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A Case of Primary Leptomeningeal Lymphoma Presenting with Hydrocephalus Characterized by Disproportionately Large Fourth Ventricle

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Abstract

Primary leptomeningeal malignant lymphoma (PLML) is a rare variant of primary central nerve system malignant lymphoma (PCNSL) which is restricted to leptomeninges. The lesions of PLML can often be detected as abnormal enhancement on the surface of central nervous system or the ventricular wall on magnetic resonance imaging (MRIs). Cerebrospinal fluid (CSF) evaluation together with such MRI findings provides the definitive diagnosis of PLML. Here, we present a 45-year-old female case of PLML in which hydrocephalus with disproportionately large fourth ventricle was observed at presentation with gait instability. Head MRI revealed no abnormal enhancement and CSF cytology was negative, leaving the cause of hydrocephalus undetermined. Endoscopic third ventriculostomy (ETV) was effectively performed for hydrocephalus and her symptoms disappeared. Nearly 2 years later, she was brought to emergent room due to unconsciousness with the recurrence of hydrocephalus. MRI showed expanded fourth ventricle and abnormal enhancement on the ventricular wall. The endoscopic surgery for improving CSF flow was successful and inflammatory change was endoscopically observed on the ventricular wall involving aqueduct. Pathological diagnosis of the specimen from the ventricular wall proved B-cell lymphoma. Because neither brain parenchymal masses nor systemic tumors were identified, she was diagnosed with PLML and treated by high-dose methotrexate. She was in a stable state 2 years after the diagnosis of PLML. We report and discuss the characteristics of this case.

Keywords: leptomeningeal, lymphoma, hydrocephalus, fourth-ventricle

Introduction

Primary central nervous system lymphomas account for approximately 5% of all brain tumors[1)] and typically presents as a solitary parenchymal mass.[2,3)] While leptomeningeal dissemination can be seen as a late manifestation of systemic lymphoma or synchronously with primary central nerve system malignant lymphoma (PCNSL), lymphoma isolated to the leptomeninges, which is categorized as primary leptomeningeal malignant lymphoma (PLML), is exceedingly rare.[4,5)] The clinical presentation of PLML varies depending mainly on the locations involved by lymphomatous lesions, and hydrocephalus can also be the trigger for disclosing underlying intracranial malignant lymphoma.[4,6–10)] As for diagnostic workup for PLML, recognizing suggestive findings on magnetic resonance imaging (MRI), such as abnormal enhancement on the surface of brain or ventricular wall, is the key, and definitive diagnosis requires histopathological confirmation via cerebrospinal fluid (CSF) or biopsy.[6–9)]

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Here, we present a case of PLML in which hydrocephalus manifested nearly 2 years prior to the definitive diagnosis of PLML. Notably, the hydrocephalus exhibited a unique feature of disproportionately large fourth ventricle. The development of hydrocephalus was presumably attributable to concomitant PLML, but no positive findings were observed on initial MRIs or CSF examination, making the diagnosis delayed. The characteristics of this case are discussed, especially focusing on the clinical course from the onset to the diagnosis.

Case Report

A 45-year-old woman with an unremarkable medical history visited our hospital with gait instability followed by headache and nausea. Head computed tomography (CT) and MRI showed hydrocephalus with fourth ventricle disproportionately enlarged (Figs. 1a and 1b), which required an emergent ventricular drainage. MRI showed no abnormal enhancement in the cranial space (Figs. 2a and 2b) and no abnormality was found in CSF cytology and CSF profile including cell number, sugar, and protein. Then, endoscopic third ventriculostomy (ETV) was performed for the permanent treatment of hydrocephalus, which was effective enough for her symptoms to disappear (Fig. 1d). Although preoperative MRI suggested aqueduct stenosis (Fig. 1c), endoscopic observation revealed the patency of aqueduct and no abnormality on the ventricular wall, providing no suggestive findings to determine the cause of hydrocephalus at this point. The patient was discharged in an independent state and continued to be followed up with MRI periodically taken.

Twenty-two months after onset, she was brought to our emergent room with conscious disturbance, and head CT showed recurrence of hydrocephalus with expanded fourth ventricle (Figs. 1e and 1f). The endoscopic surgery was successfully performed for improving CSF flow by placing tubes to aqueduct and the floor of third ventricle. Endoscopic observation revealed prominent inflammatory change on the ventricular wall involving aqueduct (Fig. 3a), which apparently obstructed the CSF flow. Small specimen was taken from the wall of the ventricles and sent to pathological evaluation, which resulted

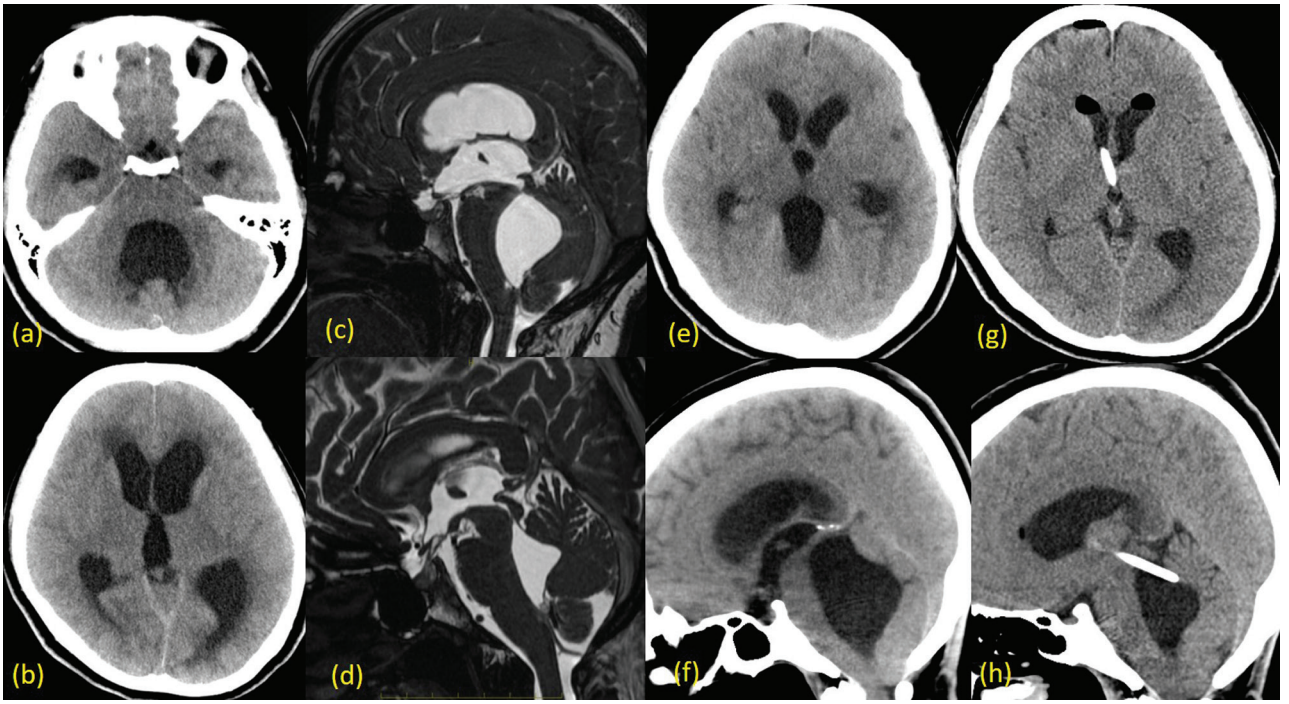

Fig. 1 (a, b) Head CT at presentation showed hydrocephalus with disproportionately large fourth ventricle. (c) MRI T2WI taken before ETV clearly showed enlarged fourth ventricle and suggested aqueduct stenosis, which was denied by endoscopic observation. (d) MRI taken after ETV showed normalization of the size of fourth ventricle and aqueduct seemed patent. (e, f) Plain head CT showed recurrence of hydrocephalus with expanded fourth ventricle. (g, h) CT taken after second endoscopic surgery showed the appropriate placement of the tube in aqueduct and the improvement of hydrocephalus. CT: computed tomography, ETV: endoscopic third ventriculostomy, MRI: magnetic resonance imaging, T2WI: T2-weighed image.

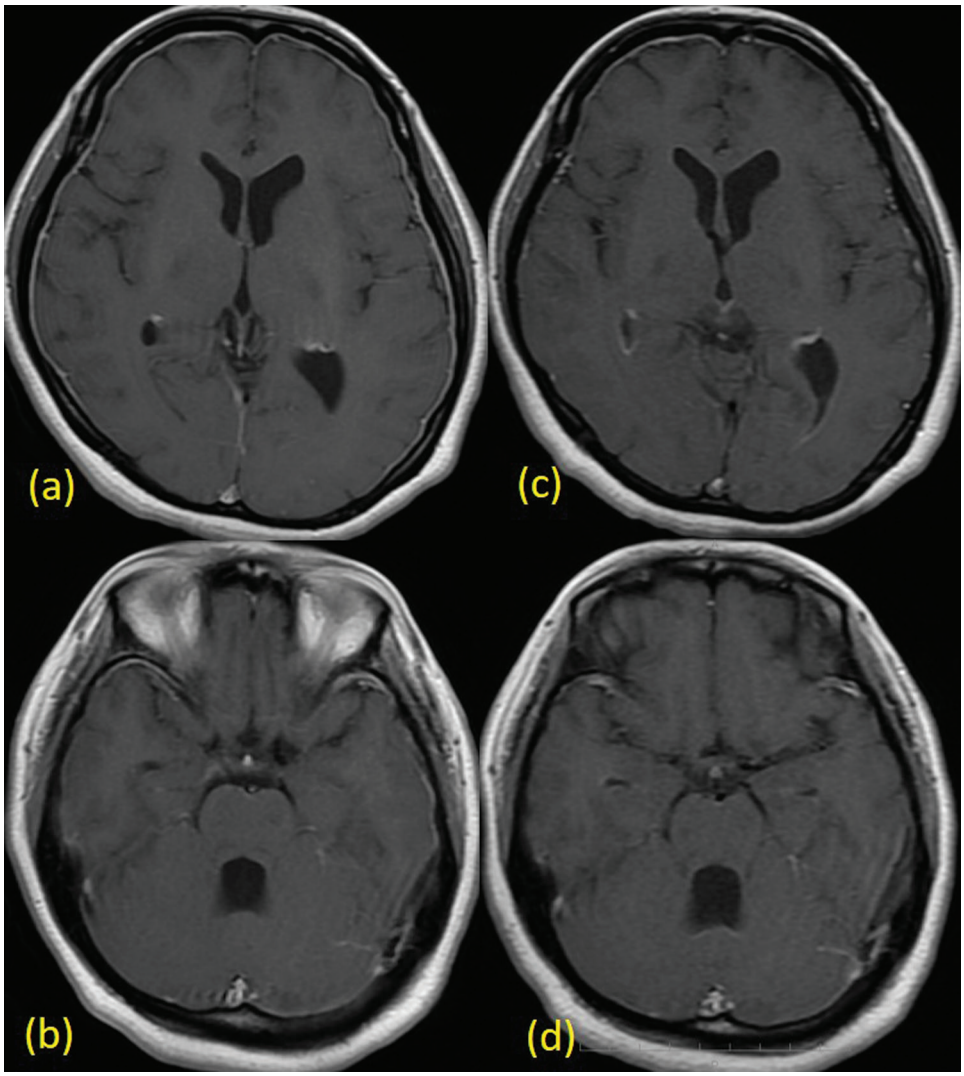

Fig. 2 (a, b) MRIs with gadolinium taken after ETV showed no abnormal enhancement on ventricular wall. Possible dural enhancement was seen, which might have been caused by the change in intracranial pressure after ETV. (c, d) Contrast MRI taken after second endoscopic surgery showed abnormal enhancement on the ventricular walls in lateral and fourth ventricle. Dural enhancement was not obvious. ETV: endoscopic third ventriculostomy, MRI: magnetic resonance imaging.

in B-cell lymphoma (Figs. 3b and 3c). Neither parenchymal brain lesions nor systemic tumors were identified, thereby fitting the diagnosis of PLML. Hydrocephalus improved and she returned to an independent state. The patient was transferred to another hospital for the treatment of malignant lymphoma and received the systemic chemotherapy by high-dose methotrexate. The patient was reported to be in a stable state 2 years after the diagnosis of PLML.

Discussion

In this case, the patient presented with symptoms caused by hydrocephalus, which was characterized by disproportionately large fourth ventricle. Because of negative findings both on MRIs and in CSF cytology, we treated the patient as a hydrocephalus of an unknown etiology. After nearly 2 years, the hydrocephalus progressed with leptomeningeal enhancement, and lymphoma was revealed by pathological examination. Her findings were in good agreement with the diagnostic criteria of PLML.[4,10] The unique pattern of hydrocephalus with large fourth ventricle could fit in a diagnostic entity termed disproportionately large communication fourth ventricle (DLCFV).[11,12] DLCFV is a category of hydrocephalus with large fourth ventricle characterized by patency of the aqueduct and is considered to be caused by the occlusion in or

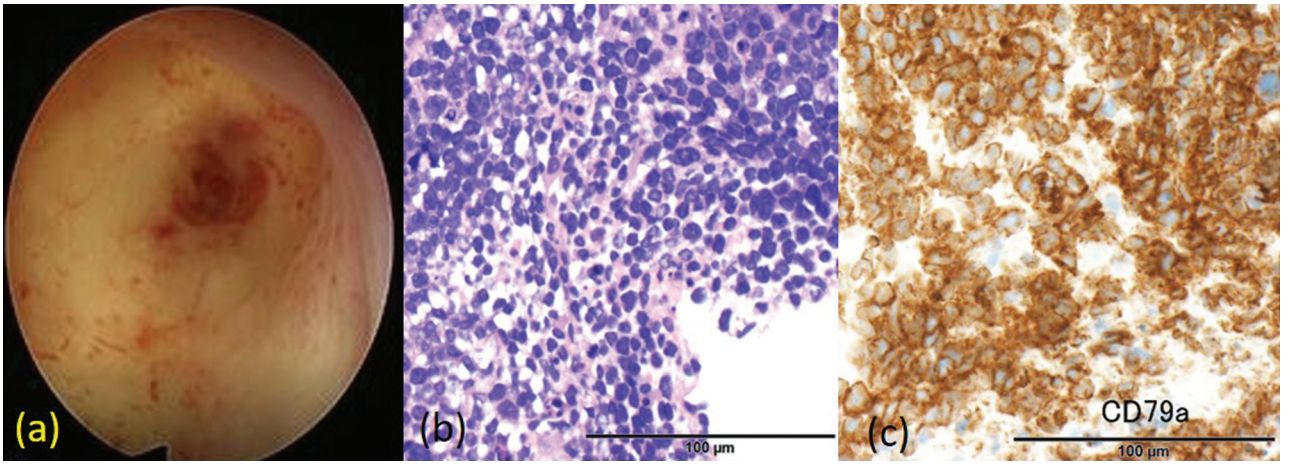

Fig. 3 Surgical view of third ventricle around aqueduct under endoscope on second operation and pathological findings of the tissue from ventricular wall. (a) Prominent inflammatory change on the ventricular wall and the obstruction of aqueduct with membrane were observed on second operation. (b) Pathological examination showed diffusely proliferation of atypical small cells with large nuclei and (c) immunostaining for CD79a was strongly positive, compatible with B-cell lymphoma.

near the fourth ventricular outlet, which sometimes can occur idiopathically.[11,12] In our case, because PLML was not proven initially and the aqueduct was endoscopically seen patent, there is a possibility that the initial hydrocephalus was idiopathic DLCFV and then PLML separately happened to occur lately to occlude aqueduct leading to isolated expanded fourth ventricle. However, considering that the coincidence of those two different disorders appears less likely, we would rather speculate that her hydrocephalus at two different time points was sequential and occult PLML was the cause to develop large fourth ventricle from the onset. The patterns of hydrocephalus seen throughout her clinical course had similarity, which could support our speculation. If that be the case, our case would represent the difficulty in diagnosing PLML at early stage.

Imaging study is the initial step for diagnosing PLML and Taylor et al.[4] reported the details regarding the findings of MRI or CT in the series of 48 patients diagnosed with PLML, showing leptomeningeal enhancement in 74% and hydrocephalus in 9%. As some patients in their series did not take contrast MRI, the positive rate of leptomeningeal enhancement could be higher and that finding is thought to be the most suggestive of PLML.[4] Among the patients showing hydrocephalus, their data indicated that all of them showed leptomeningeal enhancement. Of another three separately reported cases of PCNSL presenting with hydrocephalus, abnormal enhancement was obvious on ventricular walls in all cases.[7–9] Therefore, PCNSL patients presenting with hydrocephalus mostly show leptomeningeal enhancement, and the absence of abnormal enhancement despite obvious hydrocephalus in our case is thought to be rare. In addition, the pattern of disproportionately large fourth ventricle seen in our case appears quite unique and is described for the first time in the literature, to our knowledge.

For the definitive diagnosis of PLML, histological confirmation is essential and tumor cell findings in CSF are the most reliable basis.[5] However, positive CSF cytology is dependent on the proportion of malignant cells in the sample and the integrity of the sample, and negative CSF is not uncommon.[4,10,13,14] Further analysis by flow cytometry for monoclonal population or by gene rearrangement is proposed to yield higher sensitivity.[5,13,15] Besides CSF cytology, CSF profile including leukocyte, protein, and glucose is reported to be always abnormal in patients with PLML[4] and could be an important suggestive finding. In our case, it should be noted that the initial CSF profile was almost normal, misleading into ruling out malignancy. However, repeated lumbar puncture is sometimes required to obtain positive results in PLML patients,[4,10,13,14] and the importance of suspecting malignancy should be emphasized in case of hydrocephalus with an unknown cause.

Endoscopic observation is another important diagnostic modality for ventricle-related diseases as it has a potential to reveal malignant diseases even in the situation of negative CSF cytology.[16] In our case, the observation through ventricles in the initial endoscopic surgery provided no evidence of

abnormality. However, it needs to be addressed that fourth ventricle was inaccessible, and the possibility of some obstructive changes happening in the fourth ventricle could not be denied.

Considering that PCNSL has a highly fulminant course and misdiagnosis or late diagnosis may lead to early mortality,[17] nearly 2-year duration of symptom-free status without any treatment after the onset of hydrocephalus appears exceptional. One possible scenario that could explain her clinical course might be that the tumor initially arose around fourth ventricle, where the tumorous cells caused some inflammation around the membrane[16] to obstruct CSF flow at so early time point that they was indetectable either on MRI or in CSF. Intriguingly, it is suggested that activation of lymphocytes located in the stroma of choroid plexus seeding to the wall of the ventricles is the source for development of lymphoma,[18] and lymphomatous cells can cause inflammation in the ventricles.[16] Those suggested mechanisms could well explain our speculation because choroid plexus exists around the outlet of fourth ventricle. Then, presumably owing to slowly growing nature of the tumor, it took nearly 2 years for the spreading tumor cells to finally obstruct CSF flow again to exacerbate hydrocephalus. This speculation seems reasonable because it is reported that some PLML patients exhibited a more indolent course.[4,19,20] Kim et al.[19] described an interesting case of PLML with long-term survival in which idiopathic intracranial hypertension was initial diagnosis and shunt surgery provided good response for 3 years until symptoms recurred leading to the diagnosis of PLML. Their case has similarity to ours in the points of exhibiting high intracranial pressure at presentation and years to take until diagnosis. Some of the patients with PMLM may experience long term of latency unless PLML happen to cause hydrocephalus or high intracranial pressure at early stage.

In conclusion, our case demonstrates that PLML can manifest as an atypical hydrocephalus and the definitive diagnosis could be challenging in the early stage of the disease. A hydrocephalus case of unknown etiology warrants a high level of suspicion of malignant diseases such as PLML, and evaluation by repetitive neuroimaging and lumbar puncture for revealing an underlying disease may be needed.

Conflicts of Interest Disclosure

The authors declare that they have no conflict of interest.

References

1) Olson JE, Janney CA, Rao RD, Cerhan JR, Kurtin PJ, Schiff D, Kaplan RS, O'Neill BP: The continuing increase in the incidence of primary central nervous system non-Hodgkin lymphoma: a surveillance, epidemiology, and end results analysis. *Cancer* 95: 1504–1510, 2002
2) Schlegel U: Primary CNS lymphoma. *Ther Adv Neurol Disord* 2: 93–104, 2009
3) Haldorsen IS, Espeland A, Larsson EM: Central nervous system lymphoma: characteristic findings on traditional and advanced imaging. *AJNR Am J Neuroradiol* 32: 984–992, 2011
4) Taylor JW, Flanagan EP, O'Neill BP, et al.: Primary leptomeningeal lymphoma: International Primary CNS Lymphoma Collaborative Group report. *Neurology* 81: 1690–1696, 2013
5) Zhao H, Ma M, Zhang L, et al.: Diagnosis of central nervous system lymphoma via cerebrospinal fluid cytology: a case report. *BMC Neurol* 19: 90, 2019
6) Takagi M, Oku H, Kida T, Akioka T, Ikeda T: Case of primary leptomeningeal lymphoma presenting with papilloedema and characteristics of pseudotumor syndrome. *Neuroophthalmology* 41: 149–153, 2017
7) Boshrabadi AP, Naiem A, Ghazi Mirsaeid SS, Yarandi KK, Amirjamshidi A: Hydrocephalus as the sole presentation of primary diffuse large B-cell lymphoma of the brain: report of a case and review of literature. *Surg Neurol Int* 8: 165, 2017
8) Kim JH, Kang JK, Lee SA: Hydrocephalus and hyponatremia as the presenting manifestations of primary CNS lymphoma. *Eur Neurol* 55: 39–41, 2006
9) Ishizaki T, Mitsui T, Uchiyama Y, et al.: Primary leptomeningeal B-cell lymphoma with normal pressure hydrocephalus at diagnosis. *Rinsho Ketsueki* 56: 2441–2446, 2015 (Japanese)
10) Lachance DH, O'Neill BP, Macdonald DR, et al.: Primary leptomeningeal lymphoma: report of 9 cases, diagnosis with immunocytochemical analysis, and review of the literature. *Neurology* 41: 95–100, 1991
11) Chari A, Karponis D, Craven CL, Khan AA, Thorne L: Disproportionately large communicating fourth ventricle: pearls for diagnosis and management. *Cureus* 10: e3547, 2018
12) Osaka Y, Shin H, Sugawa N, et al.: "Disproportionately large, communicating fourth ventricle" due to membranous obstruction of Magendie's foramen. *No Shinkei Geka* 23: 429–433, 1995 (Japanese)
13) Bromberg JE, Breems DA, Kraan J, et al.: CSF flow cytometry greatly improves diagnostic accuracy in CNS hematologic malignancies. *Neurology* 68: 1674–1679, 2007
14) Glantz MJ, Cole BF, Glantz LK, et al.: Cerebrospinal fluid cytology in patients with cancer: minimizing false-negative results. *Cancer* 82: 733–739, 1998

15) Fischer L, Martus P, Weller M, et al.: Meningeal dissemination in primary CNS lymphoma: prospective evaluation of 282 patients. *Neurology* 71: 1102–1108, 2008
16) Park SW, Yoon SH, Cho KG: An endoscopically proven ventriculitis-type, cyst-like intraventricular primary lymphoma of the central nervous system. *Acta Neurochir (Wien)* 148: 981–984, 2006
17) Kridel R, Dietrich PY: Prevention of CNS relapse in diffuse large B-cell lymphoma. *Lancet Oncol* 12: 1258–1266, 2011
18) Zucca E, Conconi A, Mughal TI, et al.: Patterns of outcome and prognostic factors in primary large-cell lymphoma of the testis in a survey by the International Extranodal Lymphoma Study Group. *J Clin Oncol* 21: 20–27, 2003
19) Kim HJ, Ha CK, Jeon BS: Primary leptomeningeal lymphoma with long-term survival: a case report. *J Neurooncol* 48: 47–49, 2000
20) Carlson CL, Hartman R, Ly JQ, Beall DP: Primary leptomeningeal lymphoma of the lumbar spine. *Clin Imaging* 27: 389–393, 2003

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