no history of autoimmune disease or immunodeficiency. Systemic staging with PET and CT of the abdomen and pelvis showed no evidence of extracranial involvement. CSF analysis and ophthalmologic evaluation were not performed. The patient underwent left temporo-parietal craniotomy in early July 2021, and the lesion was excised. Within 24 hours postoperatively, the patient developed acute neurological deterioration, with a drop in GCS from 15 to 11 (E3M5V3). Computed tomography of the brain revealed a haematoma at the surgical site, necessitating emergency re-exploration and evacuation. Following surgery, the patient developed profound right-sided motor deficit, with MRC power of 0/5 in the right upper limb and 1/5 in the right lower limb, corresponding to a KPS of 20. Her postoperative course was further complicated by multifocal ischaemic infarcts involving the posterior circulation, as demonstrated on MRI performed during the first week of intensive care unit admission.

Histopathological examination revealed high-grade B-cell lymphoma (Figure 2) with c-MYC amplification and BCL-2 and BCL-6 rearrangements. Immunohistochemistry showed positivity for LCA, CD20, BCL-2, BCL-6, and c-MYC, with a Ki-67 proliferation index approaching 100%. After approximately three weeks in intensive care, the patient was successfully weaned off mechanical ventilation and transferred to the ward. Approximately one month after surgery, she developed clinical and radiological features of disease progression on emergency MRI (Figure 1B), for which systemic chemotherapy was initiated. Immediately before initiation of chemotherapy, her neurological examination demonstrated a power of 1/5 in the right upper limb and 2/5 in the right lower limb, with a KPS of 50, reflecting partial neurological recovery from the severe postoperative deficit but persistent significant functional impairment.

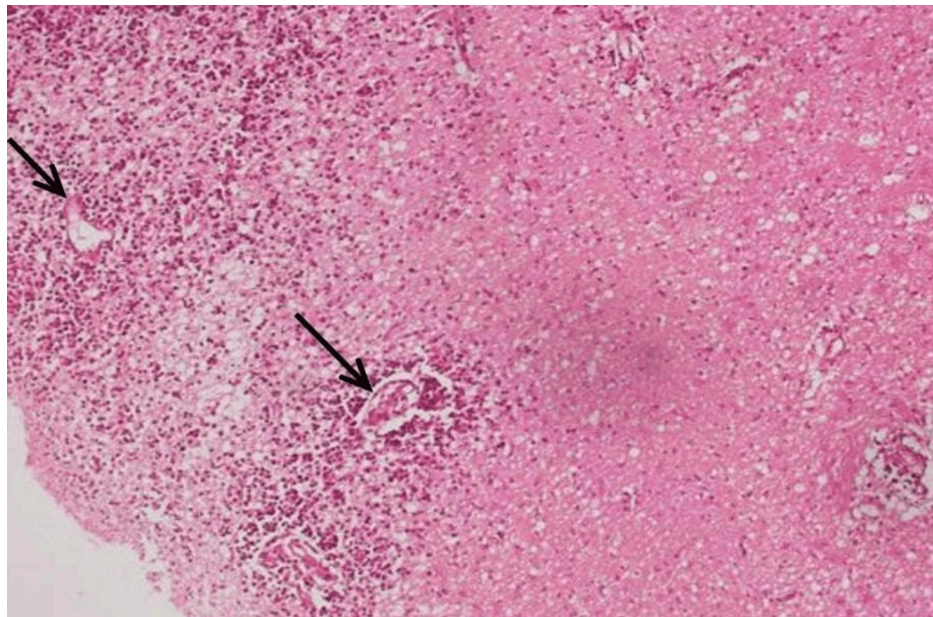


FIGURE 2: Primary central nervous system high-grade B-cell lymphoma, neoplastic cells (in black arrows) around the blood vessels with normal brain parenchyma on the right side (×10).

From August 2021 onwards, the patient received high-dose methotrexate-based chemotherapy in combination with rituximab, followed by whole-brain radiotherapy (WBRT) in December 2021. Maintenance therapy with temozolomide was continued until January 2023.

Following completion of chemotherapy and during the subsequent rehabilitation period, further neurological improvement was observed. At completion of chemotherapy, power had improved to 2/5 in the right upper limb and 4/5 in the right lower limb, with a corresponding KPS of 60. The patient subsequently underwent intensive physiotherapy rehabilitation, including electrical muscle stimulation (EMS) to the involved limbs twice daily. Speech and language therapy was conducted twice weekly, along with maxillofacial physiotherapy three times daily, addressing difficulty in initiating and completing sentences, anomia, drooling from the right side of the lips, and dysphagia to liquids. Clinical psychology sessions were also conducted twice weekly to facilitate adjustment and functional recovery. The patient continued to attend physiotherapy sessions twice weekly, with additional physiotherapy performed by family members at home; speech therapy was discontinued approximately one year ago.

At the current five-year follow-up, the patient remains in remission with stable neurological status. Serial follow-up MRI examinations initially performed every three months and subsequently every six months for the past two years showed no evidence of residual or recurrent disease. The most recent MRI, performed in March 2026, demonstrated chronic infarcts, ventricular dilatation, and the postoperative surgical-site defect, without evidence of residual disease. Her current neurological examination demonstrates power of 3/5 in the right upper limb and 4/5 in the right lower limb, with a KPS of 80. She is able to ambulate independently under supervision and remains independent in most activities of daily living, with residual right upper-limb weakness and occasional speech difficulty.

The treatment received during the initiation, consolidation, maintenance, and rehabilitation phases is summarised in Table 2. The available treatment records documented the dosing and frequency shown in Table 2; cumulative chemotherapy doses, treatment delays, and specific chemotherapy-related toxicities were not documented in the available records. The longitudinal neurological course, including MRC motor power and KPS at the major clinical stages, is summarised in Table 3.

Treatment Phase	Treatment/Intervention	Dose/Details	Frequency/Duration
Initiation phase (mid-August to the start of November 2021)	High-dose methotrexate (HDMTX)	4 g/1000 mL of N/S IV	Every 15 days
	Leucovorin	25 mg IV over 6 hours	Every 15 days
	Rituximab	600 mg/600 mL of N/S IV	Every 15 days
	Temozolomide	100 mg/m ² daily for 5 days	Every 4 weeks
Consolidation phase (December 2021)	Whole-brain radiotherapy (WBRT)	36 Gy	18 fractions
Maintenance phase (January 2022 to January 2023)	Temozolomide	300 mg/m ² daily for 5 days	Every 4 weeks
Rehabilitation phase (January 2022 to date)	Intensive physiotherapy rehabilitation	Electrical Muscle Stimulation (EMS) to the involved limbs	Twice daily
	Speech and language therapy	Therapy with a speech pathologist	Twice weekly
	Maxillofacial physiotherapy	Addressing difficulty in initiating and completing sentences, anomia, drooling from the right side of the lips, and dysphagia to liquids	Three times daily
	Clinical psychology sessions	Grief recovery, enhancement of self-esteem, adaptability to the new lifestyle, maintaining the patient's position as a significant pillar of the family, and confidence building	Twice weekly
	Bladder training	Bed pan following removal of the urinary catheter	As required
	Assisted ambulation	Walking cane, covering approximately 12 metres daily	Daily
	Functional activities of daily living (ADLs)	Washing the face, combing the hair, brushing the teeth, untying shoe laces, eating food using a spoon, drinking a glass of water, operating a television remote controller, and holding a pen using the healthy hand	Ongoing
Follow-up	MRI scans	Every 3 months	To date

TABLE 2: Treatment therapy received during the initiation, consolidation, maintenance, and rehabilitation phases by the patient to date.

Abbreviations: HDMTX, high-dose methotrexate; N/S, normal saline; IV, intravenous; EMS, electrical muscle stimulation; ADLs, activities of daily living; MRI, magnetic resonance imaging; WBRT, whole-brain radiotherapy; Gy, Gray.

Clinical Stage	Motor Function	Power Right Upper Limb	Power Right Lower Limb	KPS	Functional Status
Preoperative (June–July 2021)	Normal motor power	5/5	5/5	90	Functionally independent
Postoperative	Severe right-sided hemiplegia following surgery and postoperative complications	0/5	1/5	20	Bedbound and fully dependent
Pre-relapse/before chemotherapy	Persistent severe right-sided weakness with partial recovery	1/5	2/5	50	Dependent with assistance
Post-relapse	Worsening right-sided weakness associated with disease progression	0/5	1/5	20	Bedbound and highly dependent
Post-chemotherapy completion	Significant neurological recovery, particularly in the right lower limb	2/5	4/5	60	Able to stand/ambulate with assistance
Current five-year follow-up	Continued neurological recovery with residual right upper-limb weakness	3/5	4/5	80	Ambulates independently under supervision; independent in most ADLs

TABLE 3: Timeline of neurological recovery following treatment.

Abbreviations: KPS, Karnofsky Performance Scale; ADL, activities of daily living.

The patient demonstrated a marked postoperative decline in neurological and functional status, followed by gradual recovery with disease-directed therapy and intensive rehabilitation. The most substantial improvement was observed in the right lower limb, which progressed from 1/5 postoperatively to 4/5 following treatment, while right upper-limb power improved from 0/5 to 3/5. Overall functional status, as reflected by KPS, improved from 20 immediately postoperatively to 80 at five-year follow-up.

As the patient was unable to provide informed consent because of her neurological impairment, written proxy consent for publication, including the accompanying images, was obtained from her spouse. Additionally, the authors apologise for the limited neuroimaging available for this case, due to unavoidable institutional server data corruption in March 2026 that permanently affected archival records.

Discussion

PCNSL is a high-grade extranodal lymphoma increasingly recognised in both immunocompromised and immunocompetent individuals [3,9]. Clinical manifestations are frequently non-specific, which may result in delayed or inaccurate initial diagnoses, particularly when symptoms resemble benign neurological conditions, as seen in this case [4,9].

Neuroimaging typically demonstrates a contrast-enhancing lesion, frequently solitary in immunocompetent patients, and may mimic other intracranial tumours such as gliomas or metastases [3,4]. Definitive diagnosis relies on histopathological evaluation, characterised by perivascular infiltration of atypical lymphoid cells and a high proliferative index [5].

A key feature of this case is the occurrence of early postoperative intracranial haemorrhage, an uncommon but recognised complication of neurosurgical intervention. Although haemorrhagic events are not a typical feature of PCNSL, factors such as tumour-associated vascular fragility and surgical manipulation may contribute. The clinical course was further complicated by multifocal ischaemic infarcts, resulting in significant neurological impairment. The coexistence of these sequential pathological events represents a rare and challenging scenario in the management of PCNSL. Reports describing such sequential oncologic and vascular injury in PCNSL remain limited in the literature.

Despite severe neurological compromise, the patient demonstrated gradual functional improvement over time. Her KPS declined from 90 preoperatively to 20 immediately after surgery, subsequently improving to 50 before chemotherapy, 60 after completion of treatment, and 80 at five-year follow-up. Similarly, right lower-limb power improved from 1/5 immediately postoperatively to 4/5 after treatment, while right upper-limb power improved from 0/5 to 3/5 at five-year follow-up. This longitudinal recovery pattern illustrates substantial functional improvement despite severe initial neurological injury. Although formal year-by-year quantitative measures of speech and rehabilitation gains were not available, continued physiotherapy and

family-assisted exercises were associated with progressive improvement in functional independence. This underscores the potential for neurological recovery following combined oncologic and vascular injury when supported by coordinated multidisciplinary care, including structured neurorehabilitation. Comparable outcomes have been reported in selected cases of central nervous system malignancies receiving intensive treatment and rehabilitation, where initial deficits do not necessarily predict long-term functional status [10,11].

High-dose methotrexate-based chemotherapy remains the cornerstone of treatment, commonly administered with rituximab and, in selected cases, supplemented with WBRT [2,3]. Advances in therapeutic approaches have contributed to improved survival, even in complex clinical scenarios [12,13]. In the present case, adherence to standard treatment protocols, along with supportive care, resulted in sustained remission at five-year follow-up.

In this case, contrast-enhanced T1-weighted MRI demonstrated a strongly enhancing lesion more suggestive of a high-grade glioma as opposed to PCNSL. The imaging appearance of this lesion was atypical of the classical presentation of PCNSL (multifocal, predominantly periventricular lesions with typically intense and relatively homogeneous contrast enhancement) [14]. However, imaging findings are insufficient to reliably distinguish PCNSL from high-grade glioma, and histopathological confirmation remains essential. Given the preoperative suspicion of a high-grade glioma, surgical excision was considered rather than biopsy alone. Based on the preoperative clinical assessment and diagnostic MRI, we proceeded with surgical resection as an institutional norm rather than stereotactic biopsy. The neurosurgical approach may be affected in low- and middle-income country (LMIC) settings due to restricted availability of stereotactic biopsy facilities, timely surgical facilities, and modern neuroimaging. Our strategy also took into account the practical considerations of the local healthcare environment, where patients may find it more difficult to undergo a biopsy followed by a definitive resection due to the financial burden, the scarcity of specialised facilities, and the potential delays associated with sequential procedures.

Although stereotactic biopsy remains the conventional diagnostic procedure for suspected PCNSL, emerging literature has questioned whether resection should always be excluded. A 2023 meta-analysis by Stifano et al. suggested that, in carefully selected patients with solitary, superficial PCNSL, surgical resection may not be inferior to biopsy with an acceptable risk profile and reported no significant difference in progression-free survival between the two [15]. Von Baumgarten et al. emphasise that the neuroradiological appearance of PCNSL can be nonspecific and may overlap considerably with that of malignant glioma. While stereotactic biopsy is generally recommended for establishing the diagnosis, the authors note that selected single lesions have previously been associated with potential benefit from resection, although there is no established role for routine resection of infiltrative PCNSL [16].

Historically, a multidisciplinary approach consisting of high-dose methotrexate (HD-MTX) plus consolidation chemotherapy and/or WBRT has been the gold standard in PCNSL management [17]. HD-MTX represents the most accepted standard of care induction therapy for newly diagnosed PCNSL [17]. Following a combination of HD-MTX-based chemotherapy as the cornerstone of our treatment with WBRT and neuro-rehabilitation, our patient's neurologic status and quality of life improved from 2021 to 2025, and she could independently mobilise by the end of 2025.

The therapeutic path of patients with primary brain tumours ranges from diagnosis and active therapy to rehabilitation and, if necessary, palliative and hospice care. Rehabilitation is an essential part of this continuum since patients may have neurological, cognitive, physical, and psychosocial impairments [18]. Rehabilitation was incorporated throughout the patient's treatment and follow-up as part of a multidisciplinary approach to her neurological and functional deficits. Given the concurrent effects of surgical management, re-exploration, systemic chemotherapy, radiotherapy, and natural neurological recovery, the contribution of rehabilitation cannot be separated from these other factors in this single case. Nevertheless, continued physiotherapy, speech and language therapy, and family-assisted functional exercises provided ongoing supportive care during her recovery and may have contributed to maintaining and maximising functional independence after the acute treatment phase. Although the amount and time of recovery differ amongst patients, rehabilitation has been linked to better functional results after a brain injury [19].

This case highlights that, despite the aggressive nature of PCNSL and the occurrence of serious complications, favourable long-term outcomes with meaningful neurological recovery are achievable. Early recognition, accurate diagnosis, and comprehensive multidisciplinary management are essential in optimising patient outcomes.

Conclusions

PCNSL can occur in patients without a documented history of immunodeficiency and may present with nonspecific neurological symptoms that mimic other conditions. In this patient, severe postoperative neurological complications were followed by substantial functional recovery and sustained remission during five years of multimodal treatment and follow-up. This single case highlights the potential for meaningful recovery despite severe neurological injury, while the observed outcome should not be interpreted as

evidence of treatment or rehabilitation effectiveness in the broader PCNSL population.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Supervision: Haseeb Mehmood Qadri

Concept and design: Hasan Saeed, Khawar Anwar

Drafting of the manuscript: Hasan Saeed, Manal Khan, Warda Rauf, Hafza Bushra Razaq

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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