Diagnostic Pathology

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A case report of surgery-radiotherapy-chemotherapy cured primary diffuse large B-cell lymphoma of the central nervous system associated with HIV infection

Qiaoqiao Zhang[1,2,3], Jingzhen Lai[2], Sufang Ai[1], Shulin Song[4], Junjun Jiang[2*] and Zhiman Xie[1*]

Abstract

Background Diffuse large B-cell lymphoma (DLBCL) is one of the most common complications in patients with Acquired Immune Deficiency Syndrome (AIDS), yet its prognosis is generally poor. The impact of surgery on DLBCL remains controversial. We present a case of DLBCL associated with HIV infection, in which the patient achieved complete remission following surgical removal, radiotherapy, and sequential dose-adjusted EPOCH (DA-EPOCH) chemotherapy.

Case summary A thirty-year-old man presented with dizziness and headache on September 24, 2019. He had a history of AIDS and pulmonary tuberculosis. He was initially diagnosed with left cerebellar astrocytoma and chronic pneumonia at a local hospital. At our hospital, following magnetic resonance imaging (MRI) and surgical intervention, pathology and immunohistochemistry results indicated DLBCL in the left cerebellar hemisphere. He subsequently underwent resection of the tumor in the left cerebellar hemisphere, received radiotherapy for half a month, and completed sequential DA-EPOCH chemotherapy for seven cycles. His symptoms improved, and the prognosis was favorable, with no signs of recurrence after 4 years of follow-up.

Conclusion Surgery is applicable to isolated and superficial lesions. However, it should be combined with radiotherapy and chemotherapy to achieve better treatment.

Keywords DLBCL, PCNSL, HIV, Surgery, DA-EPOCH

*Correspondence:
Junjun Jiang
jiangjunjun@gxmu.edu.cn
Zhiman Xie
20060830xzm@163.com
[1]Department of Infectious Diseases, The Fourth People's Hospital of Nanning, Nanning, China
[2]Guangxi Key Laboratory of AIDS Prevention and Treatment & Guangxi Universities Key Laboratory of Prevention and Control of Highly Prevalent Disease, School of Public Health, Guangxi Medical University, Nanning, China
[3]School of Public Health, Guangxi Medical University, Nanning, China
[4]Department of Radiology, The Fourth People's Hospital of Nanning, Nanning, China

Background

Primary central nervous system lymphoma (PCNSL) is a relatively rare brain tumor [1]. It commonly affects individuals with congenital or acquired immunodeficiency, such as HIV infection and primary B cell deficiency disease. Immunosuppressed patients with prolonged survival are at greater risk for PCNSL [2]. The AIDS epidemic of the early 1990s led to a high incidence of PCNSL, with 47.2% of central nervous system lymphomas occurring in AIDS patients [3]. PCNSL is commonly found in the white matter, basal ganglia, periventricular regions, or corpus callosum [3], accounting for 1–2% of non-Hodgkin lymphomas [4]. It is estimated that there are 150,000 new cases worldwide every year [5]. Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype representing about 84.6% of the cases [6, 7]. Additionally, approximately 98% of DLBCL cases express the B-cell antigen marker CD20 [8] which is a hallmark of B-cell lymphoma. There are several methods for treating PCNSL, including surgery, radiotherapy, chemotherapy, and other approaches. Unlike other tumors, surgery is not typically the preferred treatment for PCNSL due to its often multifocal nature. Surgery is frequently contraindicated because of involvement of deep structures, or the presence of ocular or leptomeningeal disease [9]. Moreover, many reports suggested that surgery can lead to complications and a poor prognosis [9–11]. However, with advancements in surgical techniques and medical equipment, the role of surgical resection in treating PCNSL has gained renewed attention. Research indicates that complete resection is associated with better overall survival (OS) rates compared with biopsy and partial resection [12]. Additionally, Weller et al. found that the progression-free survival (PFS) and OS of 526 patients with PCNSL undergoing total or partial resection were longer than those of patients who had only a biopsy [13].

Case description

A 30-year-old man with dizziness and headache was admitted to our hospital in late September 2019. He had been previously diagnosed with left cerebellar astrocytoma, chronic pneumonia and chronic gastritis at a local hospital. Due to a lack of improvement in his condition, he was transferred to our facility. The patient had an 8-year history of AIDS and pulmonary tuberculosis, and reported a history of homosexual intercourse. In July 2019, he initiated antiviral therapy (Tenofovir Disoproxil Fumarate, Lamivudine, Efavirenz) as he had only 20 CD4+T cells/ μL. Upon admission, physical examination revealed chronic disease facial features. His physiological reflexes were normal and no pathological reflexes were observed. Routine blood tests showed: 6.4×10^9 leukocytes/ L, hemoglobin (129 g/ L), 157×10^9 platelets/ L, neutrophil ratio (60.8%), lymphocyte ratio (21.1%), C-reactive protein (<5 mg/ L). Cerebrospinal fluid analysis revealed an off-white color, muddy transparency, no clots in appearance, and a positive Pandy's test (3+). The cerebrospinal fluid white blood cell count was 520×10^6/L, with 53% mononuclear cells and 47% coenocytes. Biochemical analysis of the cerebrospinal fluid showed a protein level of 1770 mg/L and lactate dehydrogenase level of 55 U/L. Infection immunology testing indicated positive IgG antibodies for rubella virus, cytomegalovirus, and herpes simplex virus type 1 T-lymphocyte analysis revealed a CD4+T-cell count of 69 cells/μL and a CD4+/CD8+T-cell ratio of 0.1. MRI scans demonstrated a cystic-solid mixed signal mass measuring 3.3 cm × 3.3 cm × 2.7 cm in the left cerebellar hemisphere, suggestive of a space-occupying lesion (Fig. 1).

Due to the inability to establish a diagnosis from the external hospital materials, a craniotomy was planned to obtain tissue for pathological biopsy. After determining that surgical intervention was indicated, lesion resection via craniotomy was performed. The surgery proceeded smoothly, and postoperative pathology confirmed DLBCL (Fig. 2). MRI scans confirmed that the tumor was successfully removed (Fig. 3A- D). Postoperatively, the patient developed intracranial edema, minor bleeding, and an increase in the polysaccharide content of Cryptococcus neoformans capsulatus in the cerebrospinal fluid. Consequently, cryptococcal meningitis was diagnosed, and antifungal treatment was initiated. On November 11, 2019, he began a course of radiotherapy, receiving a total dose of 3000 Gy over 10 sessions at another hospital. Chemotherapy commenced on January 7, 2020. T-lymphocyte examination revealed a CD4+T-cell count of 144 cells/μL and a CD4+/CD8+T-cell ratio of 0.16. The patient declined intrathecal injection and opted for sequential dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (DA-EPOCH) chemotherapy. The first cycle of chemotherapy lasted 5 days. His general condition remained good, and he did not experience any discomfort. He subsequently received six additional cycles of chemotherapy. Recombinant human granulocyte colony-stimulating factor was administered to increase leukocyte levels due to episodes of leukopenia during the second, fifth, sixth, and seventh cycles of chemotherapy. Overall, the chemotherapy process was smooth.

Three months, half a year and a year after the seventh cycle of chemotherapy was done, the tumor markers (carcinoembryonic antigen and carbohydrate antigen) were checked up. The results showed that the tumor markers kept normal. Two years (Fig. 3E- H) and four years (Fig. 3I- L) after sugery, his MRI scans showed there wasn't evidence of recurrence. His general condition was good and he didn't feel uncomfortable.

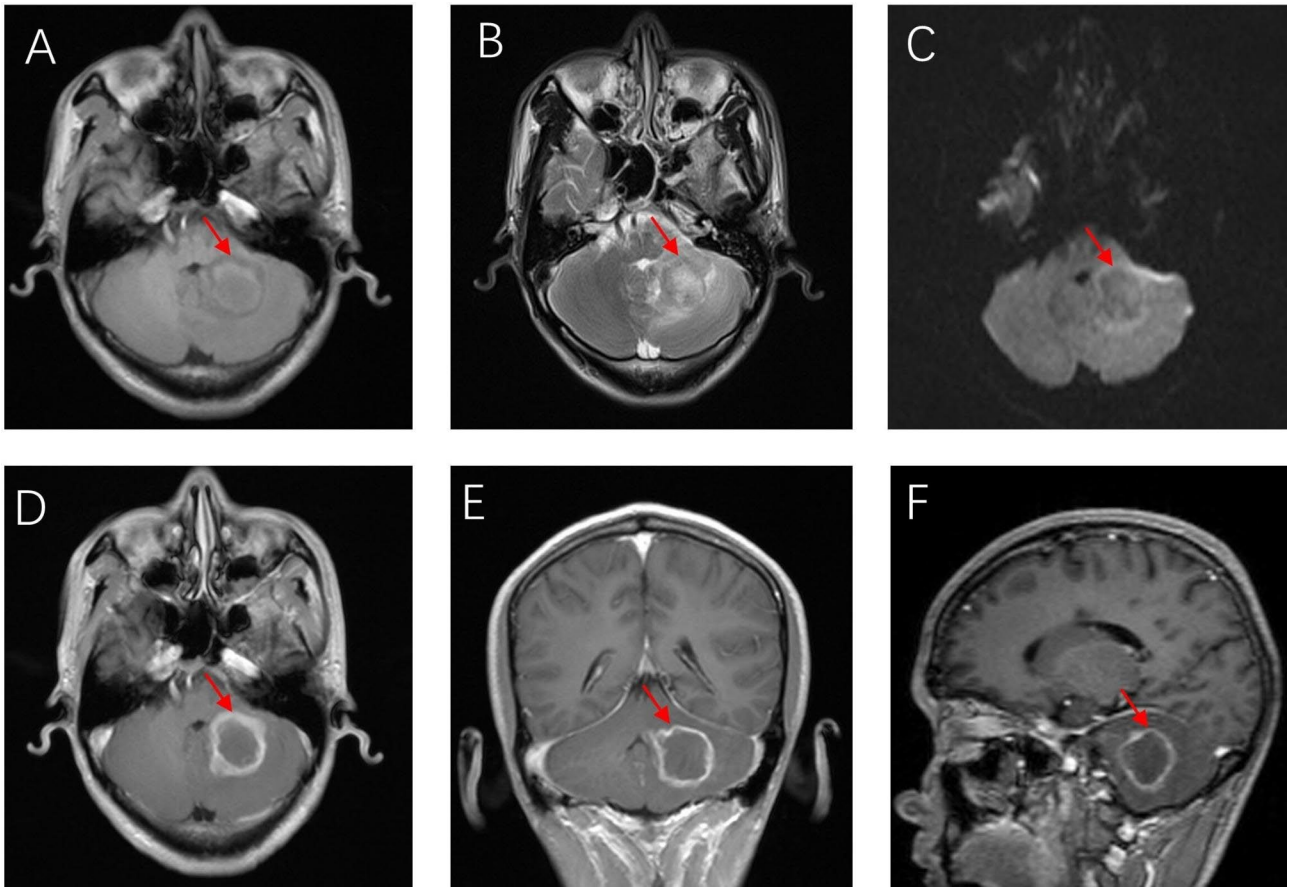

Fig. 1 The MRI before surgery. A space-occupying lesion on the left cerebellar hemisphere with associated compression and narrowing of the fourth ventricle. (**A**)Axial T1-weighted image (T1WI) : Displaying iso- to slightly hypointense signal. (**B**) Axial T2-weighted image (T2WI) : Presenting heterogeneous hyperintensity. (**C**) Diffusion weighted imaging (DWI) (b = 1000) : The lesion exhibited a slightly hyperintense ring pattern, with a hyperintense margin and iso- to slightly hypointense center. (**D**) Contrast- enhanced axial T1WI, (**E**) Contrast- enhanced sagittal T1WI, (**F**) Contrast- enhanced coronal T1WI: The lesion showed ring enhancement

Discussion

DLBCL is a common form of non-Hodgkin lymphoma, characterized by a high mortality rate and poor prognosis. Although the prognosis for DLBCL has improved over the years in the general population, it remains relatively poor in HIV-positive individuals [19, 20]. The reported survival time for patients with AIDS-related DLBCL is typically short [21–23]. Compared to germinal center B-cell-like (GCB) lymphoma, non-GCB lymphoma is associated with a worse prognosis and shorter survival time [24]. Despite the patient's diagnosis of non-GCB lymphoma, which generally carries a poor prognosis, he responded surprisingly well to surgery, radiotherapy, and chemotherapy. Follow-up data indicate that he has remained in good condition for the past four years with no evidence of tumor recurrence, which is a key point of this report.

PCNSL grows diffusely and infiltratively, making thorough excision difficult. Due to the potential damage to normal brain tissue, surgical treatment is rarely adopted by patients. Many studies have reported that surgery is typically limited to stereotactic biopsy, which generally has little therapeutic effect and offers minimal survival benefit for PCNSL patients [9–11]. However, some researchers argue that surgical resection still holds value. A retrospective analysis of more than 9,000 patients suggests that, compared with stereotactic biopsy, surgery is associated with a lower risk, better prognosis, and survival benefit independent of radiotherapy and chemotherapy [13, 25]. Other researchers have also found that surgery can be beneficial for patients undergoing radiotherapy, chemotherapy, or both [26]. Furthermore, surgery and tumor debulking may benefit patients, and surgery is not associated with an increased risk of neurological deficit [13].

PCNSL is sensitive to radiotherapy and chemotherapy, which are fully endorsed in guidelines for the diagnosis and treatment of primary central nervous system diffuse large B-cell lymphoma. These treatments have become the first choice for PCNSL management [27]. In treating

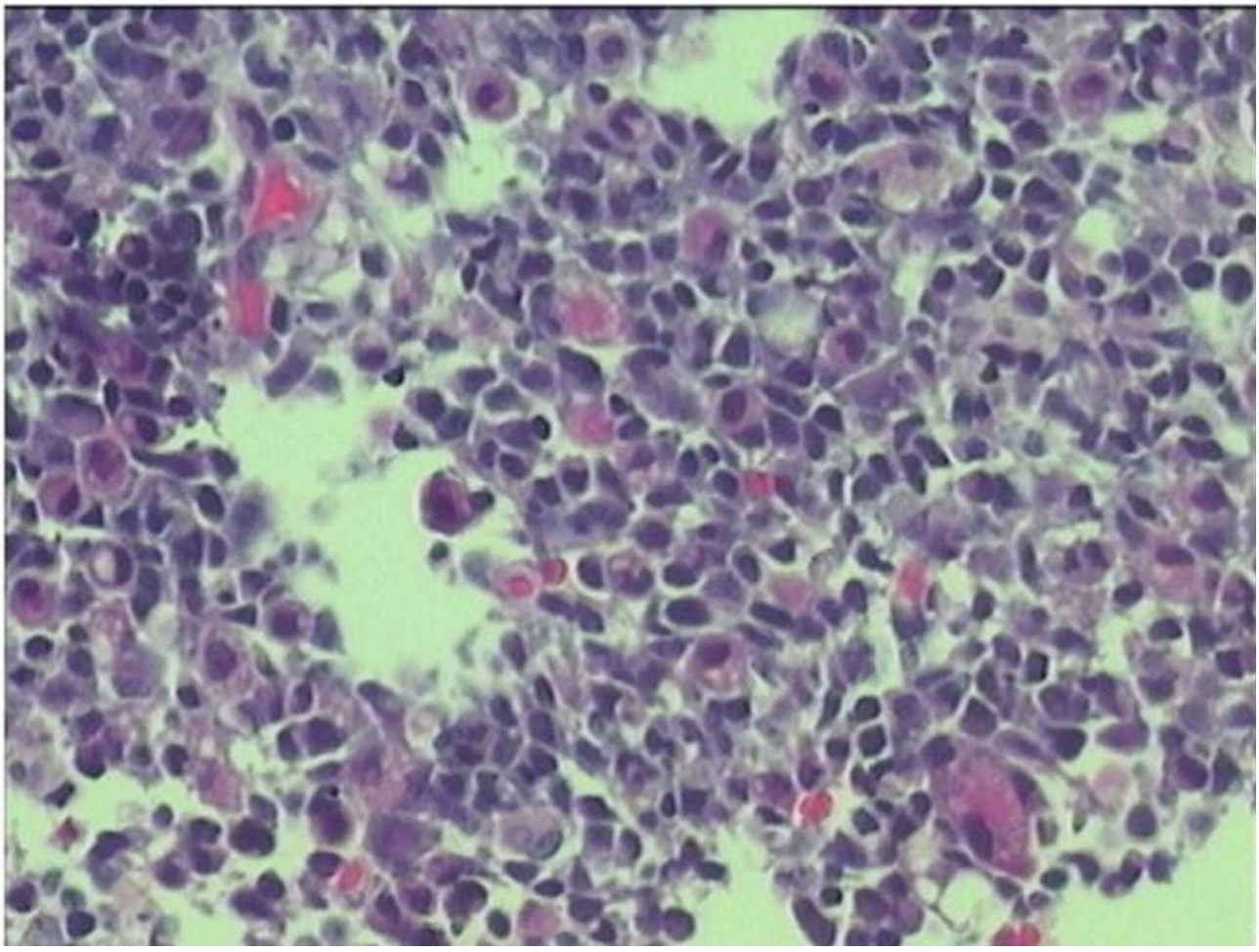

Fig. 2 The patient's histopathologic characterization revealed the following markers: CD20 (+++), CD79A (+++), CD3 (-), CD38 (++), CD138 (-), S-100 (-), GFAP (-), P53 (-), CD10 (-), Bcl-6 (-), MUM-1 (+++), Ki67 (50%), and EBERs (+). These findings supported a diagnosis of non-germinal center B-cell-like lymphoma (non-GCB). The CD20 (+++) and CD79A (+++) markers confirmed B-cell lymphoma, while CD38 (++) suggested plasmacytoma. CD10(-), Bcl-6(-) amd MUM-1(+++) were were indicative of non-GCB, suggesting the cells did not originate from the germinal center and predicting a poor prognosis. The Ki67 (50%) marker indicated a 50% proliferation rate of the lymphoma

PCNSL, unless the patient is intolerant to either treatment, a combination of both is typically used. Relevant studies have shown that in initial treatment, the combined approach of radiotherapy and chemotherapy is superior to intracranial radiotherapy alone, leading to improved patient survival rates [28, 29]. Other research has suggested that combining whole-brain radiotherapy (WBRT) with chemotherapy significantly increases patients' progression-free survival rates compared to chemotherapy alone [30, 31]. However, despite the use of chemotherapy and radiotherapy, most patients relapse or require second-line treatment within one year, with a 5-year OS rate of only approximately 15-20% [32, 33]. Moreover, we collected some similar cases (Table 1) which did not combine surgery with chemoradiotherapy and the prognosis was not as good as our patient. Therefore, while chemoradiotherapy serves as an effective adjuvant therapy, it should be combined with surgery for optimal outcomes.

PCNSL is a highly aggressive lymphoma that can recur within six months if not treated with adequate chemotherapy or radiation therapy, even after a general resection. This is also the reason why the patient also underwent radiotherapy and chemotherapy after receiving focus resection surgery. Surgical intervention can rapidly alleviate neurological symptoms, reduce tumor burden, and extend the window for effective medication, thereby creating a favorable environment for subsequent chemo-radiation therapy to be effective [13]. Thus, multimodal therapy may be advantageous for PCNSL patients. In this case, the tumor was confined to cerebellar tissue, which is relatively superficial and highly accessible for surgery. This accessibility facilitates the removal of the tumor, leading to fewer adverse neurological side effects compared to deeper tumors. It has also been proposed

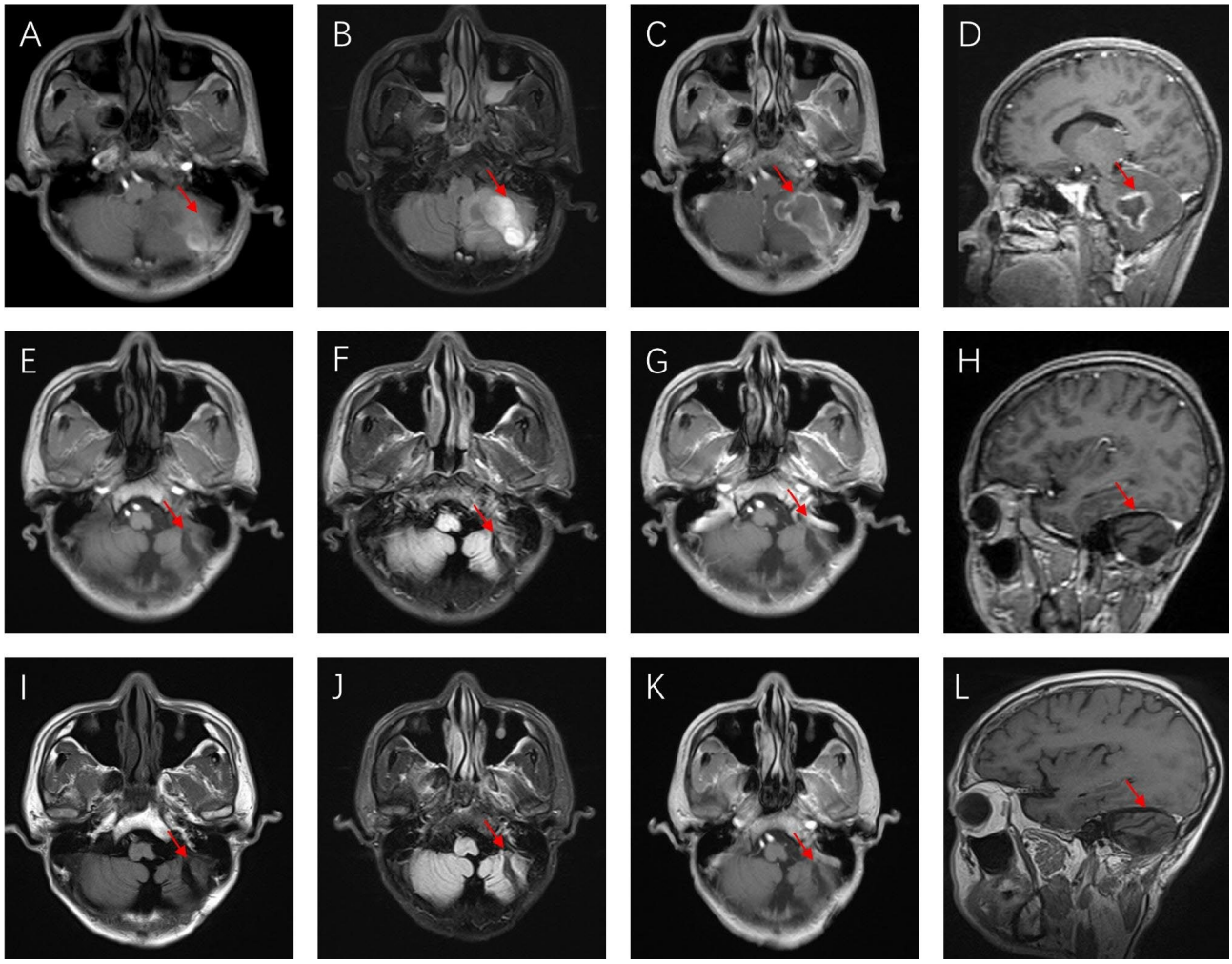

Fig. 3 The MRI after surgery, 2-year follow-up and 4-year follow-up. (**A**- **D**) : The MRI after surgery. (**A**) Axial T1WI: Reactive ring enhancement was observed at the margins of the surgical site, maybe suggestive of granulation tissue formation. The surgical area presented with mixed signal characteristics, where hyperintensity was indicative of cerebral hemorrhage. (**B**) Axial FLAIR (fluid attenuated inversion recovery) : The surgical site exhibited heter`ogeneous hyperintense signal. (**C**) Contrast- enhanced axial T1WI, (**D**) Contrast- enhanced sagittal T1WI: Marginal ring enhancement was noted in the surgical region, with narrowing of the fourth ventricle. (**E**- **F**) : 2-year follow-up MRI. (**E**) Axial T1WI: Softening lesions developed in the surgical area, presenting as hypointense signal. (**F**) Axial FLAIR: Exhibiting hypointense signal. (**G**) Contrast- enhanced axial T1WI, (**H**) Contrast- enhanced sagittal T1WI: Linear enhancement along the margins was observed, maybe suggestive of gliosis. (**I**- **L**): 4-year follow-up MRI. (**I**) Axial T1WI: Softening lesions developed in the surgical area, presenting as hypointense signal. (**J**) Axial FLAIR: Exhibiting hypointense signal. (**K**) Contrast- enhanced axial T1WI, (**L**) Contrast- enhanced sagittal T1WI: No enhancement was observed within the surgical site

that microsurgical resection of a single large tumor can improve survival rates [26]. In this case, the patient's tumor presented as a large, isolated space-occupying lesion, which was easier to remove and was excised more thoroughly compared to tumors in patients with multiple lesions, potentially leading to a better prognosis. After surgical resection, the patient underwent more than two weeks of radiotherapy, which not only consolidated the therapeutic effects of the surgery but also continuously disrupted the "shelter" effect of the blood-brain barrier. This disruption facilitated the penetration of subsequent chemotherapy drugs into the central nervous system, enhancing their efficacy. Relevant studies have shown that WBRT has lower neurotoxicity in young patients [34], which may explain the absence of significant neurotoxic symptoms in this patient following radiotherapy, contributing to a favorable prognosis. DeAngelis L. M. and other researchers have proposed that PCNSL is associated with significant damage to the blood-brain barrier, though this damage may be confined to large tumor areas [28], thereby providing a pathway for subsequent drugs to reach the affected site. The sequential DA-EPOCH therapy administered to this patient was initially proposed by Wilson W. H. et al. This is a dynamic assessment treatment plan that adjusts drug concentration and dosage according to the patient's response and tolerance, while

Table 1 Primary diffuse large B-cell lymphoma of the central nervous system with HIV infection cases reported in the last 10 years

Author	Year	Age/Sex	Location	Extent of resection	Adjuvant chemoradiation	Outcome
Zhou Y, Wang X, Lin X, et al. [14]	2023	41-year-old man	corpus callosum	none	chemotherapy	complete response (CR) for 22 months
Zhou Y, Wang X, Lin X, et al. [14]	2023	39-year-old man	right cerebellar hemisphere	none	chemotherapy	CR for up to 20 months
Acharya I, DeBoer S R, Bhansali D. [15]	2023	51-year-old woman	right parietal lobe	gross total resection (GTR)	chemotherapy	stable disease (SD)
Gijs P, Clerc O. [16]	2021	65-year-old man	right frontal lobe and left parietal lobe	none	radiotherapy	CR for 3 years
Findakly D. [17]	2021	39-year-old woman	Lateral occipital	none	chemotherapy	partial remission (PR)
Zafar S, Javed M, Rockwood N, et al. [18]	2017	31-year-old man	brainstem, cerebellum, basal ganglia and both cerebral hemispheres	none	chemotherapy	PR

maintaining the fundamental principle of maximizing the efficacy of chemotherapy drugs within the patient's physical limitations [35]. Wilson W. H.'s study also found that with constant drug dose rates, plasma concentration decreases as the treatment cycle progresses, eventually falling below the recommended therapeutic dose. Additionally, clinical toxicity is lower than that observed with CHOP chemotherapy. Therefore, it is particularly important to dynamically adjust medication dosage. Although CHOP chemotherapy is widely used in clinical practice, DA-EPOCH chemotherapy demonstrates superior outcomes in AIDS patients. A study of 1,546 patients from 19 prospective clinical trials showed that EPOCH provides better OS than CHOP in AIDS-associated DLBCL patients [36]. Many centers use dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (DA-R-EPOCH) chemotherapy to treat HIV-associated DLBCL patients, as it is the preferred regimen in the National Comprehensive Cancer Network (NCCN) guidelines [37]. This also explains why sequential DA-EPOCH chemotherapy achieved good efficacy in this case.

The sequence of surgery, radiotherapy, and chemotherapy is closely interconnected, with each step laying a solid foundation for the efficacy of the subsequent treatment, thereby maximizing the overall therapeutic effect.

Conclusion and limitation

Surgical intervention yielded excellent outcomes in this patient; however, most doctors do not choose this approach. Although surgery is not the preferred treatment for DLBCL, it should not be overlooked. It can be particularly beneficial for isolated and superficial lesions and should be combined with appropriate radiotherapy and chemotherapy to achieve effective treatment.

The prognosis for patients with central lymphoma is generally poor; however, this case suggests that a better outcome achieved with complete surgical resection combined with radiotherapy and chemotherapy. Nevertheless, this is a single case, and more similar cases must be evaluated to reach a more scientifically sound conclusion.

Abbreviations

DLBCL	Diffuse large B-cell lymphoma
AIDS	Acquired Immune Deficiency Syndrome
DA-EPOCH	Dose-adjusted etoposide, prednisone,vincristine, cyclophosphamide and doxorubicin
MRI	Magnetic resonance imaging
T1WI	T1-weighted image
T2WI	T2-weighted image
DWI	Diffusion weighted imaging
FLAIR	Fluid attenuated inversion recovery
PCNSL	Primary central nervous system lymphoma
OS	Overall survival
PFS	Progression free survival
non-GCB	Non-germinal center B-cell-like lymphoma
GCB	Germinal center B-cell-like
WBRT	Whole brain radiationtherapy
CHOP	Cyclophosphamide, hydroxydoxorubicin, oncovin and prednisone
DA-R-EPOCH	Dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin
NCCN	National Comprehensive Cancer Network
CR	Complete response
PR	Partial remission
SD	Stable disease
GTR	Gross total resection

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Author contributions

Qiaoqiao Zhang contributed to the manuscript drafting. Sufang Ai contributed to the collection of documents. Shulin Song contributed to collect and analyze the MRI. Zhiman Xie and Jingzhen Lai contributed to revise the editable manuscript. Junjun Jiang and Zhiman Xie contributed to the study concept and design. All authors read and approved the final manuscript. Qiaoqiao Zhang was the first author and Jingzhen Lai was the co-first author. Junjun Jiang and Zhiman Xie were the co-corresponding authors.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The patient was verbally informed of the nature and purpose of the report, and signed the informed consent forms.

Consent for publication
The patient was verbally informed of the nature and purpose of the report, and signed the informed consent forms.

Competing interests
The authors declare no competing interests.

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