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Primary CNS Lymphoma and Role of Surgery – A Narrative Review with Illustrative Cases

ABSTRACT

Aim: Primary central nervous system lymphoma (PCNSL) accounts for 6.7% of malignant primary central nervous system (CNS) tumors and is the second most common malignant tumor of the brain after gliomas. The most common type of CNS lymphoma is the primary diffuse large B cell lymphoma of the CNS which occurs in the immunocompetent individual. However, it is also prevalent in immunocompromised patients and recently has been classified as a separate subgroup. The prognosis has shown a substantial improvement in these patients with the advent of high-dose methotrexate (HDMTX) and rituximab-based regimens with or without radiotherapy. Conventionally, surgery in the form of only a biopsy was considered for the definitive diagnosis of PCNSL though craniotomy for surgical excision is being recommended by some recent studies. This article focuses on the role of surgery in PCNSL in immunocompetent patients. **Background:** The role of surgical intervention has been limited to stereotactic biopsy. Older research articles demonstrated a high rate of complications and no additional benefit with craniotomy/surgical excision. However, more recent studies have reported a similar or a lower complication rate with excision and are associated with better overall survival in selected patient subsets. **Conclusion:** HDMTX with rituximab-based regimens with or without radiotherapy remains the cornerstone for the management of PCNSL. The diagnosis is established through stereotactic biopsy in cases with deep-seated, multiple lesions, older age, and poor KPS score. Cytoreductive surgery has shown improved survival in the selected subset of patients with solitary lesions in superficial locations, especially in the younger age group, and good KPS score. However, the strength of the present evidence is low, and future prospective trials may better elucidate the role of surgery in the management of PCNSL.

Key words: Chemotherapy, Diffuse large B-cell lymphoma, Primary CNS lymphoma, Stereotactic biopsy, Surgical excision

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) or the primary diffuse B cell lLymphoma (DLBCL) of the central nervous system (CNS) as per current classification[1,2] accounts for 6.7% of malignant primary CNS tumors.[3] PCNSL is the second most common primary malignant CNS tumor of the brain after gliomas. The incidence rate ratio by sex (M: F) for PCNSL is 1.21. Over the past few decades, the incidence has increased 10-fold. The current age-adjusted incidence rate of PCNSL is 0.45/1 million person-years which is higher as compared to the earlier reports. The incidence is higher in whites as compared to blacks.[3] The new classification includes primary DLBCL of the CNS, immunodeficiency-associated CNS lymphoma, and other rare entities as described later.[1,2]

Over the past five decades, the approach to treating PCNSL has significantly changed. Whole-brain radiation therapy (WBRT) has been replaced with high-dose methotrexate-based (HDMTX) chemotherapy regimens. The prognosis for patients who do not receive treatment is poor with a survival time of only 3–4 months. Treatment with WBRT improved survival to about 12 months but the benefit has to be weighed against the higher risk of neurotoxicity in the elderly population subgroup.[4] The survival time has substantially improved, to 32–37 months, with HDMTX-based chemotherapy, and even more so with the addition of rituximab.[5]

The diagnosis of PCNSL is usually established through stereotactic biopsy. The role of surgical resection or craniotomy is not fully evaluated in the management of PCNSL. Given the rarity of PCNSL, there is a need for further research to improve our understanding of the disease, its pathogenesis, and optimal treatment approaches. In this narrative review, we focus on the role of surgery in PCNSL. In the following article, we refer to PCNSL as the primary DLBCL of lymphoma in immunocompetent patients.

Amol Mittal, Chandrashekhar Deopujari, Chandan Mohanty, Vikram Karmarkar

Department of Neurosurgery, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra, India

Corresponding Author:
Dr. Chandrashekhar Deopujari, Department of Neurosurgery, Bombay Hospital Institute of Medical Sciences, Mumbai - 400 020, Maharashtra, India. E-mail: d.chandrashekhar11@gmail.com

Evolution of pathological classification

The PCNSL has been described with various nomenclatures such as perithelial sarcoma in 1929,[6] primary reticulum cell sarcoma in 1938,[7] microglioma in 1948,[8] primary mesenchymal tumor of the brain in 1950,[9] diffuse histiocytic lymphoma in 1966,[10] and Non-Hodgkin lymphoma in 1982 respectively.[11] However, it was recognized as a separate entity in the 2008 WHO classification of CNS tumors.[12] The latest classification includes primary DLBCL of the CNS (80–85%) and immunodeficiency-associated CNS lymphoma (8–10%) which are the two most common subtypes present. Other include MALT lymphoma of the Dura, secondary lymphoma of the CNS, lymphomatoid granulomatosis, other low-grade B-cell lymphomas of the CNS, anaplastic large cell lymphoma ALK+/ALK-, intravascular large B-cell lymphoma of the CNS, T-cell and natural killer/T-cell Lymphoma, and lymphomatosis cerebri.[1,2]

Epidemiology and pathophysiology of PCNSL

The primary DLBCL of CNS, retina, and testes are primary DLBCL of the immune-privileged sites.[1,2] The pathogenesis of PCNSL involves recurrent alterations that affect the B-cell receptor signaling axis, the Toll-like receptor signaling pathway, and nuclear factor kappa B activity. MYD88 and CD79B mutations are frequently observed in PCNSL, and the disease more closely resembles lymphomas found in immune-privileged organs.[13] In addition, these mutations may be detected in plasma and the CSF, which helps in the initial diagnosis and assessment of the treatment response.[1]

The primary DLBCL of CNS accounts for 80–85% of the PCNSL. It is the most common subtype. It is Epstein-Barr virus (EBV) negative and is present in immunocompetent individuals.[1] It is the most common subtype reported in the Indian literature.[14-16] The majority of patients were immunocompetent and only one patient was found to be Human Immunodeficiency Virus (HIV) positive.[15] The incidence of immunopositivity reported was similar among other studies reported from Indian literature as compared to the West.[14,16,17] This may be attributed to universal access to anti-retroviral drugs.[18]

The DLBCL in immunocompromised patients has been recognized as a separate subgroup known as immunodeficiency-associated lymphoma. It accounts for 8–10% of the cases. The essential criteria include DLBCL and EBV positivity. In contrast to primary DLBCL of the CNS, the immunodeficiency-associated lymphoma is usually deep and multiple. They are necrotic with areas of hemorrhage and show ring enhancement. Other rare types of CNS lymphoma include lymphomatoid granulomatosis and MALT lymphoma of the Dura. The former occurs in immunocompetent individuals[2] and is usually preceded by chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). The CLIPPERS is considered to be a sentinel lesion.[19]

PCNSL is distinct from secondary lymphoma of the CNS as there is no evidence of any extraneural disease at the time of presentation whereas in the latter, it usually arises from metastasis of a systemic disease.[1,2] The median age at diagnosis of PCNSL is 67 years.[3] However, the median age reported in India is 50 years which is a decade earlier as compared to the West.[15,16] The risk factors for PCNSL include HIV, iatrogenic immunosuppression, CNS vasculitis, neurosarcoidosis, rheumatoid arthritis, and systemic lupus erythematosus.[20]

The PCNSL usually presents as solitary or multiple lesions with a predilection for the corpus callosum, periventricular region, and basal ganglia. It is usually supratentorial in more than 80% of the cases and is exceptionally rare in the spinal cord and posterior fossa.[1] Cerebellar involvement is seen in 9% of the cases.[21] The frontal lobe is most commonly affected.[16,22] In the majority of studies from the Indian subcontinent, PCNSL presented as multiple lesions – 60%, 77%, and 81.8%, respectively.[14-16] Furthermore, the location of these lesions was found to be primarily periventricular, in the basal ganglia, corpus callosum, or periventricular white matter, with callosal lesions present in 23% of patients.[14]

Clinical features of PCNSL

The presentation of PCNSL may be a focal neurological deficit, neuropsychiatric symptoms, seizures, or with raised increased intracranial pressure.[15,22] The median time from symptoms onset to the diagnosis was 60 days and the patients had a better OS who received early treatment.[15] In another retrospective study from AIIMS, the median duration from symptoms to diagnosis was 3.5 months.[16] The diagnosis of PCNSL is established through a stereotactic brain biopsy. In cases where brain biopsy is not feasible, the diagnosis can be established by analyzing the cerebrospinal fluid or vitreous aspirate in patients with eye involvement.[23] Approximately 15–20% of PCNSL patients have concurrent leptomeningeal involvement, and 5–20% have ocular involvement. The involvement of the eyes carries a poor prognosis.[24]

Imaging in PCNSL

Magnetic resonance imaging (MRI) is the investigation modality of choice for PCNSL. The sequences include T1-weighted (T1w), T2w-weighted (T2w), diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), T1w contrast, ^{1}H-MR spectroscopy, and dynamic susceptibility contrast-perfusion-weighted imaging (DSC-PWI) in the recent consensus. Lymphomas show hyper-attenuation on the CT scan. They are hypointense on T2w images with marked diffusion restriction on DWI. On ^{1}H-MR spectroscopy, they have increased choline peak with reduced NAA levels. On PWI, PCNSL shows a unique time-intensity curve morphology which rises above the baseline. In addition, the CBV is low to intermediate with a higher proportion of signal recovery. In addition, lymphoma shows homogenous uptake

on fluoro deoxy-glucose positron emission tTomography which helps in differentiating lymphomas from glioblastoma and metastasis.[25]

Treatment

The treatment involves a remission-induction phase, followed by a remission-consolidation phase. Corticosteroids should be avoided as they disrupt cellular morphology. For the induction phase, intravenous HD-MTX, ranging from 1 to 8 g/m^2 is preferred. For effective results and sufficient CSF concentrations, it is recommended to administer HD-MTX at doses of 3 g/m^2 or higher as an initial bolus, followed by a 3-h infusion every 10–21 days. HDMTX monotherapy is associated with an increased risk of neurotoxicity and hematological toxicity.[26]

The addition of rituximab to HDMTX and cytarabine improved the overall response rate, OS, and Progression-free survival (PFS). This has been validated in a randomized Phase 2 trial, the International Extranodal Lymphoma Study Group – 32 (IELSG32) study (MATRix regimen).[27] A retrospective study from AIIMS Hospital, New Delhi, showed that the addition of rituximab to methotrexate, vincristine, and procarbazine (MVP) in 27 patients led to a higher objective response rate, complete remission, 2-year Event-free survival, and 2-year OS, though the differences were not statistically significant for all outcomes.[16] In another retrospective study conducted at Tata Memorial Hospital, Mumbai, HD-MTX with rituximab was given to 72.8% of patients. The response rate was 94.2%, and the median PFS and overall survival (OS) were 21 and 37 months, respectively. On multivariate analysis, the patients who aged <60 years, received more than five cycles of HD MTX with rituximab predicted better OS.[15]

For the consolidative phase, the options include WBRT, chemotherapy, or high-dose therapy, followed by autologous stem cell transplantation. In the Phase 3 randomized multicenter trial between patients receiving HDMTX alone and those receiving HDMTX and WBRT, the latter group had a longer PFS period, but the difference in the OS between the two groups was not significant.[28]

The prognosis and survival rate of PCNSL as compared with systemic DLBCL is poor. The 5-year and 10-year relative survival rate of PCNSL is 37% and 28.9%, respectively. In addition, the 5- and 10-year survival rate is better in younger age groups.[3] The survival rate is also less in HIV related PCNSL with a median survival of 2 months in contrast to non-HIV-related PCNSL of 1 year.[29]

A study from Bombay Hospital, Mumbai, showed that the response rate in immunocompetent patients treated with MVP plus cytarabine, with or without WBRT, was 72.7%, which was consistent with other reports.[14] In another collaborative, multicenter phase two trial, 44 patients with PCNSL were treated with induction chemotherapy composed of HDMTX, rituximab, and temozolomide. The consolidative therapy included intravenous etoposide and cytarabine. Two-thirds (66%) of these patients achieved complete remission, and the entire group had a median PFS of 2.4 years. These outcomes were comparable to those obtained from regimens that involve consolidative WBRT.[30]

The risk of delayed neurotoxicity is higher with the usage of WBRT. The risk is additive with the use of HDMTX and even more pronounced in the elderly subgroup. Chemotherapy is the preferred treatment option for this subgroup. A meta-analysis of 783 PCNSL patients aged 60 or older revealed that survival rates improved when HDMTX regimens were used. WBRT was associated with better survival rates, but the risk of neurotoxicity was high in the elderly subgroup.[4]

Surgical considerations in PCNSL

The role of surgical resection on OS is well documented in cases of glioma and metastasis. However, in cases of PCNSL, HDMTX-based regimens with rituximab with or without WBRT are the cornerstone for treatment and achieving remission.[28] Several studies have evaluated the role of surgical resection and biopsy in the management of PCNSL. Earlier studies documented that surgical resection was unfavorable or not desirable owing to a higher number of complications, unfavorable prognosis, or lower median OS. Helle *et al*. in 1984 investigated 22 patients of PCNSL and found that there was no benefit of resection over biopsy on two separate analyses when chemotherapy and radiotherapy were controlled.[31] DeAngelis *et al*. in 1990 noted a 40% complication rate of cytoreductive surgery as compared to biopsy which subsequently favored the role of diagnostic biopsy given high complications in the former.[32] A similar study by Caroli *et al*. reported a complication rate of 14.3% in the craniotomy cohort.[33] However, with the advancement in MR neuroimaging and microneurosurgical techniques, fewer complications have been reported in the more recent articles.[34,35]

The previously, a decrease in OS in the resection cohort was observed as compared to the biopsy.[22] Another study in 2000 concluded that partial surgical resection was associated with unfavorable prognosis.[36] Jahr *et al*. noted no significant difference in the OS and the PFS in the resection group as compared to the biopsy cohort. However, nearly 30% of the patients were aged more than 70 years. In those patients, more than 50% had multiple lesions and KPS <70.[37] A more recent single-center cohort study comparing resection and biopsy for a single lesion PCNSL demonstrated no significant difference in the OS and PFS. However, the preference for surgical resection was based on preoperative neuroimaging where the imaging was not in concordance with the typical features of the PCNSL. In cases where PCNSL was established with imaging, the diagnosis was established with stereotactic biopsy. In addition, the retrospective nature of this study limited its usefulness.[38] The recent studies by Rae *et al*., Weller *et al*., and Wu *et al*.[39-41] demonstrated improved survival in the resection group as compared to the biopsy cohort which was

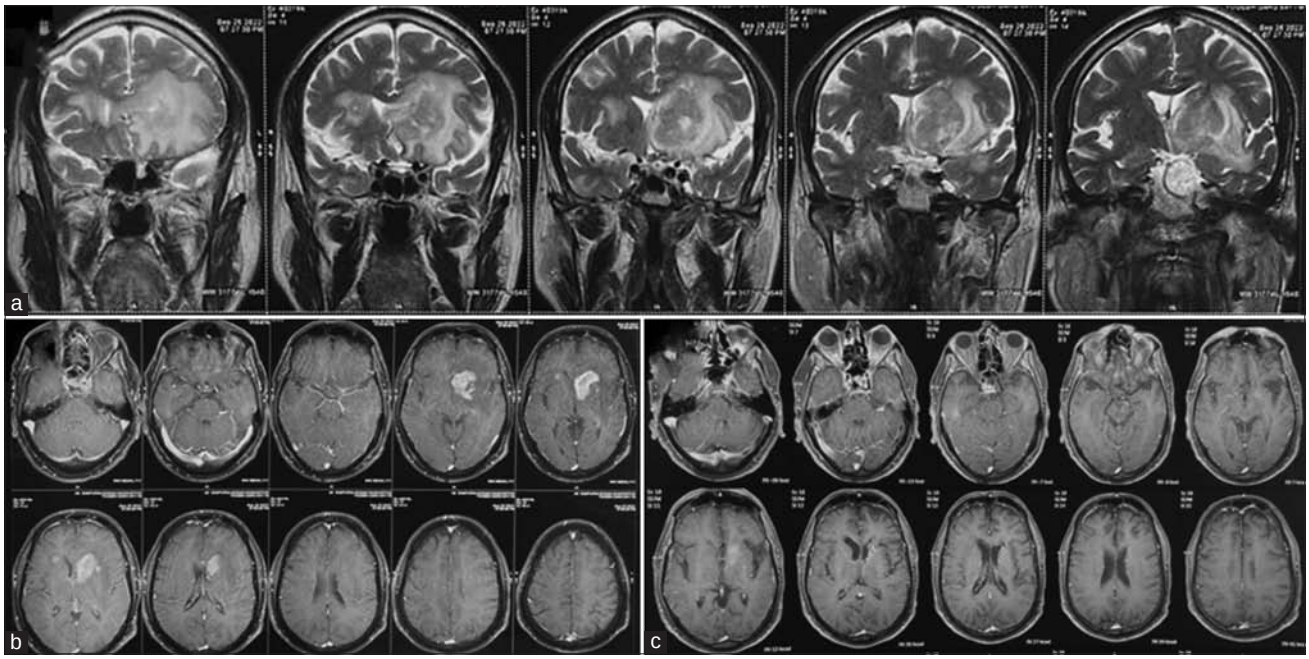

Figure 1: Left frontal periventricular primary central nervous system lymphoma. (a) T2w coronal image showing left frontal periventricular iso to hypointense lesion predominantly involving the left caudate nucleus with perilesional edema. (b) Post-contrast T1w image showing heterogeneous contrast-enhancement. (c) Post-contrast T1w image at 4-months follow-up showing significant resolution of the lesion after receiving five cycles of high dose methotrexate-based chemotherapy regimens

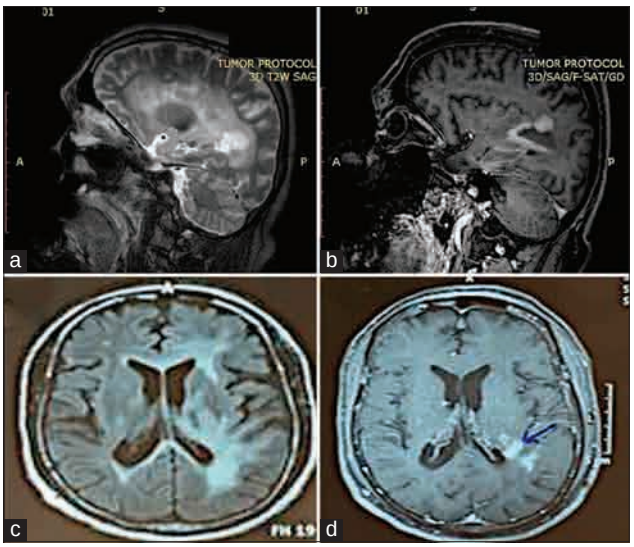

Figure 2: Left parietal periventricular primary central nervous system lymphoma. (a) Sagittal T2w image showing a left periventricular hyperintense lesion in the region of the left atrium. (b and d) Sagittal and axial post-contrast T1w image showing moderate contrast-enhancement. (c) FLAIR sequence showing perilesional edema in the region of left atrium extending up to the region of left thalamus and left frontal horn

likely influenced by the HDMTX-based chemotherapeutic regimens and WBRT. The effect of surgical resection on the OS has also been validated by a systematic review and two recent meta-analyses.[42-44]

The location of the tumor also decides the management of the lesion. The odds of taking a biopsy were higher in the presence of deep and multiple lesions. In addition, the data from the National Cancer Database (n = 8936) suggests that biopsy was preferable in case of deep location.[39] The patients undergoing the biopsy are older, with poor KPS, and with multiple and deep lesions.[41] The patients undergoing surgical resection had superficial locations and solitary lesions.[44] The studies from the Indian subcontinent noted that the majority of the PCNSL lesions were multiple and located mostly in the periventricular region.[14-16] The median age at presentation was 50 years. In those cases, a biopsy is preferable. In addition, surgical debulking or surgical resection was done in 28 and 45% of the cases. However, surgical debulking was not advisable in either one of them due to the infiltrative behavior of the lesion. The main role was to establish prompt diagnosis through stereotactic biopsy.[15,16] Furthermore, in cases of involvement of the pituitary stalk, hypothalamus, fourth ventricular, and cerebellar deep lesion a biopsy seems to be adequate due to the risk of surgical morbidity or procedure-related complications.[45]

Another important factor for surgical considerations is patient selection. A good KPS score, young age, solitary, and superficial lesion tended to favor cytoreductive surgery over biopsy. A low IELSG score predicts a better prognosis. Age and HDMTX with or without radiotherapy are the predictive factors for better

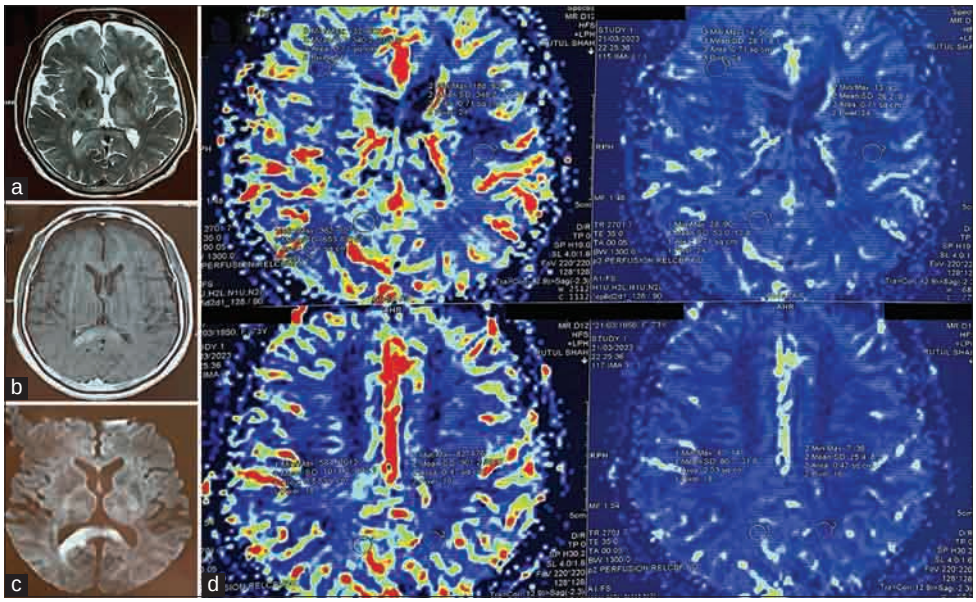

Figure 3: Primary central nervous system lymphoma involving the splenium of the corpus callosum. (a) T2w images showing a hypointense lesion involving the splenium of the corpus callosum. (b) Post-contrast T1w images showing minimal post-contrast-enhancement. (c) Diffusion-weighted imaging sequence showing high diffusion restriction. (d) dynamic susceptibility contrast-perfusion-weighted imaging showing low-to-intermediate CBV in the region of the splenium of the corpus callosum

OS and PFS.[38] Age is an independent factor for OS and the PFS as emphasized by IELSG and MSKCC.[46,47] The location and multiple lesions have also been shown to be a predictor for the OS in some studies.[37,40] The usage of KPS, Eastern co-operative oncology group (ECOG), IELSG, and MSKCC scores helps in the selection of surgical candidates and in prognostication and predicting complications. Their usage has been highlighted in the systematic review by Labak *et al*. comparing surgical resection with biopsy in PCNSL.[43] The patients presenting with increased intracranial pressure, progressive neurological deterioration, and large space-occupying lesions are candidates for surgical resection. Among patients who received radiation, chemotherapy, or a combination of both, surgical removal showed a positive effect on survival. However, the infiltrative behavior and frequently multicentric appearance of PCNSL limited the role of surgery in its treatment.[48]

The foremost study which reflected a paradigm shift in the surgical management of PCNSL was reported in 2012 by Weller *et al*. in a post hoc analysis of the German PCNSL randomized trial. The analysis revealed that the GTR group had the presence of solitary lesions and better KPS at presentation. The resection group had a longer OS as compared to the biopsy cohort. It should be noted that this study was retrospective and the subset analysis may have been affected by selection bias. The improvement in the OS was lost when controlled for the number of lesions.[40] A study done by Jelicic *et al*. in 2016 showed improved median OS in patients with PCNSL receiving GTR as compared to the STR and the biopsy cohort. The GTR was performed in patients presenting with solitary lesions and in more than 50% of cases the ECOG score was >3. The ECOG performance status and the IELSG score influenced the OS.[49]

The largest data on survival benefits from surgical resection of PCSNL comes from Rae *et al*. According to the National Cancer Database, craniotomy was linked to a longer median survival time compared to biopsy, even after receiving subsequent radiation and chemotherapy (19.5 months versus 11.0 months). Similarly, the author's institutional series revealed a comparable trend in survival for craniotomy versus biopsy (HR 0.68, $P = 0.15$). In the Surveillance, Epidemiology, and End Results Program, gross total resection was linked to a longer median survival time compared to biopsy (29 months vs. 10 months, HR 0.68, $P < 0.001$). The author also noticed that the survival benefit of GTR was independent of chemotherapy, baseline characteristics, and radiotherapy.[39] Schellekes *et al*. examined a cohort of 113 patients and provided evidence in favor of surgical resection for a subset of PCNSL patients with solitary brain lesions and age <70 years. The impact of patient selection on OS was statistically significant.[50] Another retrospective single-center study showed better OS and PFS in the surgical resection cohort as compared to the biopsy. The presence of a solitary lesion and the resection were favorable prognostic factors for PCNSL.[41] It is now evident from the above studies that cytoreductive surgery plays an important role in the management of PCNSL in selected subsets of patients. Hence, patient selection is of paramount importance.

In the first systematic review by Labak *et al*. in 2019 comparing surgical resection with biopsy for PCNSL, 9/24 studies showed evidence in favor of cytoreductive surgery. The post-operative complications were few in comparison to the older studies and

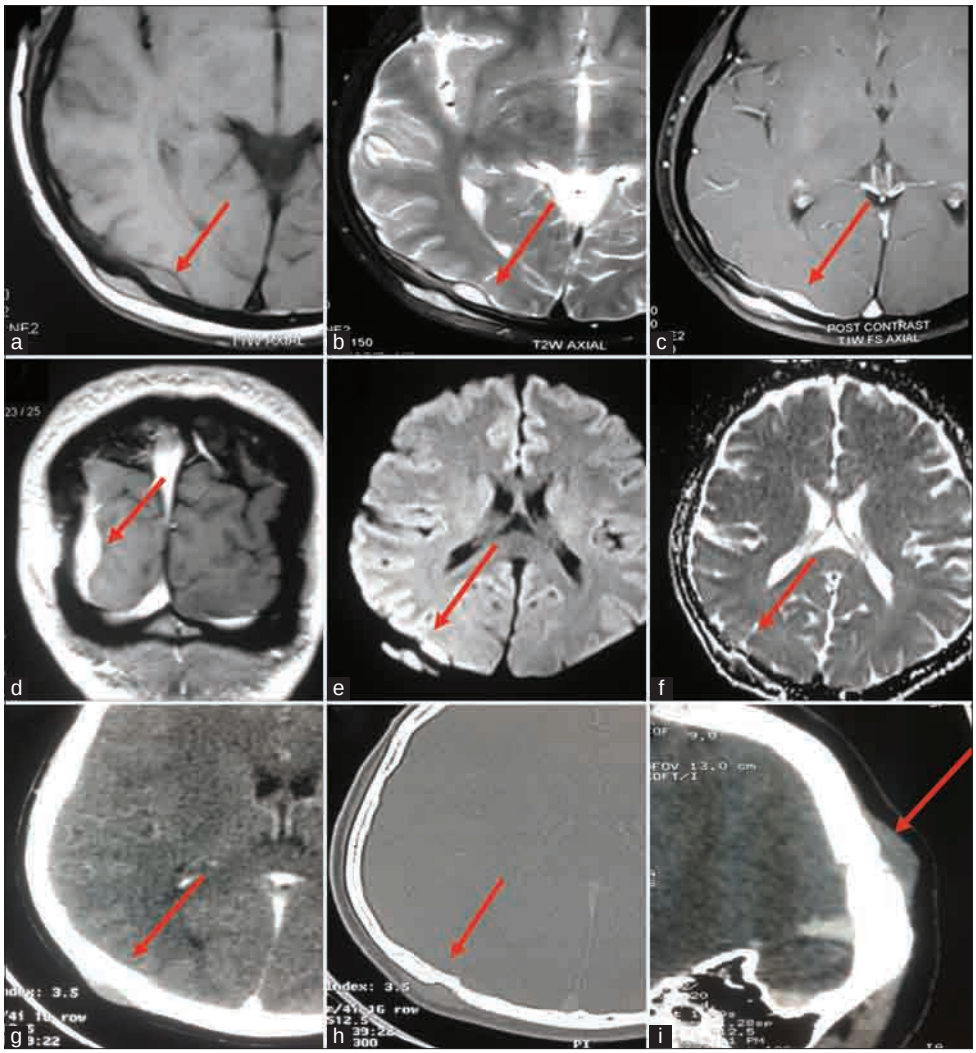

Figure 4: MALT dural lymphoma. (a) T1w-weighed imaging showing an extra-axial isointense lesion on both sides of diploic bone. (b) T2w images showing a hyperintense lesion with CSF cleft. (c and d) Post-contrast T1w images showing homogenous contrast enhancement with wide dural base. (e and f) Diffusion-weighted Imaging and ADC images showing diffusion restriction with corresponding black signal on the ADC. (g-i) CT brain plain showing bone calvaria with minimal sclerosis

the recent evidence suggests similar complication rates in the biopsy and the resection group.[43] The surgical resection was associated with a better OS in a meta-analysis of seven studies when compared to biopsy. For PFS, a meta-analysis of four studies showed a better PFS in the respective group. Overall, the results obtained pointed toward surgical resection due to a lower risk of death and disease progression along with a similar complication rate in the resection and biopsy patients.[42]

CASE ILLUSTRATIONS

Case 1

A 64-year-old male presented with complaints of behavioral problems, increased sleep, and memory impairment in the past 2 months. Contrast-enhanced MRI brain shows a left frontal periventricular T2 hypo to isointense lesion with heterogeneous contrast-enhancement predominantly involving the left caudate nucleus. The patient underwent a navigation-guided burr hole biopsy of the lesion. At 4-month follow-up after completing five cycles of HDMTX-based regimens, a contrast-enhanced MRI scan shows significant resolution of the lesion [Figure 1].

Case 2

A 54-year-old male presented with complaints of increasing lethargy, right hemiparesis, slowness of activity, gait imbalance, slurring of speech, memory impairment, and urinary incontinence which developed for 6 months. Contrast-enhanced MRI brain showed a left parietal periventricular ill-defined lesion near the

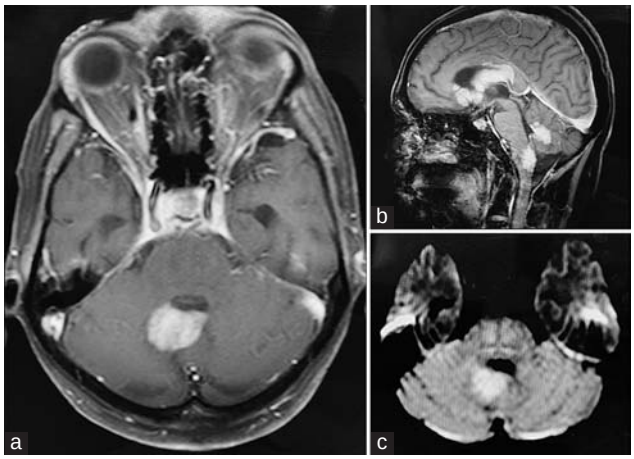

Figure 5: Multifocal supra and infratentorial primary central nervous system lymphoma. (a) Post-contrast T1w axial image showing a periventricular lesion with homogenous contrast enhancement. (b) Post-contrast T1w sagittal image showing a homogenous enhancing lesion in corpus callosum, cerebellum, and lower medulla posteriorly. (c) Diffusion-weighted Imaging image showing a periventricular lesion with diffusion restriction

atrium of the left lateral ventricle. The lesion is hyperintense on T2w images with perilesional edema on the FLAIR sequence and moderate contrast-enhancement. The patient underwent a navigation-guided burr hole biopsy of the lesion [Figure 2].

Case 3

A 72-year-old female presented with complaints of memory impairment, gait imbalance, and headache for the past month. Contrast-enhanced MRI brain shows a lesion involving splenium of the corpus callosum which is hypointense on T2w images, minimal contrast enhancing, showing diffusion restriction on DWI sequence, and low-to-intermediate CBV on DSC-PWI sequence. The patient underwent a navigation-guided burr hole biopsy of the lesion [Figure 3].

Case 4

A 42-year-old male presented with complaints of swelling over the scalp in the right parieto-occipital region since past 1 year. The swelling was firm and non-tender. On CT brain plain, a sub-galeal swelling was seen with underlying bony changes. Contrast-enhanced MRI brain showed a T1w isointense, T2w hyperintense, homogeneous contrast-enhancement with involvement of the leptomeninges, diffusion restriction on DWI with corresponding dark signal on ADC. The patient underwent primary excision of the lesion. Histopathology revealed MALT dural lymphoma. The patient was later offered methotrexate-based chemotherapeutic regimen [Figure 4].

Case 5

A 47-year-old male patient presented with complaints of headache and gait imbalance for 2 years which was gradual in onset. MRI brain revealed a multifocal lesion involving the lower brainstem, cerebellum, lateral ventricle, and corpus callosum. The patient underwent navigation-guided burr hole biopsy of the cerebellar lesion. Histopathology confirmed it to be DLBCL. The patient was started on methotrexate-based regimens. However, the patient was not able to tolerate the adverse effects of the chemotherapy regimen and died subsequently [Figure 5].

CONCLUSIONS

The primary DLBCL of the CNS is the most common type of CNS lymphoma. The current treatment standard is stereotactic biopsy along with adjuvant HDMTX-based regimens with rituximab with or without radiotherapy. The treatment includes an induction and a consolidation phase. The recent evidence has highlighted that surgical resection results in improved OS and PFS in patients with solitary lesion in superficial location, especially in younger age and with good KPS score Young age, good KPS, and low IELSG score, superficial tumor location predicts better OS. Stereotactic biopsy is preferred in old age, poor KPS, deep-seated, and multiple lesions. In addition, the complications of craniotomy have decreased and its occurrence is similar in both cohorts. However, the strength of the evidence is low as most of the data is based on retrospective studies. Hence, future prospective trials are needed to fully evaluate the role of surgical resection in the management of PCNSL.

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