Multiple primary central nervous system lymphoma in the ventricular system and interpeduncular cistern: A case report

QING OUYANG[1], BING SUN[1], HAODONG SUN[1], JIANING LUO[1], ZHEN XU[2] and YUAN MA[1]

[1]Department of Neurosurgery, General Hospital of The Western Theater Command, Chengdu, Sichuan 610083, P.R. China; [2]Department of Pathology, General Hospital of The Western Theater Command, Chengdu, Sichuan 610083, P.R. China

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Abstract. Multiple primary central nervous system lymphoma (PCNSL) in the ventricular system is rare. The present study describes a case of multiple PCNSL in the left lateral ventricle, 4th ventricle, medulla and interpeduncular cistern and reviews the relevant literature. A 67-year-old male with no previous medical history presented with nausea and vomiting for 6 months and orthostatic hypotension for 2 weeks. Magnetic resonance imaging showed multiple homogeneously enhancing lesions in the left lateral ventricle, 4th ventricle, medulla and interpeduncular cistern. A midline posterior fossa craniotomy was performed with maximal safe resection of the lesion in the 4th ventricle, and histopathology of this lesion was consistent with diffuse large B-cell lymphoma. The symptoms of the patient were relieved after surgery. Postoperative chemotherapy was administered within 3 weeks and the patient was followed up for 1 year. The case of multiple PCNSL in the ventricular system, medulla and interpeduncular cistern likely originated from the choroid plexus and spread through the cerebrospinal fluid. Currently, resection and chemotherapy is considered the best treatment option for PCNSL. PCNSL in the 4th ventricle is suitable for the combination of maximal safe resection and chemotherapy, which can reduce the possibility of obstructive hydrocephalus.

Introduction

Primary central nervous system lymphoma (PCNSL) is a type of non-Hodgkin lymphoma that originates in the intracranial lymphoreticular system. The average annual incidence rate of PCNSL was 0.44 cases/100,000 individuals/year in the US in 2017-2021, and the incidence of PCNSL was significantly higher in males than females (incident rate ratio=1.20, P<0.0001). PCNSL accounts for 4-6% of extra-nodal lymphomas and 1.8% of all brain and other central nervous system tumors. In addition, the 1-, 5- and 10-year survival rates for PCNSL were 56.8, 40.2 and 32.5% in 2004-2020. Therefore, PCNSL had a low incidence, high mortality and poor outcomes (1-3). Diffuse large B-cell lymphoma (DLBCL) is the most common subtype, accounting for ~90% of PCNSLs (4,5). Most PCNSL lesions are supratentorial and periventricular, often involving the corpus callosum, basal ganglia, central grey matter, hypothalamus, posterior fossa or thalamus (6,7). The occurrence of multiple PCNSL extending into the ventricle system, medulla and interpeduncular cistern is rare. In the present study, a case of multiple PCNSL arising in the ventricle system, and involving the medulla and interpeduncular cistern, is reported. The present study also summarized cases of PCNSL arising in the ventricular system, aiming to raise awareness of this rare brain tumor and describe the treatment experience.

Case report

A 67-year-old male with no history of immunosuppression presented with nausea and vomiting after a meal without any obvious inducement for 6 months, and recent onset of orthostatic hypotension 2 weeks prior to being admitted to the General Hospital of the Western Theater Command (Chengdu, China) in December 2024. Neurological examination showed no focal deficits.

Magnetic resonance imaging (MRI) demonstrated multiple slightly longer T1 and T2 signal soft-tissue lesions in the left lateral ventricle, 4th ventricle, medulla and interpeduncular cistern (Fig. 1A and B). These lesions showed notable uniform enhancement after injection of gadolinium-based contrast medium (Fig. 1C and D). The lesion in the 4th ventricle extended to the medulla with perilesional edema, and without obstructive hydrocephalus. The lesion in the medulla showed a slight diffusion restriction on diffusion-weighted imaging and a low signal using apparent diffusion coefficient imaging (Fig. 2A). Furthermore, magnetic resonance spectroscopy demonstrated elevation of total choline and a decrease of N-acetylaspartate levels at the location of the medulla lesion (Fig. 2B). An MRI of the spine revealed no obvious malignant neoplasm. Tumor markers such as CA19-9, α-fetoprotein, CA125 and carcinoembryonic antigen were negative. A malignant lymphoma was

Correspondence to: Dr Yuan Ma, Department of Neurosurgery, General Hospital of The Western Theater Command, 270 Rongdu Avenue, Jinniu, Chengdu, Sichuan 610083, P.R. China
E-mail: tianfu_47@163.com

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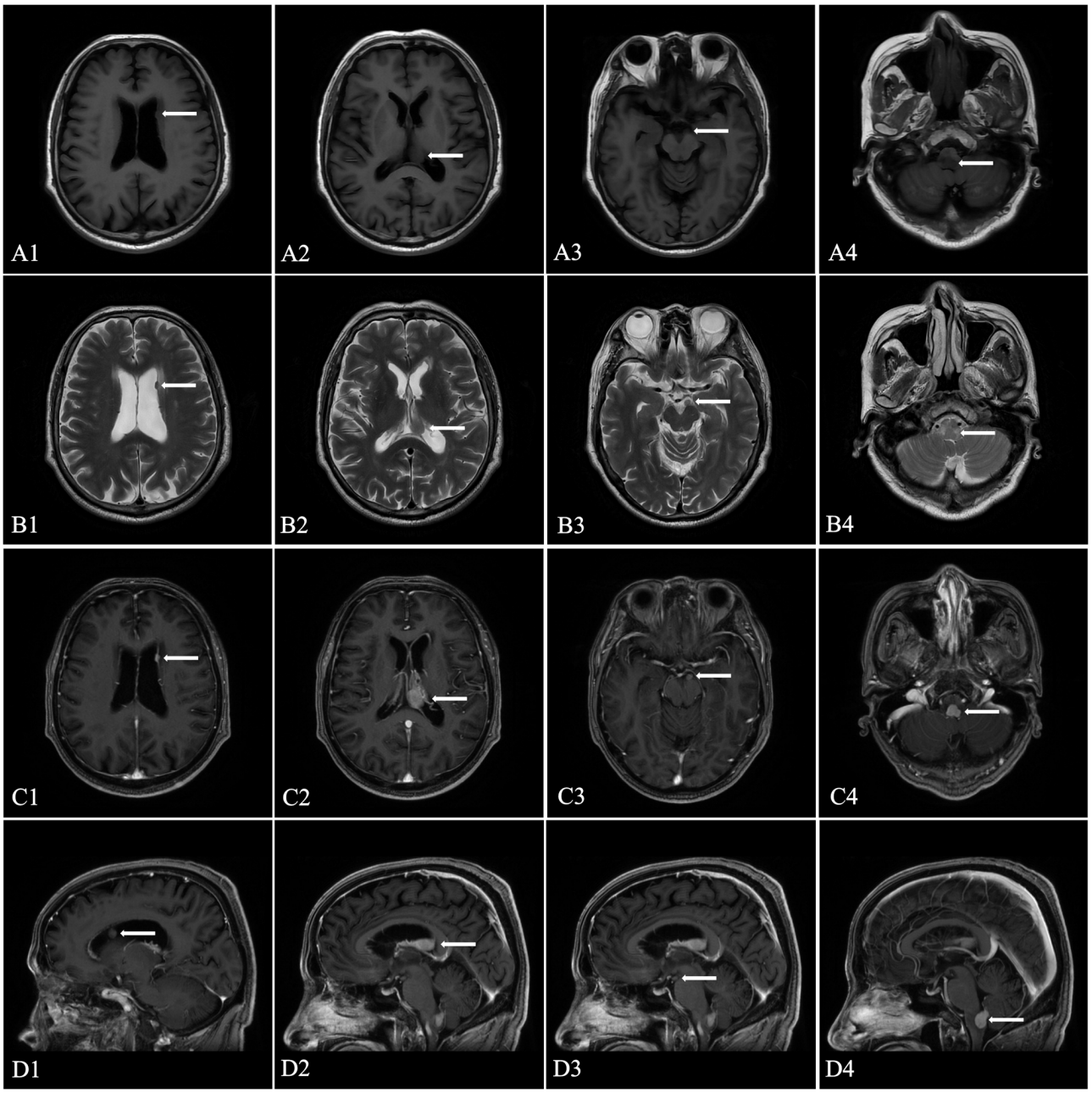

Figure 1. Pre-operative MRI. (A1-4) Lesions (arrow) in the lateral ventricle, interpeduncular cistern and 4th ventricle and medulla showed a slightly longer signal on axial T1-weighted MRI. (B1-4) The lesions (arrow) in the lateral ventricle, interpeduncular cistern and 4th ventricle and medulla showed a slightly longer signal on axial T2-weighted MRI. (C1-4) The lesions (arrow) in the lateral ventricle, interpeduncular cistern and fourth ventricle and medulla showed a notable enhancement on axial gadolinium-enhanced MRI. (D1-4) The lesions (arrow) in the lateral ventricle, interpeduncular cistern, 4th ventricle and medulla showed a notable enhancement on sagittal gadolinium-enhanced MRI. MRI, magnetic resonance imaging.

suspected, but ependymoma, glioma or metastasis could not be excluded.

A retrospective analysis of 9,000 patients in 3 datasets reported that craniotomy is associated with increased survival compared with a biopsy for patients with PCNSL (8). The pressure on the medulla from the lesion may cause orthostatic hypotension; thus, the maximum safe resection of the lesion in the 4th ventricle was performed by a midline posterior fossa craniotomy (Fig. 2C and D). H&E staining [tissues were fixed in 4% paraformaldehyde for 2 h, dehydrated in 70-90-100% ethanol (10 min each) sequentially, and cleared twice in xylene (5 min). Paraffin slices (5 μm) were incubated in Mayer's hematoxylin solution (1 min) and differentiated in 1% HCl ethanol (30 sec). Sections were stained with eosin Y solution (1 min), dehydrated through 70-100% ethanol and cleared with xylene. Slides were mounted with neutral-buffered formalin-based medium and covered with glass slides. All of the above steps were performed at room temperature (21-25˚C). Finally, slides were observed under a microscope (BX45; Olympus Corp.)] indicated that there was atypical lymphocyte infiltration, medium size rounded cells with irregularly shaped hyperchromatic nuclei, morphological homogeneity, prominent nucleoli and a small amount of eosinophilic cytoplasm (Fig. 3A). The immunohistochemical

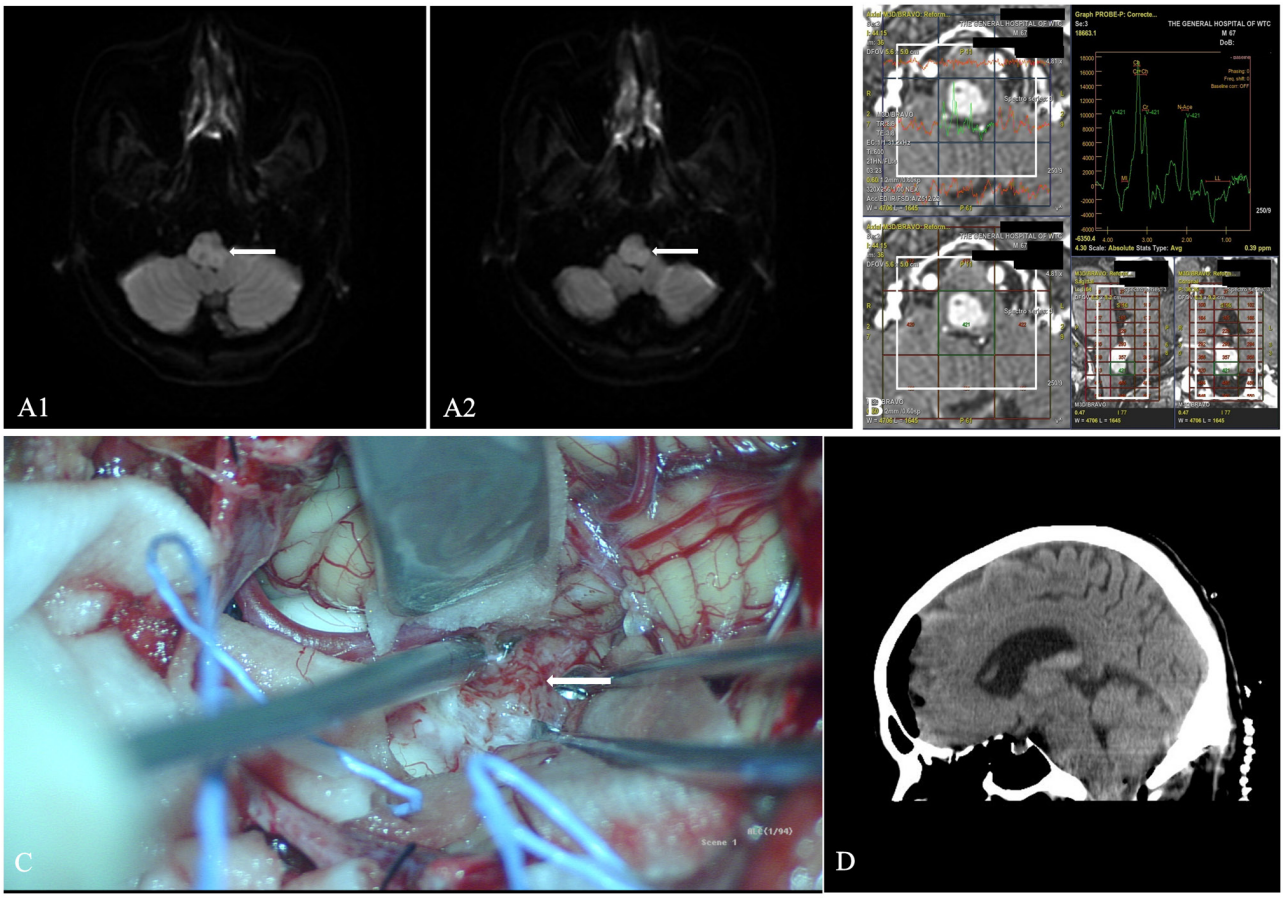

Figure 2. Pre-operative MRI, intra-operative findings and post-treatment CT. The lesion (arrow) in the medulla showed slight diffusion restriction using diffusion-weighted imaging (A1) and a low signal using the apparent diffusion coefficient (A2). (B) The lesion in the medulla showed an elevation of choline and decrease of N-acetylaspartate using magnetic resonance spectroscopy. (C) Surgical view of 4th ventricle, where the tumor (arrow) is close to obstructing the median aperture of the 4th ventricle. (D) The postoperative CT image.

staining [using the LUMATAS BIOYSTEMS fully automatic immunohistochemical instrument (Titan). Paraffin slices were deparaffinized and rehydrated (21-25˚C). After antigens were retrieved with Tris-EDTA buffer (pH 9.0) for 15 min at 100˚C, endogenous peroxidase was blocked with 3% hydrogen peroxide for 10 min (21-25˚C). The slices were incubated with primary antibodies (purchased from Maxim Biotechnologies) against ATRX chromatin remodeler (1:100 dilution; cat. no. MAB-0855), terminal deoxynucleotidyl transferase (1:100; MAB-0676), Bcl-2 (1:100; MAB-0711), Bcl-6 (1:100; MAB-0746), c-Myc (1:100; RMA-0803), CD10 (1:100; MAB-0668), CD20 (1:100; MAB-0669), CD21 (1:100; RMA-0811), CD3 (1:100; MAB-0740), CD5 (1:100; MAB-0827), pan-cytokeratin (1:100; RAB-0050), epithelial membrane antigen (1:100; MAB-1101), glial fibrillary acidic protein (1:100; MAB-0769), H3K27M (1:100; RMA-0840), isocitrate dehydrogenase 1 R132H (1:100; MAB-0733), Ki-67 (1:100; RMA-0542), multiple myeloma oncogene 1 (MUM-1; 1:100; MAB-0885), neuronal nuclear antigen (1:100; MAB-0578), p53 (1:100; MAB-0674), paired box 5 (PAX-5; 1:100; MAB-0706), S-100 (1:100; RMA-1705) and vimentin (1:100; MAB-0735) for 30 min (21-25˚C). The samples were the incubated with the secondary antibodies (undiluted highly sensitive enzyme-labeled anti-mouse/rabbit IgG polymer; cat. no. TT-0805; Maxim Biotechnologies) for 15 min (21-25˚C) and washed with PBS thrice (5 min each), followed by the addition of diaminobenzidine (DAB) (21-25˚C). At last, the slices were counterstained with Mayer's hematoxylin for 5 min (21-25˚C) and observed under a microscope (BX45; Olympus Corp.)]. The results were as follows: ATRX chromatin remodeler (-), terminal deoxynucleotidyl transferase (-), Bcl-2 (+; 80%), Bcl-6 (+; 80%), c-Myc (+; 40%), CD10 (-), CD20 (+), CD21 (-), CD3 (-), CD5 (-), pan-cytokeratin (-), epithelial membrane antigen (-), glial fibrillary acidic protein (-), H3K27M (-), isocitrate dehydrogenase 1 R132H (-), Ki-67 (+; 80%), MUM-1 (+), neuronal nuclear antigen (-), p53 (+), paired box 5 (+), S-100 (-) and vimentin (+) (Fig. 3B). After the pathological slices were processed, analysis of Epstein-Barr virus-encoded small RNAs (EBER) was performed with an EBER test Kit [*in situ* hybridization (ISH); cat. no. ISH-7001; ZSGB-BIO] according to the manufacturer's instructions, and EBER was negative (data not shown). The immunohistochemical staining indicated positive expression of B-cell markers CD20, PAX-5 and MUM-1, and the final pathological diagnosis was DLBCL with a Ki-67 proliferation index of 80% (9). In addition, the positive expression levels of Bcl-2, Bcl-6 and c-Myc are prognostic markers in PCNSL (10). The relationship between Epstein-Barr virus and PCNSL remains elusive, although EBER negativity does not exclude

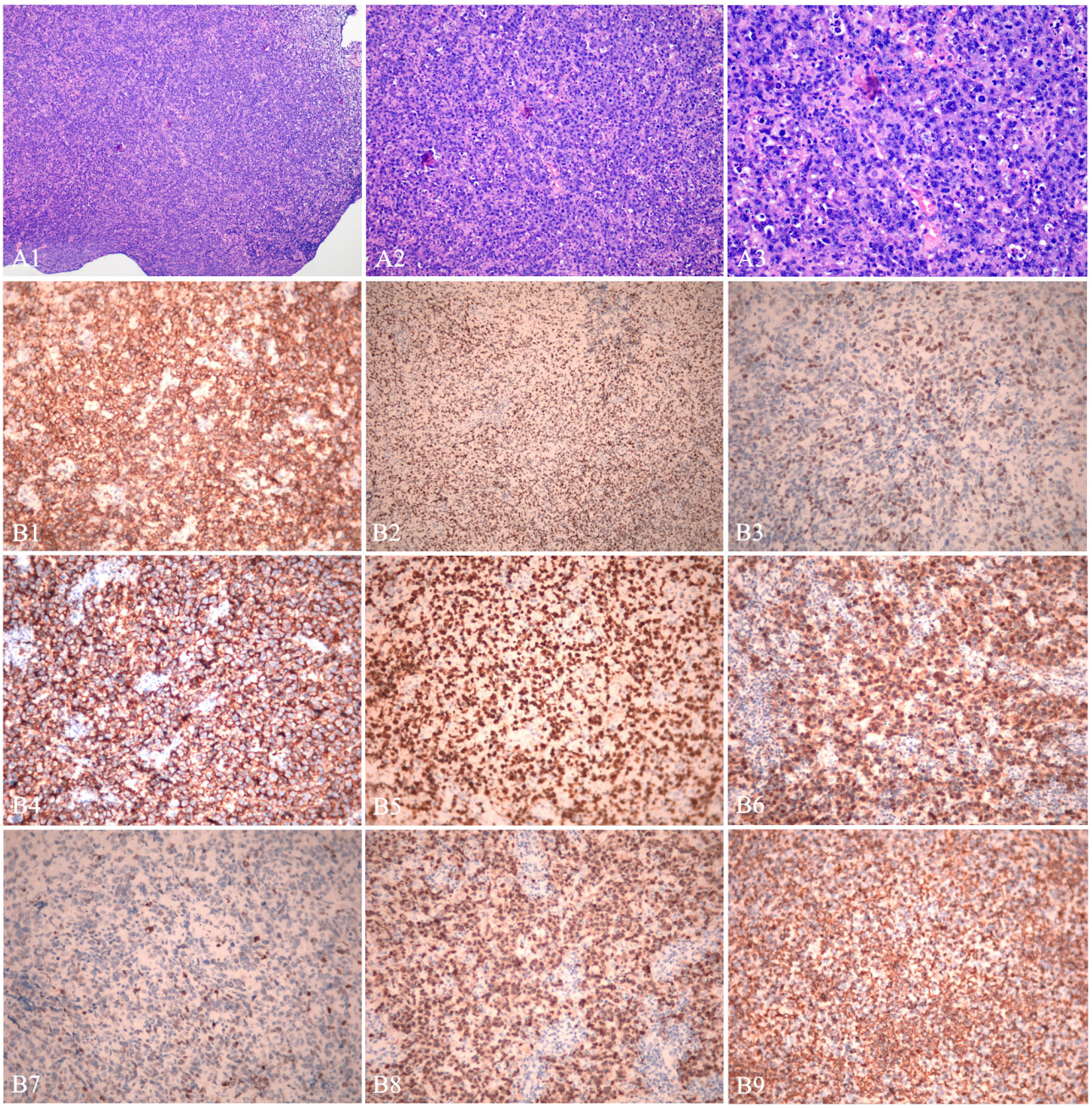

Figure 3. Tumor pathology. H&E staining at (A1) x10, (A2) x20 and (A3) x40 magnification. The tumor was positive for (B1) Bcl-2, (B2) Bcl-6, (B3) c-Myc, (B4) CD20, (B5) Ki-67, (B6) multiple myeloma oncogene 1, (B7) p53, (B8) paired box 5 and (B9) vimentin (magnification, x40).

PCNSL, but helps to exclude EBV-associated differential diagnoses such as lymphomatoid granulomatosis (11). The patient was subsequently transferred to the hematology department for chemotherapy, where he received 8 cycles of high-dose methotrexate (MTX), along with zanubrutinib and rituximab (rituximab 375 mg/m^2 on day 0, MTX 3.5 g/m^2 on day 1, zanubrutinib 80 mg for 10 days) (12,13). The patient achieved remission of symptoms after chemotherapy, the antitumor effect was excellent and the brain lesions had disappeared on the brain MRI at 6 months after treatment (data not shown). The follow up (including cranial MRI) was every 3 months in the first 2 years from the end of treatment, then every 6 months for another 3 years and subsequently on an annual basis.

Discussion

The origin of PCNSL is elusive; however, deficiency of the immune system is a notable risk factor (14,15). It has been reported that the incidence rate of patients with PCNSL without immunodeficiency is increasing, with population aging being an important factor (2,16). PCNSL is rare, accounting for ~4% of intracranial tumors. Furthermore, PCNSL occurring in the ventricle system is even rarer.

The present literature review of PCNSL originating from the ventricular system discusses 20 cases that have been reported (Table I) (1,5,16-33). In the present review, these cases revealed that PCNSL had a median age of onset of 51.4 years and had a male predominance (male:female, 14:6). Although

Table I. Literature review of 20 cases of PCNSL originating from the ventricular system.

Author, year	Age, years	Sex	Immune status	Symptoms	Location	Solitary or multiple	Lymphoma subtype	Treatment	Outcome	(Refs.)
Haegelen *et al*, 2001	33	Female	Immunocompetent	Headaches, vertigo	4th ventricle	Solitary	High-grade BCL	Resection, chemoradiation	No recurrence at 7 months	(33)
Pascual *et al*, 2002	57	Female	Immunocompetent	Visual deterioration, diabetes insipidus and mental confusion	3rd ventricle	Solitary	Diffuse non-Hodgkin lymphoma	Resection, chemoradiation	No recurrence at 6 months	(32)
Kelley *et al*, 2005	53	Male	Immunocompetent	Headaches, seizure	Lateral ventricle	Solitary	MALT lymphomas	Resection, chemotherapy	No recurrence at 6 months	(31)
Jung *et al*, 2006	63	Male	Immunocompetent	Seizure	Lateral ventricle	Solitary	MALT lymphomas	Resection, chemotherapy	No information	(30)
Jiang *et al*, 2011	14	Male	Immunocompetent	Headache	Lateral ventricle	Solitary	Burkitt lymphoma	Resection, chemoradiation	No recurrence at 18 months	(29)
Bokhari *et al*, 2013	50	Male	Immunocompetent	Vomiting, nausea	4th ventricle	Solitary	High-grade BCL	Resection, chemoradiation	No recurrence at 18 months	(16)
Rao *et al*, 2013	59	Male	Immunocompetent	Vomiting, vertigo, tremors, unsteady gait	4th ventricle	Solitary	PCNSL	Resection, chemoradiation	No information	(28)
Alabdulsalam *et al*, 2014	18	Male	Immunocompetent	Ataxia, double vision, facial asymmetry, tinnitus, dysphagia	4th ventricle	Solitary	Burkitt lymphoma	Resection, chemotherapy	No recurrence at 18 months	(27)
Liao *et al*, 2014	77	Male	Immunocompetent	Vertigo, nausea, vomiting, unsteady gait	Lateral ventricle	Solitary	MALT lymphomas	Resection, chemotherapy	No recurrence at 14 months	(26)
Cellina *et al*, 2015	65	Male	Immunocompetent	Weight loss, headaches, blurred vision, asthenia, unsteady gait	Ventricular system	Multiple	DLBCL	Biopsy, chemotherapy	No information	(25)
Hsu *et al*, 2015	61	Male	Immunocompetent	Headache, dizziness, unsteady gait	4th ventricle	Solitary	DLBCL	Resection, chemotherapy	No recurrence at 3 months	(24)
Liu *et al*, 2016	6	Male	Immunocompetent	Headache	4th ventricle	Solitary	Burkitt lymphoma	Resection, chemotherapy	No recurrence at 6 months	(23)
Brozovich *et al*, 2019	65	Male	Immunocompetent	Seizures, diplopia, vertigo, nausea, vomiting	4th ventricle	Solitary	DLBCL	Biopsy, chemotherapy	No recurrence at 10 months	(4)
Nohira *et al*, 2021	45	Female	Immunocompetent	Headache, gait instability, nausea	3rd ventricle	Solitary	PLML	Biopsy, chemotherapy	No recurrence at 24 months	(22)
Hajtovic *et al*, 2022	69	Female	Immunocompetent	Headache	Lateral ventricle	Solitary	MALT lymphomas	Biopsy, chemotherapy	No recurrence at 6 months	(21)

Table I. Continued.

Author, year	Age, years	Sex	Immune status	Symptoms	Location	Solitary or multiple	Lymphoma subtype	Treatment	Outcome	(Refs.)
Holanda *et al*, 2022	45	Male	Immunocompetent	Headache, vomiting, weight loss	4th ventricle	Solitary	PCNSL	Resection, chemoradiation	No information	(20)
Kojima *et al*, 2022	54	Male	Immunocompetent	Headache, nausea	4th ventricle	Solitary	DLBCL	Biopsy, chemotherapy	No recurrence at 20 months	(19)
Muroya *et al*, 2023	75	Female	Immunocompetent	Amnesia, gait disturbance	3rd ventricle	Solitary	DLBCL	Biopsy, chemotherapy	No recurrence at 14 months	(18)
Zhao *et al*, 2023	48	Male	Immunocompetent	Blurred vision, dizziness, staggering	4th ventricle	Solitary	DLBCL	Resection, chemotherapy	No recurrence at 9 months	(1)
Wu *et al*, 2024	71	Female	Immunocompetent	Dizziness, ataxia, gait disorder	Lateral ventricle and 4th ventricle	Multiple	DLBCL	Resection, chemotherapy	No recurrence at 12 months	(17)

MALT, mucosa-assisted lymphoid tissue; DLBCL, diffuse large B-cell lymphoma; PCNSL, primary central nervous system lymphoma; PLML, primary leptomeningeal malignant lymphoma.

immunodeficiency is a risk factor for PCNSL, no patients with immunodeficiency were found in the present literature review. However, it is possible that PCNSL in the ventricular system is very rare and the small sample size may be underpowered to demonstrate that immunodeficiency is a risk factor for PCNSL. In addition, previous studies demonstrated that there is an increase in the incidence of PCNSL with advancing age, and which has been attributed to a possible reduction in immunological surveillance or an increased number of somatic mutations that accrue over a lifetime (34,35). Despite the patients being immunocompetent, the proportion of patients aged ≥50 years was ~66.67% (14/21). Therefore, it could be considered that reduction in immunological surveillance or increased somatic mutations with age may be the potential risk factors for PCNSL as opposed to immunodeficiency.

The symptoms of PCNSL depend on the site of involvement, and according the literature review and the present case report, the most common symptom was intracranial hypertension (headache, nausea and vomiting), followed by focal neurologic deficits, seizures and altered mental state (1,4,16-33). The literature review demonstrated that the majority of PCNSL cases affect the 4th ventricle (55.6%), followed by the lateral ventricle (27.8%) and 3rd ventricle (16.7%) (1,4,16-33). According the literature review, most of the PCNSL cases were solitary (90%) and the minority were multiple (10%) (1,4,16-33). Therefore, single or multiple mass lesions in the CNS showed homogeneous gadolinium enhancement should be considered PCNSL, particularly multiple mass lesions, as multiple mass lesions are uncommon. DLBCL constituted the majority of PCNSL (35%), followed by mucosa-assisted lymphoid tissue lymphoma (20%), Burkitt lymphoma (15%) and primary leptomeningeal malignant lymphoma (5%); however, 25% of cases were undefined PCNSL, including high-grade BCL and diffuse non-Hodgkin lymphoma (1,4,16-33). While the treatment of PCNSL has evolved in the past decade, biopsy followed by chemoradiation therapy is the gold standard treatment in general (5). In the present literature review, all patients were found to have undergone biopsy or resection, adjuvant postoperative chemotherapy, radiotherapy and other measures to improve the survival rate (1,4,16-33).

In general, due to the potential of multiple PCNSL, the highly invasive features and the risk of neurologic damage and implantation metastasis post-operation, total resection of PCNSL is difficult and discouraged. In addition, previous retrospective studies have demonstrated that the extent of resection has no prognostic impact on this disease (35,36). However, the largest PCNSL trial in Germany has shown that the progression-free survival and overall survival rates of patients with subtotal or total resections are markedly improved compared with biopsied patients (37). Despite the association between the extent of PCNSL resection and prognosis not being defined, subtotal or total resection of PCNSL is encouraged in patients with single lesions if resection is safe. PCNSL is commonly treated with systemic chemotherapy including MTX (38%), steroids (13%), radiation (29%) and intrathecal chemotherapy (9%) (38).

The chemotherapy plan needs to be selected and adjusted according to the condition of the patient. Advances in molecular pathology provide more information about

unique characteristics of PCNSL, such as the mechanisms underlying the pathogenesis and drug resistance in PCNSL, which may help to identify drug targets and the choice of the therapeutic plan; however, the patient refused the molecular pathological diagnosis for personal reasons. High-dose (HD)-MTX, which is a standard first-line therapy for PCNSL, can markedly improve the overall survival rate. The CD20 antibody rituximab is a standard component of the treatment for non-Hodgkin B-cell lymphomas, including DLBCL. Thus, the current standard adjuvant therapy is HD-MTX and rituximab is applied as the first-line induction therapy, supplemented by whole-brain and whole-spinal cord radiotherapy (6). The available evidence suggests PCNSL with c-Myc and Bcl-2 positive co-expression is rarer and associated with shorter median overall survival when compared with c-Myc or Bcl-2 negative (39). The co-expression of Bcl-2 and c-Myc in the patient of the present case report indicates a poor prognosis. In addition, the NF-κB/B cell receptor (BCR) signaling pathway is highly activated in PCNSL and Bruton's tyrosine kinase (BTK) is a key bridge molecule between NF-κB and BCR. The treatment scheme containing a BTK inhibitor and HD-MTX has potential for PCNSL, including relapsed and refractory PCNSL. Therefore, HD-MTX combined with rituximab and zanubrutinib (a BTK inhibitor) may be a good prospect for a patient with c-Myc and Bcl-2 positive expression. Additionally, immunotherapy for PCNSL, such as chimeric antigen receptor T-cell therapy, has progressed in previous years (40). The lesion in the 4th ventricle of the present patient was relatively independent, caused compression of the medulla and potential hydrocephalus. The patient underwent a combination of surgical resection of the lesion in the 4th ventricle and chemotherapy with MTX, zanubrutinib and rituximab. Due to the lesions being multiple and dispersed, whole-brain radiotherapy may have caused severe neurotoxicity; therefore, radiotherapy was not a priority. Furthermore, a previous study showed that whole-brain radiotherapy was not associated with improved outcomes in patients with PCNSL (3). The mechanism of the formation of multiple PCNSL in the ventricular system in the present case was elusive; however, it has been reported that PCNSL likely originates from the choroid plexus (17,41). As seen on MRI, the patient's lymphoma may have arisen in the lateral ventricle and appeared to follow the choroid plexus into the 4th ventricle. In addition, the meningeal dissemination may also be a reason for multiple lesions in the lateral ventricle, medulla and interpeduncular cistern. Cerebrospinal fluid (CSF) cytological assessment is the gold standard for diagnosing meningeal dissemination of PCNSL. The patient in the present case study did not consent to lumbar puncture for CSF cytology. For the diagnosis of PCNSL arising from the ventricular system, histological confirmation is essential and tumor cell findings in CSF are also reliable; however, it is not uncommon for CSF samples from patients with PCNSL to be negative. Monoclonal population or gene rearrangement analyses by flow cytometry are proposed to further improve sensitivity (42-44).

In conclusion, the present case study reported a rare case of PCNSL involving the lateral ventricle, 4th ventricle, medulla and interpeduncular cistern. The present case adds to the available evidence that PCNSL is a malignancy that may predominantly arise in an immunocompetent male. Maximum resection may be performed to reduce medulla compression symptoms and the incidence of hydrocephalus to provide a benefit for patient prognosis.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

QO contributed to writing the manuscript and acquiring data. BS and JL analyzed data. HS and ZX interpretated data. YM was involved in the conception and design of the study. QO and YM confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Oral and written informed consent was obtained from the patient for the publication of the case details and any associated images.

Competing interests

The authors declare that they have no competing interests.

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