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Case Report

Primary central nervous system lymphoma in elderly: An illustrative case of the new role of surgery and integrative medical management

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ABSTRACT

Background: Primary central nervous system lymphoma (PCNSL) is a rare, aggressive non-Hodgkin lymphoproliferative neoplasm. Surgery is traditionally limited to biopsy due to past studies, but recent strong evidence continues to challenge this status quo in selected patients. Here, the authors characterize a case to illustrate the potential role of surgery and foster research on integrative medical management approaches for this disease.

Case Description: A 73-year-old woman was admitted to the hospital with aphasia and confusion. Neuroimaging suggested a lymphoproliferative process. The patient underwent cytoreductive surgery to resect the lesion. Microscopically, large infiltrating lymphoid cells that induced brain tissue damage were observed, and a diagnosis of diffuse large B-cell lymphoma was made based on immunohistochemistry. The patient evolved clinically post surgery. A complete response to further chemotherapy maintained the patient's clinical recovery.

Conclusion: This rare case highlights the potential of surgical intervention in the management of selected patients with PCNSL. The authors also underscore the recent, meta-analytic evidence on surgery followed by combined chemotherapy for the management of specific cases. The reported recovery in an elderly patient is noteworthy and adds to the literature on this rare subtype of brain tumors. Future research should consider investigating a potential profile of candidates for resection and combined chemotherapy in PCNSL.

Keywords: Brain tumor, Diffuse large B-cell lymphoma (DLBCL), Neuro-oncology, Non-Hodgkin lymphoma (NHL), Primary central nervous system lymphoma (PCNSL).

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare and aggressive non-Hodgkin lymphoproliferative neoplasm that swiftly infiltrates the brain, with a poor prognosis and limited treatment options. Over the years, the role of surgery in PCNSL has been a subject of debate. Historically, cytoreductive surgery was not a first-line approach due to concerns about the tumor's diffuse nature, potential dissemination, and the belief that systemic chemotherapy alone would suffice. Resection has been typically discouraged in PCNSLs since 20th-century studies fostered

the notion that the inherent risks outweigh the potential benefits. The tumor's deep location or proximity to critical brain structures often made resection challenging without compromising neurological function. However, while chemotherapy has contributed to significant improvements in the management of PCNSL, these patients' median overall survival (OS) rate is still only marginally better than that of glioblastomas (GBM).

Recent evidence, illustrated by the case we discuss herein, has begun to challenge the traditional stance, suggesting a potential role for surgical intervention – particularly if the tumor is exerting significant mass effect or is accessible – followed by combined chemotherapy with better outcomes in select cases. This report presents a 73-year-old woman with PCNSL who underwent symptomatic and diagnostic tumor resection, leading to the diagnosis of diffuse large B-cell lymphoma (DLBCL) based on immunohistochemistry. The patient recovered clinically post surgery and achieved a complete response with combined chemotherapy. Our report highlights the potential of an integrative medical management approach and underscores the urgency for further research on multimodal treatment options to determine a possible profile for such PCNSL patients.

CASE PRESENTATION

A 73-year-old, right-handed Caucasian woman, presented to the emergency department with a 1-week history of confusion, aphasia, and fluctuating consciousness. She experienced a decline in mental status and headaches the day before. Neurological examination showed a disoriented, cooperative female with severe mixed expression aphasia and a left extensor plantar cutaneous reflex. Past medical history was positive for hypertension, type 2 diabetes mellitus, and dyslipidemia, and the patient had no previous cardiovascular events. Non-contrast head CT showed a median shift to the right and suggestive findings of brain edema. Magnetic resonance imaging (MRI) revealed a 3.3 × 2.4 cm lesion in the left temporal lobe with hyposignal on T2, an intermediate signal on T1, diffusion restriction, and intense homogeneous contrast enhancement [Figures 1, a-c, respectively]. Laboratory findings in the blood serum excluded human immunodeficiency virus (HIV), Epstein–Barr virus (EBV), and opportunistic infections. A cerebrospinal fluid (CSF) analysis was not performed due to the high risk of brain herniation associated with the patient's condition. Metastatic cancer workup was negative. The patient was transferred to the neurosurgery service and underwent left frontotemporal craniotomy, anterior temporal lobectomy, and intraoperative frozen section of the sample specimen, suggestive of lymphoma. Histopathological and immunohistochemistry confirmed DLBCL [Figure 2]. She was discharged on the 10th postoperative day with a Glasgow Coma Scale (GCS) score of 14 due to disorientation. Fifteen days of hospital discharge, neurosurgical follow-up revealed continuous clinical improvement with a maximal GCS score (full orientation restored), and fluent speech. Two-month postoperative, MRI showed partial resection of the left temporal lobe lesion [Figure 3]. The referral to hematological care was promptly initiated. Most guidelines recommend a 3-month MRI for better surgical outcome evaluation; the tumor's known aggressiveness, however, was crucial for an earlier MRI request. Ninety days post surgery, she was undergoing combination chemotherapy with rituximab plus 2 g/m^2 methotrexate (MTX) and 2 g/m^2 cytarabine in a 15-day interval regimen. Control MRI revealed the absence of the previous lesion [Figure 4], suggesting a complete response. After the second follow-up with a sustained recovery, the patient was scheduled for regular 6-month interval visits at the neurosurgery clinic. Diffusion tensor imaging, fiber tractography (DTI tractography), and fractional anisotropy data were collected [Figure 5], the Western aphasia battery was applied, and the aphasia quotient calculated to assess residual symptoms, which showed mild sensory aphasia related to naming objects. The patient's severe initial presentation and the importance of an early pathological diagnosis led us to perform DTI postoperatively. Tractography studies are neither routinely requested nor widely accessible in our public health system. The PCNSL diagnosis, poor prognosis, and high recurrence rates were critical to obtaining this data. The patient continued follow-up and chemotherapy, tolerating the treatment well to reach six infusions. After the therapeutic regimen was completed, she was discharged from the hematology services. Thus far, the patient has survived 10 months since hospital admission.

DISCUSSION

PCNSLs represent an aggressive subtype of non-Hodgkin lymphoma (NHL), originating within the brain, spinal cord, and eyes. They are predominantly characterized by their histological features, with DLBCL being the most common type. This central nervous system (CNS)-DLBCL subtype is composed of large, abnormal lymphocytes that rapidly proliferate and infiltrate the brain, often detected at high-grade stages.[12]

The histological profile is pivotal in guiding the treatment approach and determining the patient's prognosis. Recognized by the 2021 World Health Organization classification of hematopoietic and lymphoid tissues, as well as by that of primary brain neoplasms, these lymphomas are nearly always (~95%) classified as CD20-positive DLBCL.[12,14] The T-cell NHL subtype constitutes < 5% of cases.[13] The scarcity of studies on this disease can be attributed to its rarity and frequent misdiagnosis, necessitating further research to enhance the understanding and management of PCNSLs.[5,18]

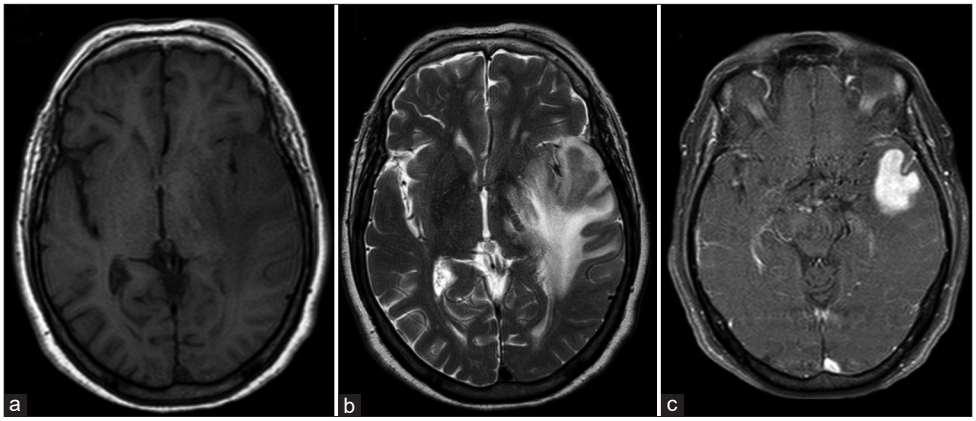

Figure 1: (a-c) Admission magnetic resonance imaging: large expansive intraparenchymal lesion in the left superior temporal gyrus with vasogenic edema, mass effect, and midline shift. Mild vascular engorgement of M2/M3 branches of the left middle cerebral artery.

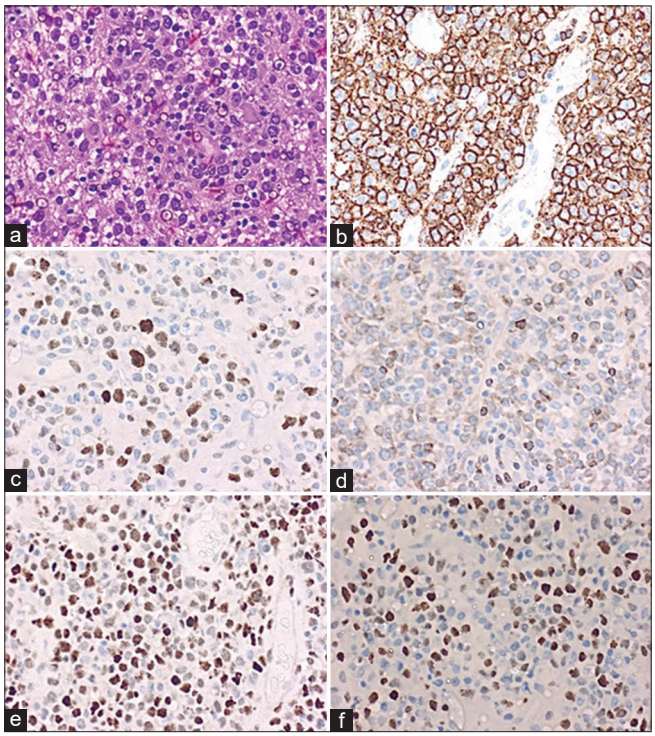

Figure 2: Pathology and immunohistochemical staining: primary central nervous system diffuse large B-cell lymphoma cells with positive staining for CD20, C-MYC, BCL-2, BCL-6, and MUM1, respectively, from (a-f) (original magnification ×200).

PCNSLs are most common in immunocompetent elderly individuals, with incidence increasing with age. They constitute 2% of all brain tumors and 4–6% of NHLs. In the general population, the incidence is 0.5–1/100,000 individuals.[12,14] Key risk factors include advanced age, HIV infection, and organ transplantation.[5] The pathogenesis is unclear, but immunosuppression seems to play a role. HIV and EBV, known to suppress defense responses, have been linked with PCNSLs. In HIV/acquired immunodeficiency syndrome patients, PCNSLs can make up to 15% of lymphomas, compared to 1% of all lymphomas and 4% of intracranial tumors in the immunocompetent population.[3] In immunocompetency, PCNSL occurrence may be linked to chronic inflammation and weakened immune systems. In this case, the patient had no active infectious diseases, as confirmed by laboratory tests.[17]

The clinical presentation can vary depending on their location. PCNSLs typically exhibit a diffuse distribution, with the most common sites being the hemispheres (38%), that is, the frontoparietal, followed by the temporal lobe, basal ganglia (16%), corpus callosum (14%), periventricular regions (12%), and rarely the cerebellum (9%).[4] The brainstem is less frequently affected, and about 1% of patients have spinal cord involvement.[4] Symptoms can manifest suddenly or gradually and range in severity depending on the intracranial pressure. Common manifestations include focal neurological deficits, headaches, and seizures. When PCNSL lesions affect the temporal lobe, deficits in language processing may occur, leading to impairments in word recognition, sensory interpretation (such as visual agnosia), verbal memory, and behavioral changes, such as the loss of fear and anger response.[8] The current patient presented with severe language impairment and mass effect-related symptoms.

The diagnosis of PCNSLs requires a brain MRI and biopsy. Radiological findings often show well-defined mass lesions that are hypointense on T1- and hyperintense on T2-weighted images, enhanced after contrast administration, with abundant edema.[4] However, distinguishing PCNSL from its peculiar differential diagnosis, GBM, is challenging, and radiological features can be subjective, requiring confirmation with histopathology. As an illustrative example of this diagnostic complexity, a recent meta-analysis using deep learning and machine learning approaches

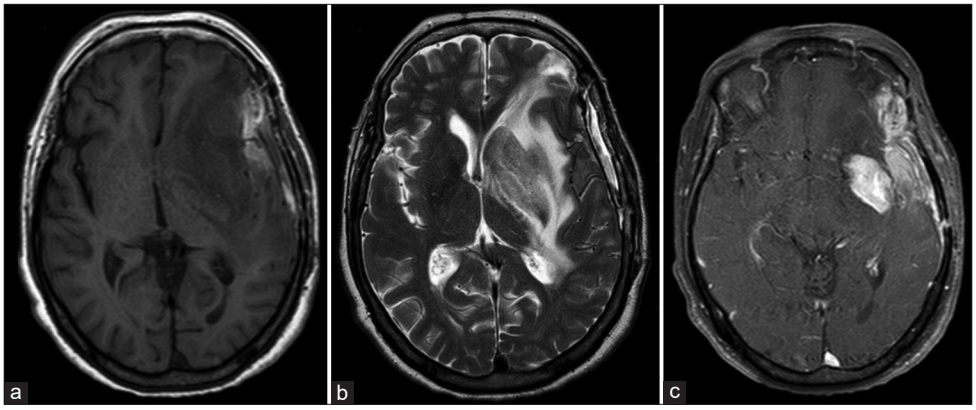

Figure 3: (a-c) Control magnetic resonance imaging 2-month post-surgery: left pterional craniotomy with extra-axial residual blood collection. Partially resected infiltrative left temporal lesion with extension to the frontal and parietal lobes. Persistent contrast-enhancing lesion with mass effect on the left lateral ventricle.

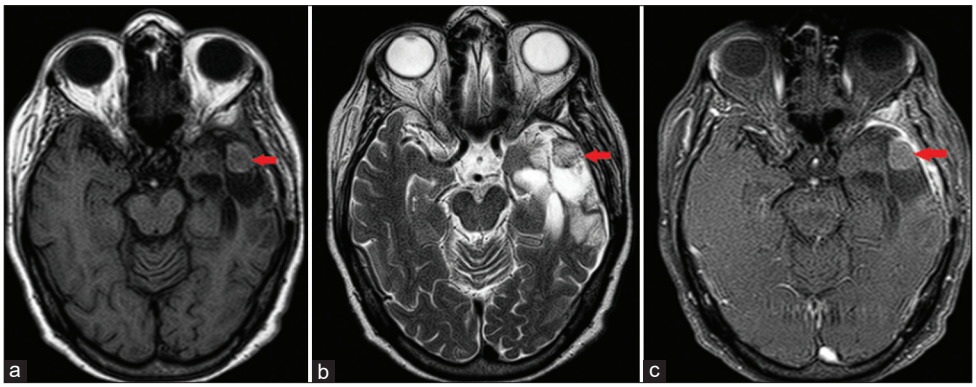

Figure 4: (a-c) Control magnetic resonance imaging after two cycles of combined chemotherapy: left pterional craniotomy with extra-axial residual surgical hemostatic material (red arrows). Extensive parenchymal left temporal resection with extension into the frontal and parietal lobes. No contrast-enhancing lesion or midline shift.

to differentiate between PCNSL and GBM still was not able to clearly define the two better than an experienced neuroradiologist.[4] In the present case, the patient had an expansive intraparenchymal lesion in the subcortical white matter of the left temporal lobe with features suggestive of a lymphoproliferative tumor, but differentials such as secondary neoplastic processes and primary glial neoplasms could not be ruled out.[9]

Moreover, a CSF analysis was precluded due to the imminent risk of brain herniation, as indicated by the significant midline shift and extensive brain edema seen in the patient's MRI.[16] This scenario mirrors a broader challenge in PCNSL management: often, patients manifest in advanced disease stages.[12,18] Recent research underscores the utility of CSF-based diagnostics, particularly related to the myeloid differentiation primary response gene 88 (MYD88) L265P mutation.[1] For instance, Yamaguchi *et al*. reported a novel rapid genotyping system, GeneSoC, which uses real-time polymerase chain reaction to detect the MYD88 mutation effectively.[19] This innovation reinforces the evolving landscape of PCNSL diagnostics, offering potential advancements for both intra- and preoperative diagnosis through CSF analysis.[19] Yet, as our case accentuates, real-world clinical challenges may sometimes preclude its utilization, underscoring the importance of individualized diagnostic and therapeutic considerations.

Immunohistopathology of PCNSLs can indicate aggressiveness and invasiveness. DLBCL is the most common subtype with the least favorable prognosis.[17] Typically, it expresses CD20+ and B-cell markers. Several biomarkers have been identified, including BCL-6, CD10, BCL-2, MUM1/IRF4, and Ki-67, with BCL-2 expression indicating a worse prognosis and Ki-67 associated with tumor aggressiveness.[13] Germinal center B-cell-like and activated B-cell-like types are the two main prognostic factors that guide targeted therapy, with CNS-DLBCLs

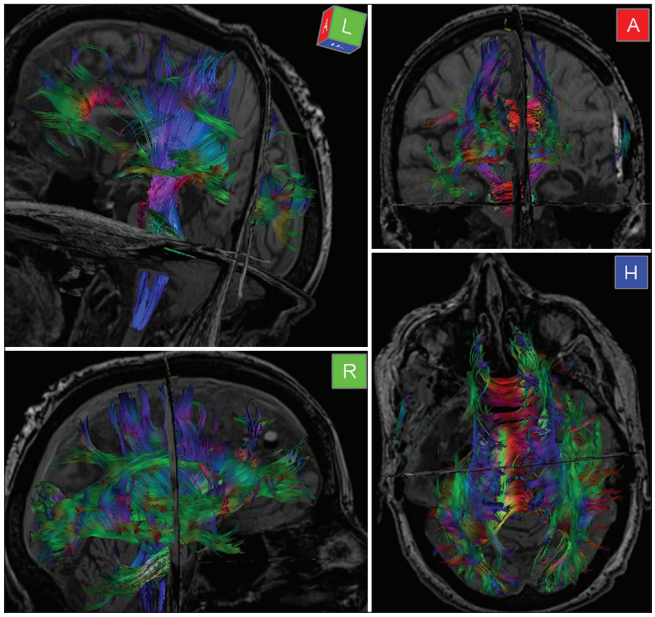

Figure 5: Diffusion tensor imaging and fiber tractography: marked reduction of fractional anisotropy (FA) in the left inferior longitudinal fasciculus and anterior corona radiata, suggesting fiber injury. Slight reduction of FA in the corpus callosum. No evidence of intracranial expansile process, hemorrhage, extra-axial collections, or midline shift.

most closely resembling a post-germinal center or ABC immunophenotype.[13,17] Histological examination of the present case showed a CNS-DLBCL. The analysis also demonstrated an ABC-like subtype, positive for expression of Ki-67, BCL-2, and C-MYC in 80–90%, 60–70%, and 70–80% of atypical cells, respectively, indicating a worse prognosis.

Surgery is essential for diagnosing PCNSL, and while the standard treatment is chemotherapy,[6] the potential role of resection in management has been controversial due to past studies.[2] Recent stronger evidence suggests a potential survival benefit associated with resection in selected cases based on tumor localization, age, and functional performance.[2] Benefits of resection include rapid improvement in neurological symptoms, relief of mass effect, and increased tolerance for chemotherapy.[2] The negative prognostic factors for PCNSL patients include involvement of deep brain structures, multiple lesions, low karnofsky performance status (KPS), and advanced age, while complication rates for surgical resection and biopsy are comparable.[2] Outdated studies do not reflect the current standard of care, and in selected patients, resection was associated with significantly better overall and progression-free survival.[2] Our report underscores that surgery might be beneficial, providing symptomatic relief in the severe, acute setting of an extensive DLBCL of the dominant temporal lobe.

The optimal management of PCNSL is still under debate but typically involves MTX-based chemotherapy.[7] The combination chemotherapy of high-dose MTX (HD-MTX), rituximab, methotrexate, and cytosine arabinoside (R-MethAraC) is one of the standard treatments for CNS-DLBCL.[20] Several studies, which showed a higher overall response, longer median progression-free survival, and OS, have supported R-MethAraC in comparison to HD-MTX monotherapy.[20] Rituximab, a monoclonal antibody against CD20, is generally a part of the induction therapy in all patients with CD20+ disease, including PCNSL.[17,20] The patient in this report received rituximab (day 1), 2 g/m^2 MTX (day 2), folinic acid, and 1 g/m^2 cytarabine (day 3) on a 15-day interval, which resulted in complete radiological response after two cycles. The patient continued follow-up and chemotherapy, tolerating the treatment well to reach six infusions. The proposed therapeutic regimen was completed, and she received a discharge from the hematology services. Thus far, the patient has survived 10 months since hospital admission.

In the intricate landscape of PCNSL management, our case illustrates the efficacy of a comprehensive medical approach. The choice between biopsy and resection is pivotal.[2] While the former could expedite the initiation of chemotherapy, this report demonstrates the transformative potential of resection, especially when the lesion is accessible.[2] The 2-month postoperative MRI, taken a month before the conventionally advised 3-month mark, may seem to suggest lymphoma progression [Figure 3]. However, this could mirror cortical reorganization, a recognized post surgical phenomenon in eloquent brain areas.[11,15] Intriguingly, despite the imaging, our patient exhibited a striking clinical improvement. This juxtaposition of imaging and clinical findings kindles a pertinent discussion: could the remarkable recovery and subsequent maintenance of function, witnessed in this case, have been achieved solely through earlier chemotherapy initiated after a biopsy? Reflecting on recent meta-analytic evidence and the patient's trajectory in our report, it becomes increasingly evident that an integrative strategy – though unconventional – possibly charted the optimal route for this patient's unique clinical outcome.

Elderly patients with PCNSL have a poor survival rate, with a median OS of 6–10 months and complete response rates at approximately 50%.[6,18] However, the disease is fatal without treatment. Recurrences after the initial response are common and generally occur within the CNS.[9] In contrast, the prognosis of relapsed disease is even worse, with a median OS of 2 months without therapy, and 7 months with it.[8] The 5-year OS rate is approximately 30%, and thus, new therapeutic approaches are necessary to improve these patients' quality of life and prognosis.[8,17]

This report highlights the benefits of resection in selected cases. Ten months after the hospital admission, surgery could provide symptomatic relief and preserved function in the severe, acute setting of an extensive lesion in noble

brain areas. Combined with chemotherapy, this integrative approach led to a complete radiological and sustained clinical response. Future clinical trials should aim to investigate and determine the best-combined treatment modalities for this rare disease and potential eligibility criteria.[10]

CONCLUSION

The article describes a 73-year-old woman with PCNSL presenting with acute mixed expression aphasia and confusion. The patient underwent resection followed by chemotherapy, which led to a rapid and sustained recovery. The authors emphasize the unexplored potential of surgical resection to improve outcomes in selected PCNSL patients, which follows recent meta-analytic evidence. The findings suggest that the combined treatment of surgery and multiagent chemotherapy could successfully treat PCNSL while promoting preserved function and prolonged survival of certain patients. Overall, this report adds to the growing literature on the management of PCNSL in the elderly and fosters future research into multimodal therapies for this aggressive neoplasm.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author(s) confirms that there was no use of Artificial Intelligence (AI)-Assisted Technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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