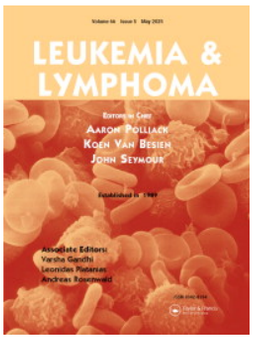

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Glofitamab induces deep and rapid response in relapsed primary central nervous system lymphoma

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ABSTRACT

Relapsed refractory primary central nervous system lymphoma (R/R PCNSL) has no recognized optimal therapy due to its grave prognosis and high mortality. This report describes a 69-year-old patient with primary central nervous system lymphoma (PCNSL) who rapidly relapsed after achieving complete remission (CR) on first-line treatment and subsequently received treatment with glofitamab to achieve CR again. Grade 1 cytokine release syndrome was observed and there were no fatal side effects. However, limited reports on glofitamab therapy are applied for relapsed and refractory PCNSL. Further *ex vivo* data demonstrated that glofitamab drove T cell activation and killing ability against lymphoma cells. Our study suggested that glofitamab may be a viable option for relapsed PCNSL patients.

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Glofitamab; CD20 × CD3; PCSNL; DLBCL

1. Introduction

Primary central nervous system lymphoma (PCNSL) is a rare category non-Hodgkin lymphoma with lesions in the brain parenchyma, spinal cord, leptomeninges, and eyes [1], which is a type of large B-cell lymphomas (LBCLs) of immune-privileged sites, according to the last 2022 WHO classifications. Standard therapy contains chemotherapy, immunotherapy, radiotherapy, and autologous stem cell transplantation [2–4]. However, 15–25% of patients are refractory to conventional therapy and 25–50% relapse after initial response [5–8]. So, PCNSL patients usually have an overall poorer prognosis compared with systemic lymphoma. Currently, the salvage treatment for relapsed/refractory PCNSL remains to be standardized and clinical trials should be considered as the preferred options for these patients. Traditional salvage chemotherapy strategies include re-treatment with HD-MTX, HD-AraC, and HSCs reinfusion in eligible patients, etc. Radiotherapy can be a cautious choice because of non-lasting response and neurotoxicity. Multiple novel molecular targeted drugs and chimeric antigen receptor (CAR) T-cell immunotherapy are under investigation for relapsed refractory primary central nervous system lymphoma (R/R PCNSL) patients [9].

Glofitamab is a CD20 × CD3 bispecific monoclonal antibody that is promising for treating relapsed and refractory B cell lymphoma. The latest phase 2 clinical study demonstrated complete remission (CR) in 39% heavily pretreated relapsed and/or refractory DLBCL patients and 78% CR patients with continuous remission at 12 months [10]. Recently, cases were reported that glofitamab has the potential in stimulating immune cell infiltration of CNS cancers and induces clinical responses in secondary CNS lymphoma [11]. Among the four patients with secondary central nervous system lymphoma (SCNSL) treated with glofitamab reported by [11], one patient receiving glofitamab monotherapy for isolated central nervous system parenchyma disease, showing objective radiological and clinical improvement after treatment. However, its efficacy in PCNSL lymphoma has not been reported. The large IgG-based macromolecules can partially penetrant the blood brain barrier and act safely on tumor cells bearing antigen. Given this promising report result, it is also worthy trying to explore the clinical use in PCNSL. Here, we first reported one

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relapsed PCNSL patient treated with CD20 bispecific antibody-based therapy in order to access the safety and efficacy of glofitamab in these PCNSL patients. The patient achieved CR after two courses of treatment with glofitamab, and continued to experience remission and maintain an optimistic survival status. Only grade 1 cytokine release syndrome (CRS) reaction occurred in the first course of treatment. We further evaluated whether the patient derived cerebrospinal fluid (CSF) samples were sufficient to induce T cell activation and cytotoxicity against CD20+ lymphoma cells *in vitro*.

2. Methods

Peripheral blood mononuclear cells were collected by leukocytosis from a healthy donor. The laboratory staff isolated the T cells by the magnetic beads coated with anti-CD3/CD28 antibodies. CSF sample was collected by lumbar puncture under direct fluoroscopy post-Glofitamab treatment. T cells were co-cultured with 5% patient derived CSF, 20% patient-derived CSF and 10 µg/ml glofitamab for 48 h. Cell suspensions were aliquoted into 96-well plates in the presence of drugs and the cell viability is analyzed by Cell Counting Kit-8 (CCK8) assay. T cells activation was determined by CD25 and CD69 up-regulation through flow cytometry. T cells cytotoxicity was performed on CD20+ lymphoma cells, OCI-Ly3, at a 5:1 effector:target ratio with drugs including control buffer, CSF and glofitamab and it was compared to conditions lacking T cells. The extent of killing ability of T cells was detected by TdT-mediated dUTP nick-end labeling (TUNNEL) assay [12].

3. Case report

A 68-year-old man suffered from continuous fever and right-sided facial paralysis for two weeks in June 2023. He denied headache, photophobia, blurriness of vision, nausea or vomiting and there was no variation in symptoms by position or movement. He had a previous psoriasis and diabetes history. Physical exam showed no other focal neurological signs (such as epilepsy, ataxia, aphemia, and sensory disturbance), and strength in all the extremities was normal. No obvious abnormalities were found in infectious indicators (including C-reactive protein, procalcitonin, Cytomegalovirus, Epstein–Barr virus, and other respiratory pathogens) and the computed tomography (CT) of head and lung. Our team arranged the whole-body positron emission tomography (PET-CT) scan for this patient because of unexplained fever and the PET-CT showed increased metabolism in the right frontal lobe (SUV max = 22.0) (Figure 1(A)). A contrast-enhanced MRI showed a mass in the above location and measured a 2.0cm mass in the above location and measured extended supero-inferiorly for 1.5 cm (Figure 1(B)). Thus, he underwent neurosurgery for the brain mass and the pathology revealed the disease of immunohistochemistry showed CD20(+), CD79a (weekly+), CD3 (scattered positive in T cells), CD10 (–), PAX-5 (+), Bcl-6 (–), MUM-1 (±), CD19 (+), Ki67 (90%+), Bcl-2 (+), C-myc (±), GFAP (–), and Olig2 (–). Although fever is an extremely uncommon presenting sign in PCNSL, there are still very few patients with this symptom [13]. Ultimately, a diagnosis of PCNSL was made on the above findings and his ECOG score of 3.

After the diagnosis was confirmed, this patient was treated with conventional chemotherapy MATRix (including rituximab 600 mg on d0, methotrexate 6 g on d1, cytarabine 5 g q12h on d2, thiotepa 20 mg on d3) for three cycles every 21 days. We also performed the lumbar puncture and prophylactic intrathecal injection of 'methotrexate 10 mg, cytarabine 50 mg, and dexamethasone 5 mg' simultaneously. He achieved CR after three cycles of induction and three cycles of R-MA regimen (including rituximab 600 mg on d0,

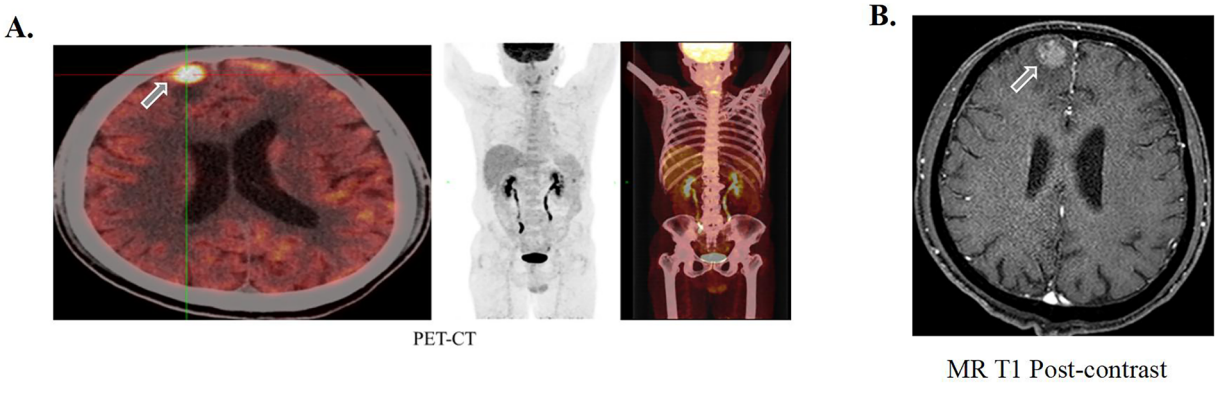

Figure 1. PET-CT and MRI images of patients at the time of first diagnosis. (A) The PET-CT images of the case. (B) The cranial magnetic resonance of the case.

methotrexate 6 g on d1, and cytarabine 5 g on d2) therapy followed (Figure 2).

Unfortunately, the patient developed slurred speech in February 2024, 2 months post-last cycle therapy, and the cranial MR showed abnormal signals in the right thalamus, two-sided bilateral ventricles, left pontine and left cerebellum. After enhancement of the lesion in the left cerebellar hemisphere, a 'sharp horn sign' can be seen, with cystic changes inside; low T1WI, high T2WI, and high FLAIR signals were observed around the lesion, but no enhancement was observed after enhancement (peritumoral edema) (Figure 3), with morphological MRI findings consistent with PCNSL. Considering that the disease relapsed and deteriorated rapidly, we recommended reexamining the lumbar puncture, but the patient refused and requested treatment as soon as possible. So, he was treated with the CD20 bispecific antibody, glofitamab, with a standard step-up dosing following obinutuzumab pre-treatment. This patient was monitored carefully and transient grade 1 CRS occurred after the first glofitamab administration. The symptoms, exhibiting fever and hypertension, were reversible and relieved through symptomatic treatment. No immune effector cell-associated neurotoxicity syndrome or other side effects were observed from treatment. This patient achieved CR according to the MRI scan after obinutuzumab pretreatment followed by two courses of treatment with glofitamab and CR was continued after 12 courses (Figure 4). He exhibited clinical improvement and received 12 cycles of treatment with glofitamab until now.

4. *In vitro* studies

CSF sample was collected from the patient at day 2 from the fifth glofitamab administration. After 48 h cocultivation, T cells can be detected in patient derived CSF group and glofitamab (Figure 5(A)). We next assessed whether the concentration of drug in patient

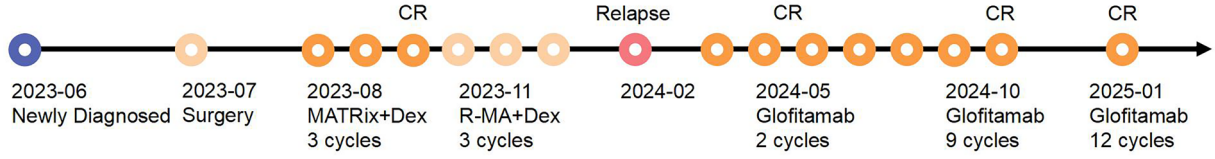

Figure 2. The therapy progress of the case.

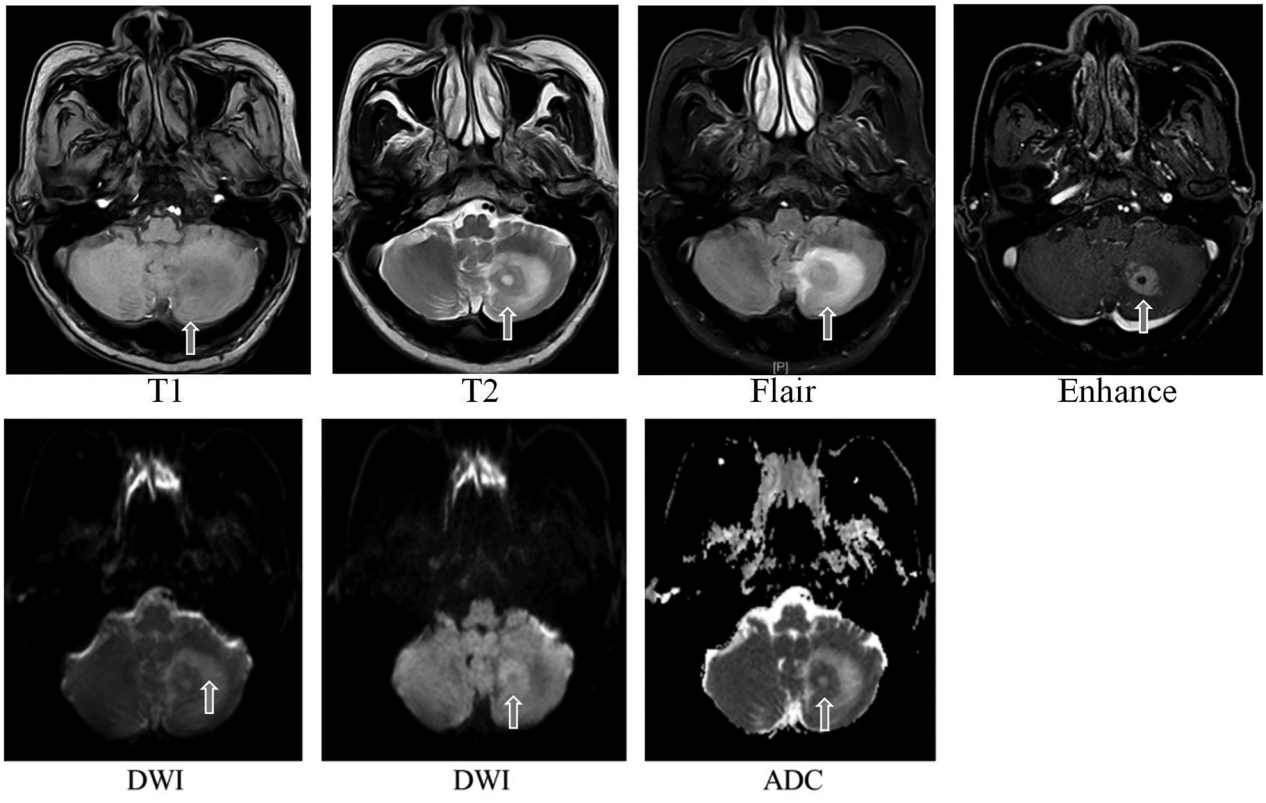

Figure 3. The cranial magnetic resonance of the case at the time of relapse.

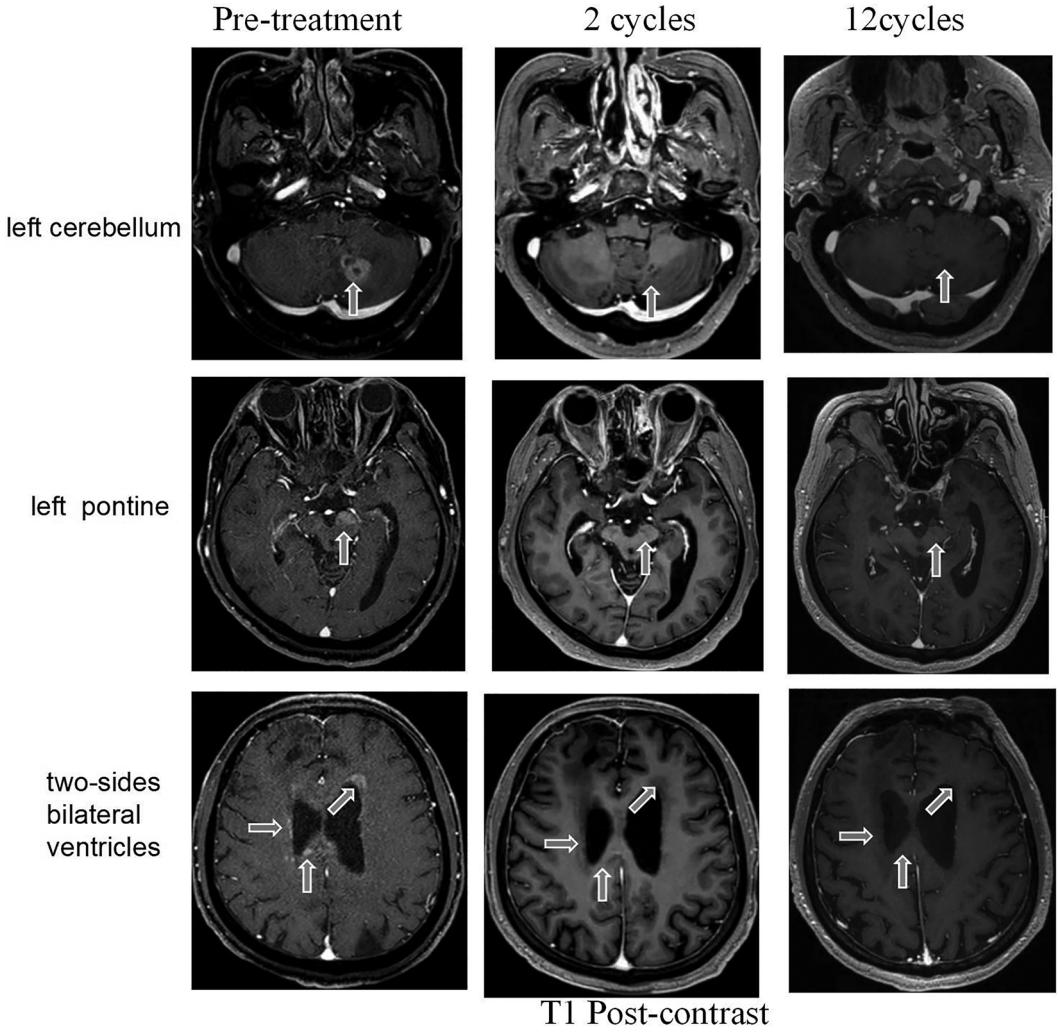

Figure 4. The cranial magnetic resonance of the case at the time of relapse, two cycles and 12 cycles post-glofitamab therapy (including abnormal signals of the left cerebellum, left pons, and bilateral lateral ventricles).

derived CSF samples was able to induce T cell activation and killing ability against CD20+ lymphoma cells *in vitro*. There was an obvious increase expression of CD25 and CD69 in CSF and glofitamab group compared to the control group (Figure 5(B)). Incubating with CD20 positive lymphoma cells, T cell-mediated cytotoxicity was observed in CSF sample group and glofitamab group (Figure 5(C)). These data indicated that glofitamab achieved a sufficient concentration in the CSF to drive T cell activation and killing ability against CD20+ lymphoma cells *in vitro*.

5. Discussion

In our study, glofitamab induced a response in a patient with PCNSL and the preclinical data showed the bispecific antibodies may have the potential in penetrating the BBB.

Elderly patients with PCNSL had poor outcomes and higher relapse rate than young population [1]. The long-term survival of patients aged over 60 years old was 15.4 months and the 5-year survival rate was just 28% [5]. A part of patients misses the opportunities for therapy because of primary resistance post multiline therapies and poor physical fitness. Multiple targeted therapeutic agents, especially small molecules that can cross the BBB are under investigation for PCNSL. Bruton's tyrosine kinase (BTK) inhibitor and oral immunomodulatory lenalidomide have been brought into the new guidelines for their potential efficacy [14].

The development of the immune therapeutics for tumor of the CNS is complicated because of the presence of the BBB. Preclinical studies indicated that CD20 bispecific antibodies work magnitude more potent than rituximab [15]. So despite the low concentration of glofitamab in the CSF, it also elicits responses in SCSNL [10]. In our study, a patient with relapsed PCNSL achieved CR to obinutuzumab pretreatment followed by two courses of treatment with glofitamab, which confirmed the effectiveness of glofitamab in PCNSL

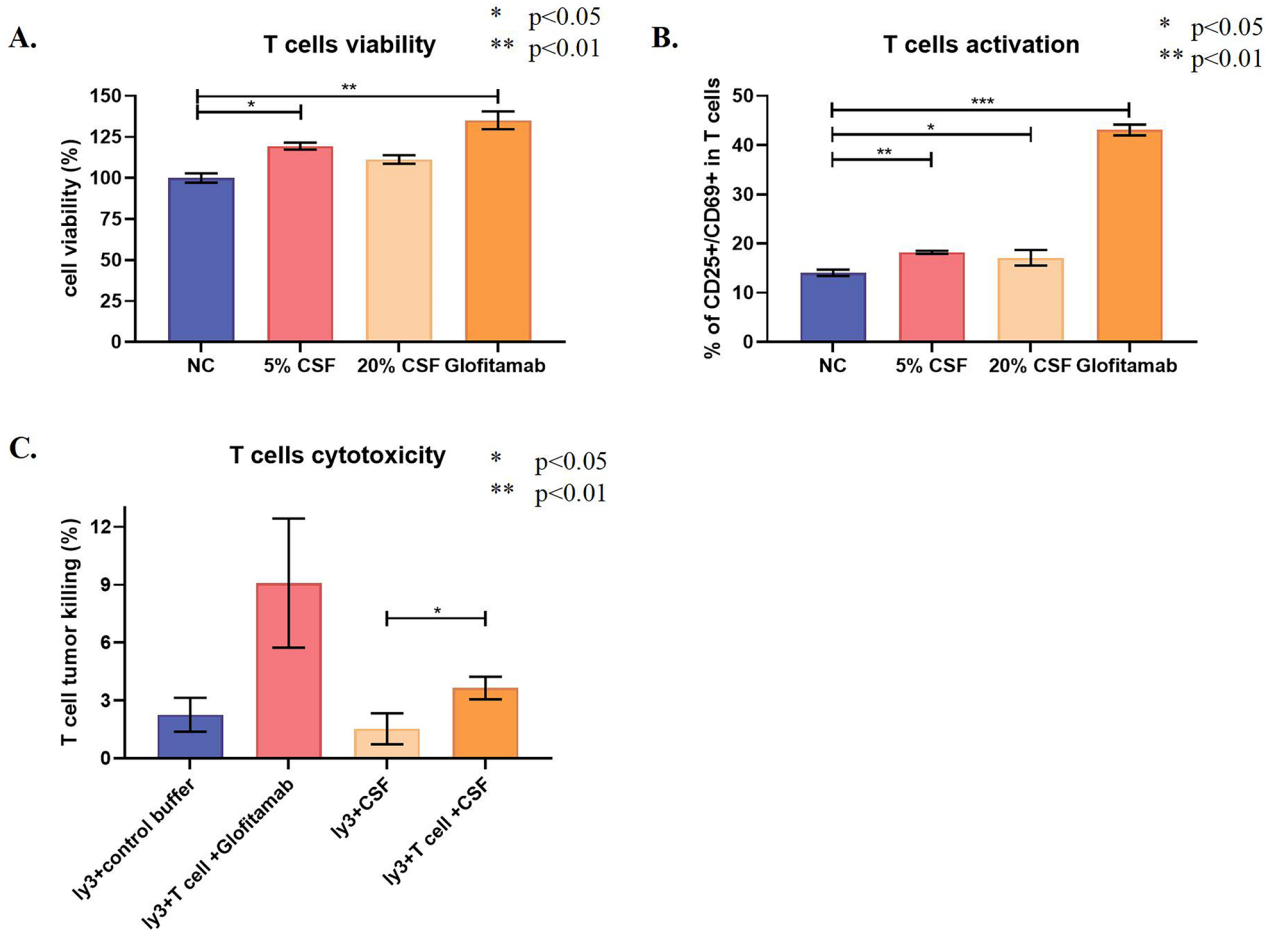

Figure 5. A CSF sample from a PCNSL patient receiving glofitamab induces T cell activation and killing of DLBCL cells *ex vivo*. (A) T cells viability of patients derived CSF and glofitamab. (B) Induction of T cells activation by CD25 and CD69 upregulation. (C) T cell cytotoxicity of OCI-Ly3 induced by the CSF sample.

(Figure 4). Although we were unable to detect the concentration of glofitamab in CSF, we evaluated whether the concentration of glofitamab in patient derived CSF samples was sufficient to induce T cell activation and cytotoxicity against CD20+lymphoma cells *in vitro*. Compared with T cells incubated with control buffer, patient derived CSF samples induced significant T cell activation determined by upregulation of CD25 and CD69, and significantly increased cytotoxicity of lymphoma cells (Figure 5(B)). Our data also indicate glofitamab achieved a sufficient concentration in the CSF to drive T cell activation and cytotoxicity against CD20+ lymphoma cells *ex vivo*. In our study, compared to the 20% CSF sample, the 5% CSF sample induced slightly more T cell activation, but there was no statistical difference. Because the concentration of glofitamab drugs penetrating the BBB into CSF is very low, there is not much difference in glofitamab concentration between 20% and 5% CSF. Further research is needed to investigate the effect of glofitamab concentration in CSF on T cell cytotoxicity. In the future, we hoped more investigation focused on the strategies of increasing effective concentration in CSF safely.

To our knowledge, this is the first report of relapsed PCNSL achieving remission through glofitamab, and further validation through *in vitro* experiments shows that after practical treatment with glofitamab, the CSF of patients has the effect of promoting T cell activation and killing CD20+ lymphoma cells. Our study suggested glofitamab may be a viable option for this type of lymphoma. Due to the lower incidence of PCNSL and the limited cases, the outcome of bispecific antibody therapy in such patients needs to be investigated in a larger, multiple clinical trial.

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Author contributions

WY Wang and MY Chen wrote the manuscript. J Lin, J Liu, T Wang, Q Song, and XZ Lu treated the patient. ZX Jia and T Chen revised the manuscript. All authors approved the final version of the manuscript.

Ethical approval

This study was approved by the Ethics Committee of the Affiliated Changzhou Second Hospital of Nanjing Medical University and was conducted in accordance with Declaration of Helsinki principles.

Consent form

The patient provided written informed consent and they have consented to publish their clinical details.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

Not applicable.

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