

Primary Central Nervous System Lymphoma in Organ Recipient

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We report a case of primary central nervous system(CNS) lymphoma in an organ recipient. A 33-years-old man who underwent a renal transplantation 3years previously presented with headache and vomiting. In Brain computed tomography scans and magnetic resonance images showed multiple periventricular cystic rim enhancing masses. Pathologic diagnosis by stereotactic biopsy revealed malignant non-Hodgkins B-cell lymphoma. After pathologic confirmation, methotrexate chemotherapy and whole brain radiation therapy were done. Having experienced such a case, the authors strongly recommend to add primary CNS lymphoma as one of the differential diagnoses to brain abscess, metastatic brain tumor and glioblastoma multiforme in cases of multiple ring enhancing periventricular lesions of immunocompromised patient or organ recipient.

KEY WORDS : Primary central nervous system lymphoma · Organ recipient · Periventricular lesion · Ring enhancement.

Introduction

Cerebral lymphoma is a malignant lymphocytic neoplasm that can occur either primarily or as a secondary manifestation of systemic disease. Primary central nervous system (CNS) lymphoma arises in the CNS in the absence of apparent systemic lymphoma¹³. Although primary CNS lymphoma develop in nervous system and in most cases do not spread elsewhere, its pathological findings are similar to those of systemic non-Hodgkins lymphoma¹³.

Risk factors associated with the occurrence of primary CNS lymphoma are immunodeficiency states secondary to acquired immunodeficiency syndrome(AIDS), immunosuppressive treatment after organ transplantation and congenital immunodeficiency⁸). Tumors in immunocompromised patients in particular may show a ring-enhancing pattern but in immunocompetent patients may show either hyper- or isodense, round or oval masses with homogeneous contrast enhancement and variable surrounding edema¹¹). In immunocompromised patients, rim or ring enhancement of lymphoma, indistinguishable from brain abscess, is frequently seen and differential diagnosis with metastasis and glioblastoma multiforme are needed also.

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In this report, we describe a case of primary CNS lymphoma in a 33-years-old man with multiple, ring-enhancing tumors.

Case Report

A 33-years-old man was referred to neurosurgery department because of headache and vomiting. He was diagnosed to have chronic renal failure 5-years prior to admission and he underwent renal transplantation, 3-years prior to admission. Until he referred to us, he had been prescribed methyprednisolone and cyclosporin.

On routine complete blood count study there was no anemia and neutropenia and there was no manifestation of systemic tumor. On neurological examination no neurological deficits were noticed.

In brain computed tomography(CT) images there were multiple masses, at right frontal lobe and splenium, with low density and rim enhancement. Magnetic resonance(MR) images showed more multiple masses- frontal lobe, thalamus and right splenium. The lesion of right splenium was the largest one and it's size was $2.5 \times 2.5 \times 3$ cm. The masses were poorly demarcated, and hypointense in T1-weighted images. In T2-weighted images, it consisted of central hyperintensity that were cystic portion and peripheral hypointense lesion, with severe perilesional edema along the white matter tract. In gadolinium enhancement images, the masses showed strong rim enhancement(Fig. 1). The cystic portion of right splenium area showed as low signal intensity on diffusion weighted(DW) images and subtle high or iso signal intensity on apparent

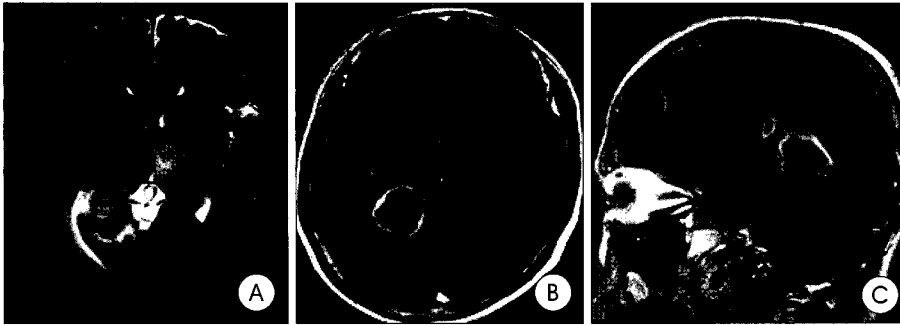


Fig. 1. Preoperative magnetic resonance image showing multiple mass – frontal, thalamus and right splenium. In T2-weighted image (A), it consists of central hyperintense and peripheral hypointense lesion, with severe perilesional edema along white matter tract. In gadolinium enhancement image axial view(B) and coronal view(C), the mass shows strong rim enhancement.

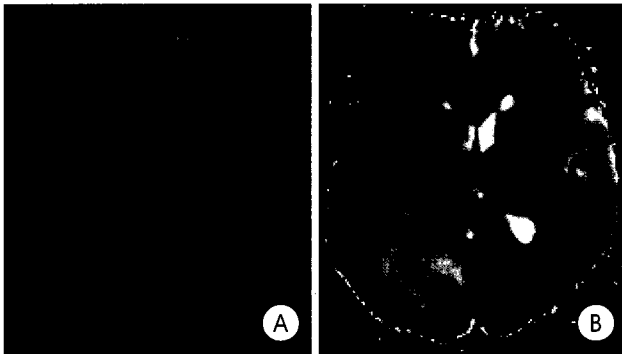


Fig. 2. Preoperative diffusion weighted magnetic resonance image(A) showing that the cystic portion of right splenium area show as low signal intensity and subtle high or iso signal intensity on apparent diffusion coefficient map(B).

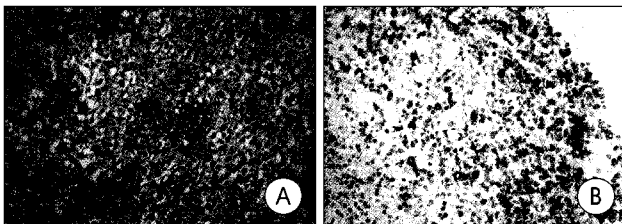


Fig. 3. Photomicrograph shows necrotic tissue and focal atypical cells, with high cellularity, irregular nucleus and prominent nucleoli. (H&E, $\times 400$) (A) In immunohistochemical stain(B) showing positive to CD79a marker($\times 400$).

diffusion coefficient(ADC) map(Fig. 2). The image findings of cystic portion were compatible with necrotic tumor cyst rather than abscess.

The patient underwent stereotactic biopsy for the splenic lesion. Pathologically, the specimen showed necrotic tissue and focal atypical cells, with high cellularity, irregular nucleus and prominent nucleoli in H&E stain(Fig. 3). Immunohistochemical stains showed CD45(+), CD79a(+), EMA(-), GFAP(-), CD3(-) and high Ki-67 index(>80%). The pathologic report was malignant non-Hodgkins B-cell lymphoma.

After pathologic confirmation, methotrexate(3.5mg/sq)

chemotherapy was done and whole brain radiation therapy(total 4500cGy) was followed after 2weeks of completion of chemotherapy. Follow-up brain CT images showed moderate response with subsequent size reduction of the masses(Fig. 4).

Discussion

PPrimary CNS lymphomas are uncommon tumors of the CNS that account for less than 2% of

primary cerebral neoplasm and 0.7 to 1.7% of malignant non-Hodgkin's lymphoma¹. They are often associated with immunodeficiency states secondary to AIDS, immunosuppressive treatment after organ transplantation and congenital immunodeficiency⁸. Patients with human immunodeficiency virus(HIV) infection are at increased risk for the development of non-Hodgkin lymphomas with an estimated risk of occurrence of 12~15% for systemic lymphomas and 1~3% for primary CNS lymphoma^{2,13}. Generally, patients in the immunosuppressed state after organ transplants may have a high chance of developing B-cell lymphomas^{2,5,14}. Inhibition of suppressor T cells by immunosuppressants fails to restrict B-cell proliferation, and Epstein-Barr virus infection is known to have a role in the development of B-cell lymphoma in some, but not all patients¹⁴. The mutagenicity of the immunosuppressant(e.g., azathioprine) has been directly related to lymphocyte chromosome injury, and then, mitotic activity in the lymphocyte system also has been suggested to be increased in the immunodepressed state^{2,5,7,14}.

Over the last decade, the incidence of primary CNS lymphoma reported in most studies has risen threefold, which cannot be entirely explained by the increased prevalence of AIDS, or the growing number of organ transplantation¹. Incidence grew significantly not only in immunosuppressed patients, but also in immunocompetent patients. Incidence of primary CNS lymphoma has risen threefold among apparently immunocompetent individual in the United States during the last 15 years⁴.

Most primary CNS lymphomas are primary non-Hodgkins lymphoma and B-cell type is predominant. Hodgkin's disease presenting as a primary CNS lymphoma is extremely rare, and only eight cases have been reported⁹. In some study, among the 160 cases of malignant non-Hodgkins lymphomas, only eight cases were T-cell type(3.6%) and the remainder were B-cell type(96.4%)¹ and in the other study, among the 70 cases of primary CNS lymphoma, there were 63 B-cell

Lymphoma in Organ Recipient

lymphomas(95.6%) and only three T-cell lymphomas(4.4%)¹³.

Primary CNS lymphoma may be solitary(86%) or multiple(14%), with a predilection for the basal ganglia, corpus callosum, thalami, and periventricular region¹. Intracerebral parenchymal lymphoma is the most frequent manifestation of primary CNS lymphoma. Other anatomical sites of involvement include infiltration of the posterior vitreous of the retina, which may

either precede or accompany the development of a brain lesion, meningeal involvement with or without subependymal nodules, and intradural spinal lymphoma⁸.

Neuroimaging studies of primary CNS lymphomas in immunocompetent patients may show either hyper- or isodense, round or oval masses with extensive homogeneous contrast enhancement and variable surrounding edema^{1,11}. But primary CNS lymphomas in immunocompromised patients in particular may show a ring-enhancing pattern¹¹ and these patterns are indistinguishable from brain abscess which is frequently seen. And differential diagnosis with metastasis and glioblastoma multiforme are difficult also, with CT scans or conventional MR images as in our case.

On MR images, the typically hypointense abscess capsule on T2-weighted sequences, which allows for the differentiation between an abscess and a tumor, can be absent. The abscess may be multiloculated and/or multifocal, thus adding to the difficulty of diagnosis on the basis of CT scans and MR images. And therefore, DW imaging has great clinical potential in differentiating brain abscess from necrotic or cystic brain tumor and that it represents a strong modality in addition to conventional T1- and T2-weighted MR images in the early diagnosis of brain abscess^{6,12}. Pus contained in brain abscesses causes strongly hyperintense signals on DW images and reduced ADC values, whereas necrotic or cystic brain tumors produce hypointense signals on DW images and elevated ADC values. There is a statistically significant difference between ADC values of brain abscesses and those of high-grade gliomas^{6,12}.

It shows that outcome of primary CNS lymphoma patient is strongly influenced by patient age and performance status, and possibly by sex, and radiotherapy dose or the addition of chemotherapy to radiotherapy did not significantly improve survival when age, sex and performance status were taken into account³. Untreated, the prognosis for primary CNS

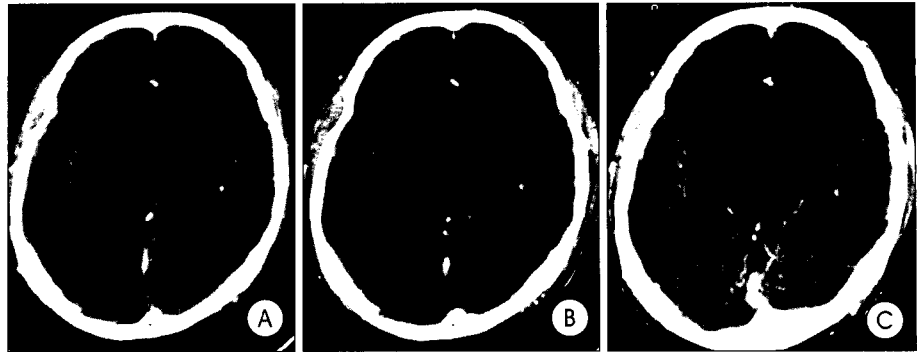


Fig. 4. Serial follow-up computed tomography image after chemotherapy(A), radiation therapy(B) and six months(C) showing reduction of mass size sequentially but diffuse white matter changes can be found also.

lymphoma is poor, with a median survival time of 4.6 months^{3,5,7}. The addition of whole-brain radiation therapy (WBRT), while providing rapid clinical and radiographic responses, increases survival time only to 10 to 18 months^{5,7}. Preirradiation chemotherapy with methotrexate(MTX) is effective in prolonging response duration and survival time in primary CNS lymphoma, especially in patients under 60 years of age, with an excellent safety profile^{5,7,10}.

High-dose MTX therapy administered before irradiation has recently been identified as an effective and relatively safe treatment for this type of tumor. However, late sequelae, including asymptomatic diffuse white matter changes, decline in cognitive function, and development of leukoencephalopathy, have been observed repeatedly in MTX therapy, because this agent is toxic for normal brain tissues⁷.

Conclusion

We experienced a primary CNS lymphoma, occurred in organ transplant recipient. In our case, imaging findings of this tumor were multiple, cystic and rim enhancing masses. These findings were different from those of immunocompetent patients. We should include primary CNS lymphoma in the differential diagnoses of multiple periventricular cystic enhancing masses in immunocompromised patient as well as metastasis, glioblastoma multiforme and abscess, and DW images and ADC map are useful to differentiate cystic tumor with abscess.

References

1. Bataille B, Delwail V, Menet E, Vandermarcq P, Ingrand P, Wager M, et al : Primary intracerebral malignant lymphoma:report of 248 cases. *J Neurosurg* **92** : 261-266, 2000
2. Chamberlain MC, Kormanik PA : AIDS-related central nervous system lymphomas. *J Neurooncol* **43** : 269-276, 1999
3. Corry J, Smith JG, Wirth A, Quong G, Liew KH : Primary central nervous system lymphoma : age and performance status are more important than treatment modality. *Int J Radiat Oncol Biol Phys* **41** : 615-620, 1998

4. Eby NL, Grufferman S, Flannelly CM, Schold SC Jr, Vogel FS, Burger PC : Increasing incidence of primary brain lymphoma in the US. **Cancer** **62** : 2461-2465, 1988
5. Glass J, Gruber ML, Cher L, Hochberg FH : Preirradiation methotrexate chemotherapy of primary central nervous system lymphoma : long-term outcome. **J Neurosurg** **81** : 188-195, 1994
6. Guzman R, Barth A, Lovblad KO, El-Koussy M, Weis J, Schroth G, et al : Use of diffusion-weighted magnetic resonance imaging in differentiating purulent brain processes from cystic brain tumors. **J Neurosurg** **97** : 1101-1107, 2002
7. Hiraga S, Arita N, Ohnishi T, Kohmura E, Yamamoto K, Oku Y, et al : Rapid infusion of high-dose methotrexate resulting in enhanced penetration into cerebrospinal fluid and intensified tumor response in primary central nervous system lymphomas. **J Neurosurg** **91** : 221-230, 1999
8. Hochberg FH, Miller DC : Primary central nervous system lymphoma. **J Neurosurg** **68** : 835-853, 1988
9. Johnson MD, Kinney MC, Scheithauer BW, Briley RJ, Hamilton K, McPherson WF, et al : Primary intracerebral Hodgkin's disease mimicking meningioma : case report. **Neurosurgery** **47** : 454-457, 2000
10. Lee CH, Lee JK, Kwun BD : Primary central nervous system lymphoma : a report of 33 cases. **J Korean Neurosurg Soc** **28** : 547-555, 1999
11. Lee YY, Bruner JM, Van Tassel P, Libshitz HI : Primary central nervous system lymphoma : CT and pathologic correlation. **AJR Am J Roentgenol** **147** : 747-752, 1986
12. Schaefer PW, Grant PE, Ginzalez RG : Diffusion-weighted MR imaging of the brain. **Radiology** **217** : 331-345, 2000
13. Tomlinson FH, Kurtin PJ, Suman VJ, Scheithauer BW, Fallon JR, Kelly PJ, et al : Primary intracerebral malignant lymphoma : a clinicopathological study of 89 patients. **J Neurosurg** **82** : 558-566, 1995
14. Urasaki E, Yamada H, Tokimura T, Yokota A : T-cell type primary spinal intramedullary lymphoma associated with human T-cell lymphotropic virus type I after a renal transplant : case report. **Neurosurgery** **38** : 1036-1039, 1996