Primary central nervous system lymphoma of the third ventricle with intra-tumoral hemorrhage: A case report and literature review

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Abstract. Primary central nervous system lymphoma (PCNSL) is a rare brain tumor that most commonly arises in the cerebral white matter, basal ganglia, peri-ventricle or corpus callosum. Confinement of PCNSL to the third ventricle is extremely rare, and seldom presents with intratumoral hemorrhage (ITH). The present study described the case of a 75-year-old woman who presented with obstructive hydrocephalus due to third-ventricle PCNSL. On magnetic resonance imaging (MRI), the tumor presented ITH on T2*-weighted images and a highly elevated regional cerebral blood volume on dynamic susceptibility contrast-enhanced MRI (DSC-MRI). Due to the high elevation of the regional cerebral blood volume, high-grade glioma was suspected as a preoperative diagnosis. The patient underwent endoscopic tumor biopsy and third ventricle PCNSL was successfully diagnosed. The patient achieved good prognosis at an early stage after the start of treatment initiation. There are many differential considerations for a third-ventricle tumor, and DSC-MRI can help the differential diagnosis of these tumors. Furthermore, the presence of ITH can lead to the inaccurate estimation of regional cerebral blood volume values. Overall, silent or microhemorrhage in PCNSL may be underestimated, and clinicians should therefore carefully evaluate tumor vascularity by MRI.

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Abbreviations: PCNSL, primary central nervous system lymphoma; ITH, intratumoral hemorrhage; HGG, high-grade glioma; MRI, magnetic resonance imaging; CT, computed tomography; CE-T1WI, contrast-enhanced T1 weighted imaging; T2WI, T2-weighted imaging; T2*WI, T2*-weighted imaging, DSC-MRI, dynamic susceptibility contrast-enhanced magnetic resonance perfusion imaging; rCBV, regional cerebral blood volume; ETV, endoscopic third ventriculostomy; DLBCL, diffuse large B-cell lymphoma; R-MPV, rituximab, methotrexate, procarbazine, and vincristine; T1WI, T1-weighted imaging; SWI, susceptibility-weighted imaging; VEGF, vascular endothelial growth factor

Key words: PCNSL, third-ventricle tumor, intra-tumoral hemorrhage, perfusion weighted image, dynamic susceptibility contrast-enhanced magnetic resonance imaging

Introduction

Primary central nervous system lymphoma (PCNSL) is a highly aggressive non-Hodgkin lymphoma confined to the central nervous system that accounts for merely 0.7-0.9% of all lymphomas, and 0.3-1.5% of all intracranial lymphomas (1). Although PCNSL is a rare intracranial tumor, its incidence has significantly increased in patients over 60 years of age in the past two decades (2). Immunodeficiency, HIV infection, and the administration of immunosuppressive agents following organ transplantation are risk factors for developing PCNSL; however, there is also an increase in the incidence of this tumor in immunocompetent individuals (1,2). PCNSL classified as haematolymphoid tumors involving the central nervous system (CNS), according to the World Health Organization Classification of tumors of the CNS. The pathogenesis of PCNSL suggests that the tumor cells correspond to mature, late germinal-center exit B cells derived from self-reactive/polyreactive precursor cells, which have escaped elimination, possibly fostered by the early acquisition of MYD88 mutations (3). The majority of PCNSLs are diffuse large B-cell lymphomas (DLBCL), regardless of the patient's immunological status (4). Clinical presentations of PCNSL can vary widely, only 50-70% of the patients present focal neurologic deficits. Commonly, initial manifestations are nonspecific cognitive or behavioral changes over a period of weeks to months, signs of elevated intracranial pressure, including headache and vomiting. Conversely, B symptoms, which are common clinical symptom of systemic hematologic malignancies, such as fever, night sweats, and weight loss, are rare in PCNSL (5). Lesions may be solitary or multiple, and are commonly located in the cerebral white matter near the corpus callosum, central grey matter, and basal ganglia-thalamus-hypothalamus region, posterior fossa, and periventricular region (1). Conversely, cases of PCNSL confined to the third ventricle are extremely rare, and can also radiologically mimic other third ventricle lesions (1,6,7).

In many cases, conventional magnetic resonance imaging (MRI) of PCNSL mimics that often high-grade glioma (HGG) which could all appear as rim-like lesion with necrosis or could manifest as homogenous enhancing masses (8,9). Additionally, peritumoral edemas in PCNSL tend to mild compared with in HGG, whereas, 23% of PCNSL lesions are lack peritumoral edema, to establish definitive diagnosis using only radiological features remains difficult, pathological and immunohistochemical examination of the brain biopsy specimen is commonly required (5,9,10).

Intratumoral hemorrhage (ITH) is accounts for 4.4-5.4% of gross intracerebral hemorrhage, and observed in 1.5-14.6% of intracranial neoplasms (11,12). HGG, including glioblastoma, is most commonly associated with ITH, following by metastatic brain tumors, meningiomas and low-grade gliomas (12). Conversely, ITH in PCNSL is extremely rare, the presence of ITH is even used to exclude PCNSL from the differential diagnosis (13). According previous report, 6.25% of the lateral ventricle tumors present with intraventricular bleeding, however, only a few cases of the ventricle tumors presenting ITH have been described (14-16). Moreover, no cases of third ventricle PCNSL presenting with ITH have not been reported previously.

Herein, we report a case of PCNSL confined to the third ventricle with ITH mimicking HGG, and discuss the clinical features and pitfalls of its radiological diagnosis.

Case report

Case presentation. A 75-year-old woman with no history of immunosuppression presented with amnesia and gait disturbance that gradually progressed in a short period. She was referred to our hospital three weeks after the initial symptoms and following identification of a brain tumor on MRI during screening at a nearby clinic. On admission, her neurological symptoms progressed, and she presented with mild disturbance of consciousness, headache, nausea, and gait disturbance. Serological examination revealed mild elevation of soluble interleukin 2 receptor levels (676 U/ml), and the blood count status was normal. The human immunodeficiency virus antibody test results were negative, and the patient had no history of immunosuppressive agents. Head CT revealed a tumor with high attenuation confined to the third ventricle, without calcification (Fig. 1A). MRI of the head revealed a tumor confined to the third ventricle and with obstructive hydrocephalus. Diffusion-weighted images and apparent diffusion coefficient maps showed no obvious diffusion restrictions. In contrast-enhanced T1 weighted imaging (CE-T1WI), the tumor showed homogeneous enhancement (Fig. 1B). The marginal zone of the tumor showed low intensity on T2 weighted image (T2WI) and T2*-weighted images (T2*WI), suggesting ITH (Fig. 1C, D). DSC-MRI, a type of perfusion-weighted imaging, showed a 5 to 10 percent elevation of regional cerebral blood volume (rCBV) in the tumor compared to the normal tissue (Fig. 1E). Based on the radiological findings, we considered high-grade glioma as the preoperative diagnosis.

The patient's clinical symptoms of obstructive hydrocephalus progressed rapidly. Subsequently, endoscopic third ventriculostomy (ETV) and endoscopic tumor biopsy were performed for pathological diagnosis (Fig. 2). The-third ventricle tumor was exposed using a transventricular approach and a neuroendoscope. The tumor was spherical, red, and hemorrhagic. ETV and tumor biopsies were successfully performed without fatal tumor hemorrhage. Immediately after surgery, a corticosteroid agent was administered, and her clinical symptoms improved. Histopathological examination of the surgical specimens obtained intraoperatively prior to chemotherapy revealed rounded cells with irregularly shaped hyperchromatic nuclei, prominent nucleoli, and a small amount of eosinophilic cytoplasm, often admixed with apoptotic cells and tingible body macrophages (Fig. 3A). Immunohistochemically, atypical cells were positive for CD20 (Fig. 3B). The diagnosis of DLBCL was confirmed based on the pathological findings. The presence of other lesions was excluded by whole-body contrast-enhanced CT and ophthalmoscopy. Finally, we diagnosed the tumor as a PCNSL confined to the third ventricle. Multiple drug chemotherapy using rituximab, methotrexate, procarbazine, and vincristine (R-MPV) was administered after surgery. After 5 Kur of chemotherapy, her clinical status improved completely, and complete response was confirmed 14 months after surgery (Fig. 1F).

Imaging data acquisition. CT was performed using a 320-row multidetector CT system (Aquilion ONE Vision Edition; Canon Medical Systems). The following imaging parameters were used: tube voltage, 120 kV; tube current, 215 mA; gantry rotation speed, 1.0 s; detector configuration, 80x0.5 mm; scan and display field of view (FOV), 240x240 mm; slice thickness, 5.0 mm; and image matrix, 512x512. All MRI studies were performed using an MR system (SIGNA Premier 3.0T; GE Healthcare) with a dedicated 48-channel phased-array coil (USA Instruments). Dynamic susceptibility contrast-enhanced magnetic resonance perfusion imaging (DSC-MRI) consisted of a GRE-EPI sequence, which was acquired with the following parameters: field of view 220 mm, slice thickness 5 mm, GAP 1 mm, repetition time 2000 ms, echo time 30 ms, flap angle 60; ASSET2; matrix, 160x160; NEX 1; 60 phase, 2 min.

Histologic study. The tissues were fixed in 10% neutral formalin for 24 h and embedded in paraffin. Routine specimen processing involved staining the slides with hematoxylin and eosin, followed by immunohistochemical analyses with the monoclonal antibody CD20 (L26, 422441, Nichirei, Japan; 1:2) as a primary antibody and BOND Polymer Refine Detection (DS9800, Leica Biosystems) including a secondary antibody using a fully automated immunohistochemistry staining system (BONDMAX; Leica Biosystems). Antigen activation was performed using ER2 for 20 min. All specimens were scanned using a vertical microscope system (NanoZoomer S360; Hamamatsu Photonics K.K.) and images were acquired using NDP. View2 (freeware available at https://www.hamamatsu.com/jp/ja/product/life-science-and-medical-systems/digital-slide-scanner/U12388-01.html).

Literature search strategy. A literature search was conducted to review third ventricle PCNSL cases. A MEDLINE search was performed using the keywords 'primary central nervous system lymphoma,' 'lymphoma,' 'third ventricle,' and 'ventricle tumor.' English language publications in PubMed (https://pubmed.ncbi.nlm.nih.gov/) were analyzed. Cases in which the lesion consisted of only a third ventricle were included. Conversely, the cases in which the lesion did not

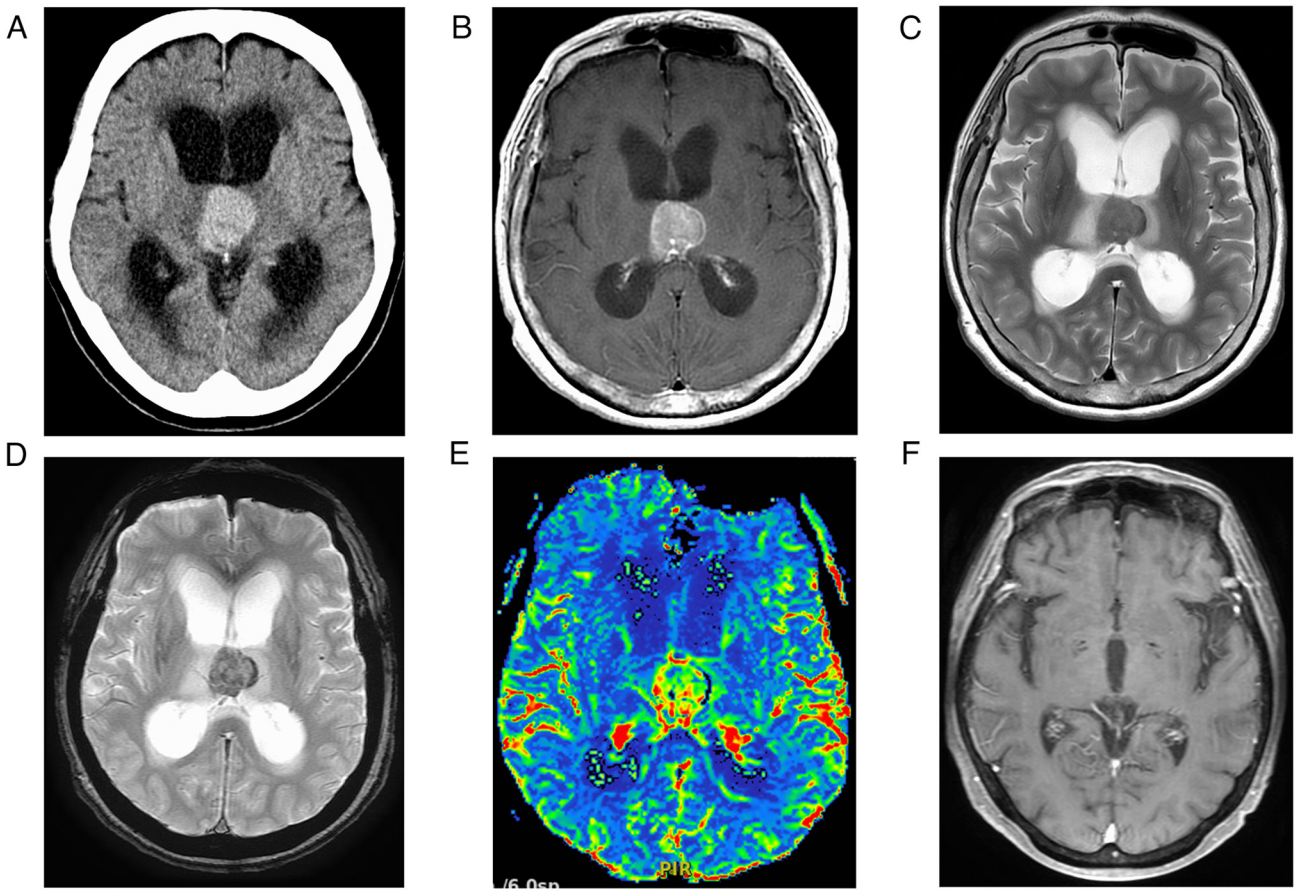

Figure 1. Pre-operative CT and pre- and post-treatment MRI. (A) Pre-treatment CT showing a high-density third-ventricle tumor with obstructive hydrocephalus. (B) Preoperative MRI showing homogenous enhancement of the tumor on CE-T1WI with (C) isointensity on T2WI and (D) heterogeneous hypointensity on T2*WI, especially in the margin of the tumor. (E) Dynamic susceptibility contrast-enhanced MRI shows a high elevation of regional cerebral blood volume in the tumor. (F) Post-treatment MRI showing disappearance of the third-ventricle tumor 14 months after surgery. CT, computed tomography; MRI, magnetic resonance imaging.

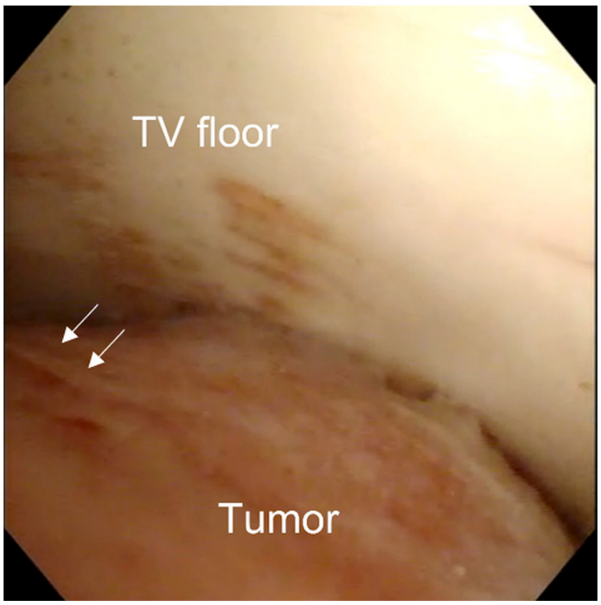

Figure 2. Intra-operative findings. The tumor obstructs the posterior third ventricle, has a reddish surface, and shows signs of hemosiderosis (arrow).

clearly consist of a third ventricle, such as multiple or disseminated lesions, were excluded.

Discussion

Third-ventricle tumors are rare, accounting for 0.1 to 0.9% of all brain tumors (17-19). These tumors are classified as involving either the anterior, the posterior, or the entirety of the third ventricle. The division between the anterior and posterior regions of the third ventricle is an imaginary line connecting the foramen of Monro and the aqueduct (20).

Differential considerations for third-ventricle tumors are plenty. In cases where tumors show vivid enhancement in adults, differential considerations include meningioma, ependymoma, germinoma, lymphoma, subependymal giant-cell astrocytoma, hypothalamic and optic astrocytoma, chordoma, and chordoid glioma of the third ventricle (17,21,22). HGG may also be present in the third ventricle, accounting for 1.4 to 2.2% (18,21). Although extremely rare, PCNSL may also be confined to the third ventricle, but only four such cases have been reported including present case (Table I) (1,6,7). These cases include two men and two women with a median age of 54.25 y (range 32-72). One patient had a history of immunocompromise and the other three did not. Symptoms associated with hydrocephalus occur as the initial manifestations in most cases. Tumors can occur in the anterior or posterior third ventricles. In most cases, the tumors presented with low intensity on T1WI; however, various intensities were observed on

Table I. Summary of pure third ventricle PCNSL.

Author, date	Age	Sex	Immunological condition	Initial manifestation	Surgery (duration form initial manifestation)	Location in TV	Hydrocephalus	MRI features	Hemorrhage	Prognosis	(Refs.)
Sasani *et al*, 2011	38	M	Competent	Headache, gait disturbance	Craniotomy (3 months)	Whole	Not severe	T1 low, T2 high	NM	Good (12 months)	(6)
Queiroz *et al*, 2017	32	M	Compromised	Headache	Biopsy (2 months)	Anterior	Not severe	-	NM	Good (NM)	(7)
Haddad *et al*, 2019	72	F	Competent	Confusion, urinary incontinence	Biopsy (several days)	Anterior	Not severe	T1 low, T2 low, DWI high, SWI no blooming	-	Good (11 months)	(1)
Present case	75	F	Competent	Amnesia, gait disturbance	Biopsy (3 weeks)	Whole	Severe	T1 low, T2 low, DWI iso, T2* low, PWI high	+	Good (14 months)	

M, male; F, female; TV, third ventricle; DWI, diffusion-weighted image; SWI, susceptibility-weighted image; PWI, perfusion-weighted image; NM, not mentioned.

Figure 3. Histopathological findings of intra-operative specimens prior chemotherapy. Histopathological examination showed (A) rounded cells with irregular, hyperchromatic nuclei, prominent nucleoli and scanty, eosinophilic cytoplasm, often admixed with apoptotic cells and tingible body macrophages. (B) Atypical cells were positive for CD20 on immunohistochemistry.

T2WI. Mild diffusion restriction was described in two cases. All cases had a good prognosis, which may be related to the fact that third-ventricle PCNSL presents with hydrocephalus at an early stage, which is easily detected. The possibility of improved prognosis with early therapeutic intervention (before tumor infiltration into the brain) has been reported, and clinicians should consider PCNSL in the differential diagnosis of third-ventricle tumors (2).

Although the preoperative differentiation of PCNSL from other third-ventricle tumors, particularly with ITH, is challenging, it is nevertheless crucial because the surgical strategies for treating different tumors may be fundamentally different. On conventional MRI, PCNSL usually presents with low intensity on T1WI, low intensity on T2WI, and homogeneous enhancement on CE-T1WI (23). However, similar features are also observed for meningioma and chordoid glioma, and differential diagnosis by conventional MRI remains difficult in some cases (24). In these cases, DSC-MRI can help in the differential diagnosis of these tumors. This technique involves the calculation of rCBV maps and the subsequent correlation of tumor vascularity with the histological grade of the malignancy (25). On DSC-MRI, tumors can present with different patterns of vascularization in chordoid glioma (rCBV=1), intraventricular meningioma (rCBV 4.6±0.7), HGG (rCBV 8.485±6.19),

and PCNSL (1.38±0.64) (26-29). PCNSLs tend to have relatively low perfusion compared to HGG, and elevation of rCBV, as evaluated by DSC-MRI, can distinguish HGG from PCNSL (8). Using this technique, the quantification of cerebral perfusion usually relies on the assumption of an intact blood-brain barrier, which remains relatively susceptible to the local magnetic field (26). Meanwhile, T2*-based DSC-MRI may lead to inaccurate estimation of rCBV values, as in the present case. In fact, the cases of ITH with PCNSL have been minimal, and concomitant hemorrhage on CT was observed in 8% of patients with PCNSL (9,30). In cases where it is difficult to detect ITH using conventional MRI, it can be detected using more sensitive hemorrhage-detecting sequences, such as susceptibility-weighted imaging (SWI) and T2*-weighted imaging. Previous reports have shown that SWI detects ITH more sensitively when used in conjunction with CT to exclude calcification, and 21% of lesions present with multiple intratumoral susceptibility signals associated with gross ITH on SWI (4). ITH has also been observed as a silent or micro-hemorrhage on T2*-weighted MRI (31). Therefore, the occurrence of silent or microhemorrhage in PCNSL may have been underestimated. Thus, clinicians should diagnose third ventricle tumors using MRI, considering the possibility of silent or micro-ITH.

However, the mechanism of ITH in a third ventricle PCNSL remains unclear. Various theories have been proposed regarding the mechanism of ITH in brain tumors: vascular obstruction due to endothelial obstruction, vessel compression and/or distortion resulting in rapid tumor growth, vessel necrosis, tumor invasion of vessel wall, and increased venous pressure associated with increased intracranial pressure (ICP) (11). In parenchymal PCNSL, DLBCL tends to develop ITH compared to other phenotypes (30), and fragile vessels traversing necrotic areas and large vessels may also cause ITH owing to thinning and rupture of the vessel wall (13). PCNSL with ITH reveals overexpression of vascular endothelial growth factor (VEGF), and progression of angiogenesis and breakdown of fragile vessels may cause ITH (13,32). Meanwhile, in specific intraventricular tumors, angiomatous lesions and abnormalities of the draining vein, such as venostasis and venous thrombosis in the subependymal layer arising from tumor extension may lead to ITH (14,33,34). In addition, a significant change in ICP may alter a cause of ITH in intraventricular tumors (35). Differences in ITH mechanisms between third ventricle PCNSL and other ventricle lesions remain unclear. However, in recent years, it has become known that CSF flow synchronized with the arterial pulsation and morphological changes in the surrounding brain parenchyma can cause CSF backflow from the third to the fourth ventricle and alter local pressure gradients in the ventricular system (36). The third ventricle, which is contiguous to the foramen of Monro and the mesencephalic aqueduct, undergoes more dynamic changes than the lateral ventricles, and the third ventricle lesions might be continuous exposed to their environment. In the present case, which contained characteristics of both PCNSL and intraventricular tumor, venostasis within the fragile vascular network might have caused micro-ITH due to tumor extension surrounding the subependymal layer and was further affected by continuously elevated ICP due to obstructive hydrocephalus and dynamic change of CSF flows due to these anatomical features, leading to micro-ITHs presenting as a hypointense rim in the marginal region on T2*WI.

In conclusion, there are numerous differential diagnoses for a third-ventricle tumor, and PCNSL only rarely presents as a pure third-ventricle tumor. Evaluation of rCBV values on DSC-MRI may be useful in aiding preoperative differentiation diagnosis; however, the presence of ITH can lead to an inaccurate estimation of rCBV values. Silent or micro-hemorrhage on PCNSL may be underestimated, and clinicians should carefully evaluate tumor vascularity. Moreover, it is difficult to differentiate third-ventricle PCNSL with ITH from other third ventricle tumors.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YM and KS drafted the manuscript and wrote the final paper. SN, YN and JY made substantial contribution to conception and design. SN, YN and JY drafted parts of the manuscript, revised the content critically and provided constructive feedback. KS and YN performed the surgery. YM and KS analyzed all images. KS and JY confirmed the authenticity of all the raw data. All authors read and approved the final 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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