Clinical Case Report

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Primary central nervous system lymphoma in a patient with systemic lupus erythematosus mimicking high-grade glioma

A case report and review of literature

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Abstract

Rationale: Primary central nervous system lymphoma (PCNSL) is a rare disease. Studies of PCNSL in patients with rheumatic diseases are lacking. Neither clinical symptoms nor radiographic manifestation is specific to PCNSL. Therefore, it could be misdiagnosed with other diseases such as brain tumors. Chemotherapy is the primary treatment for PCNSL, while the role of surgery remains controversial.

Patient concerns: We reported a 39-year-old woman with systemic lupus erythematosus (SLE) developed PCNSL after 15-year treatment with multiple immunosuppressants.

Diagnoses: Cranial magnetic resonance imaging (MRI) showed multi-focal lesions with ring-like enhancement post-contrast in the right hemisphere, which mimicked glioma radiographically. Owing to the severe symptoms of intracranial hypertension, gross tumor resection was performed. Pathological exam showed perivascular infiltration of atypical lymphoid cells with CD20 and Epstein-Barr virus (EBV) -encoded RNA (EREB) positive. The patient was diagnosed with diffuse large B-cell lymphoma (DLBCL).

Interventions: The patient received six cycles of chemotherapy and autologous stem cell transplantation (ASCT) subsequently.

Outcomes: The patient remained complete remission until this article was written.

Lessons: PCNSL in immunocompromised hosts may present heterogeneous contrast enhancement, which should be differentiated from other diseases especially high-grade glioma.

Abbreviations: AIDS = acquired immune deficiency syndrome, ANA = anti-nuclear antibody, ASCT = autologous stem cell transplantation, AZA = azathioprine, CsA = cyclosporin A, CT = computed tomography, CYC = cyclophosphamide, DLBCL = diffuse large B-cell lymphoma, dsDNA = double strained deoxyribonucleic acid, EBER = EBV-encoding RNA, EBV = Epstein-Barr virus, FLAIR = fluid-attenuated inversion recovery, HCQ = hydroxychloroquine, ICH = immunohistochemistry, ISH = in situ hybridization, MMF = mycophenolate mofetil, MRI = magnetic resonance image, MTX = methotrexate, NHL = non-Hodgkin lymphomas, PCNSL = primary central nerve system lymphoma, PET-CT = positron emission tomography-computed tomography, PTLD = post-transplant lymphoproliferative disease, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus, T1WI = T1-weighted image, T2WI = T2-weighted image.

Keywords: immunosuppressant, lymphoma, magnetic resonance imaging, surgery, systemic lupus erythematosus

1. Introduction

Primary central nervous system lymphoma (PCNSL) is a rare disease that accounts for up to 1% of non-Hodgkin lymphomas (NHL) and approximately 3% of primary brain tumors.[1] Risk increases in patients with rheumatic diseases, partially due to the use of immunosuppressant.[2] Magnetic resonance imaging (MRI) manifestation is not specific to PCNSL and mimics other brain tumors. Herein, we reported a 39-year-old woman with systemic lupus erythematosus (SLE) who developed PCNSL after years of multiple immunosuppressant treatment. The radiographic presentation of PCNSL mimicked glioma. Ethics committee of the First Affiliated Hospital of Sun Yat-sen University approved the research. Informed consent was obtained from the patient.

2. Case report

A 39-year-old woman was admitted because of headache and nausea for 2 weeks. She was diagnosed with SLE for 15 years and

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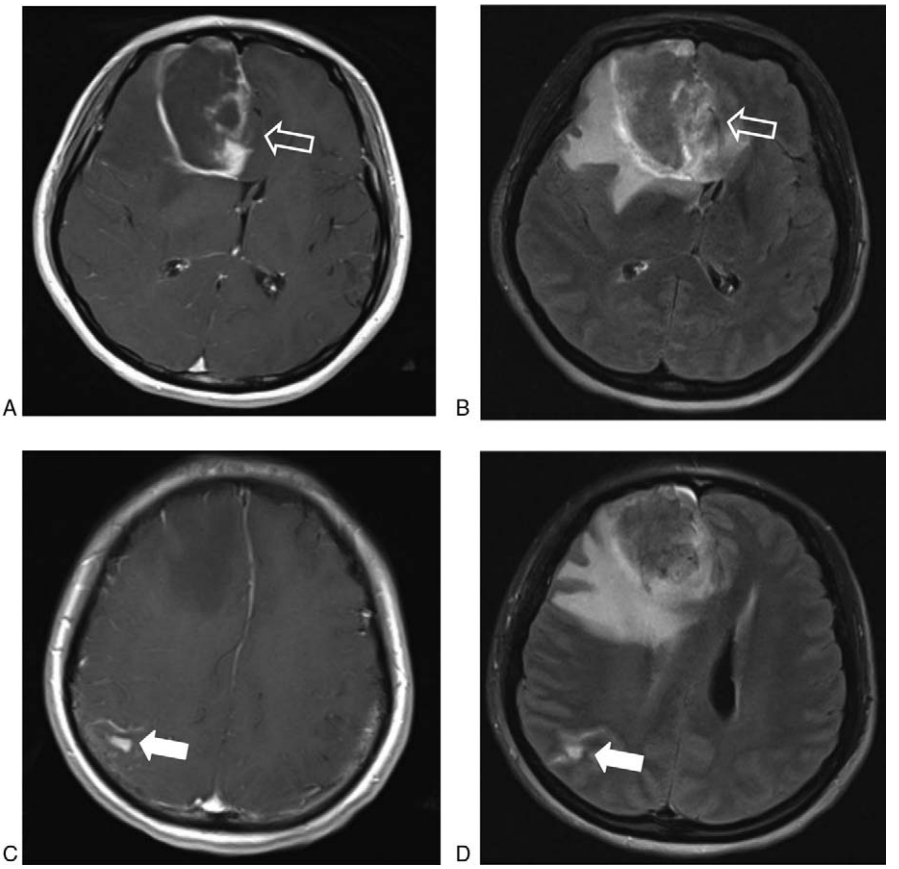

Figure 1. Magnetic resonance imaging (MRI) scan of the brain. (A) Postcontrast T1WI image showed a lesion in the right frontal lobe with ring-like enhancement (*empty arrow*). (B) T2 FLAIR showed a lesion with isointensity or slightly high signal intensity in the right frontal lobe with surrounding edema (*empty arrow*). (C) Postcontrast T1WI image showed the lesion in the right parietal lobe was strongly enhanced (*white arrow*). (D) T2 FLAIR showed a lesion with slightly high signal intensity in the right parietal lobe without apparent edema (*white arrow*).

had been treated with prednisone and hydroxychloroquine (HCQ). Five years after disease onset, she had lupus nephritis. Methotrexate (MTX) and cyclosporin A (CsA) were added. One and a half years before admission, mycophenolate mofetil (MMF) 1 g twice a day was prescribed instead of MTX and CsA. Physical examination showed neck stiffness. Serum C3 level was 0.64 g/L. Titer of ANA was 1:1000 in speckled pattern. Titer of anti-dsDNA antibody was 364.61 IU/mL (normal range 0–12 IU/mL). Anti-SSA and anti-SSB antibodies were negative. The MRI showed a massive tumor of 60 mm × 47 mm × 34 mm in the right frontal lobe (Fig. 1A, B) and a nodular nidus in the cortex of the right parietal lobe (Fig. 1C, D). Lesion in the frontal lobe was diagnosed with glioma, radiographically. Lesion in the parietal lobe was considered as cerebral infarction. Considering the acute symptoms of intracranial hypertension, gross tumor resection was carried out. Intraoperative frozen section examination found coagulation necrosis as well as atypical cell infiltration. Glioblastoma was diagnosed according to the pathological finding. However, pathological examination postoperatively showed atypical lymphoid cells accumulated in perivascular site (Fig. 2A, B). Immunohistochemical staining for CD20 was positive (Fig. 2C). The Ki-67 proliferation index was 50%. In situ hybridization for EBER was positive (Fig. 2D). She was diagnosed with diffuse large B-cell lymphoma (DLBCL). MMF was discontinued before surgery. Bone marrow biopsy was normal. Positron emission tomography-computed tomography (PET-CT) performed postoperatively showed an increased uptake within the nidus located in the right parietal lobe. SUVmax value was 12.1. She received 6 cycles of chemotherapy with methotrexate, cytarabine, temozolomide and rituximab, and autologous stem cell transplantation (ASCT) subsequently. The symptom of intracranial hypertension was relieved postoperatively, and the patient remained complete remission until this article was written.

3. Discussion

PCNSL is well studied in patients with acquired immune deficiency syndrome (AIDS) or organ transplantation. However, it is rarely diagnosed in rheumatic diseases. Scattered cases of immunodeficiency-related PCNSL have been reported in patients with rheumatoid arthritis (RA), myasthenia gravis, and Crohn disease.[3–5]

Until recently, only 8 cases of SLE accompanied with PCNSL were reported in English literature. Radiographic information was recorded in 7 patients and is summarized in Table 1.[2–8] Among the 7 cases, 3 had multiple lesions. One lesion was infratentorial, while the others were supratentorial. MRI showed homogeneous enhancing lesions in 2 patients, and peripheral enhancing lesions in the other 5 cases. Three cases were considered as infectious diseases initially, including toxoplasmosis, nocardia, and abscess. Mass excision was performed in 2 cases. Detection of EBER was positive in 5 cases and negative in 1.

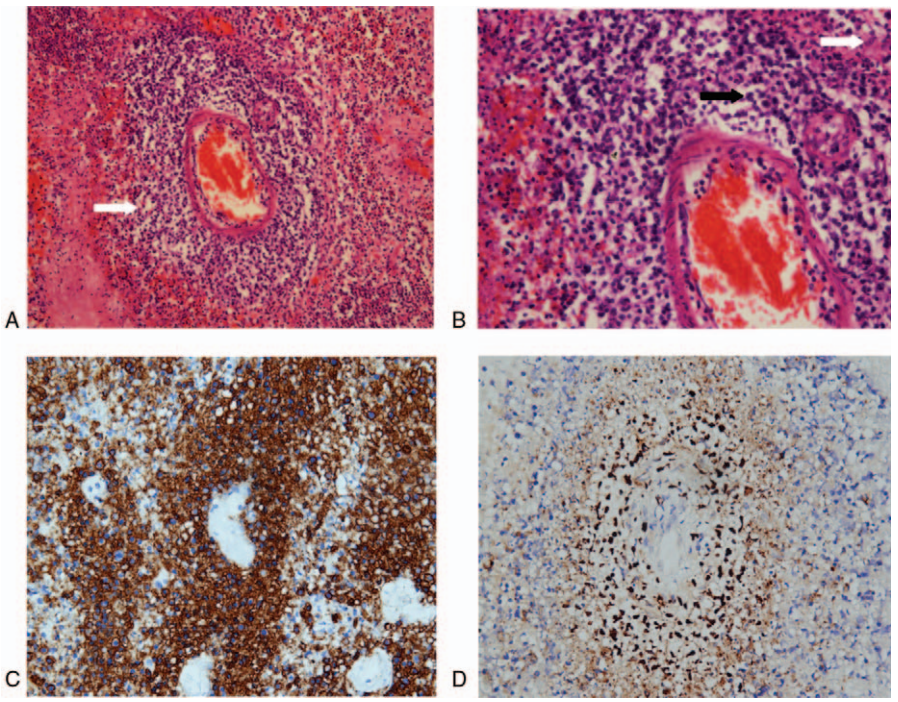

Figure 2. Pathological findings in tumor tissue obtained from brain tumor resection. (A) Atypical lymphoid cells accumulated in perivascular sites (*white arrow*). Haematoxylin-eosin (HE) stain. Original magnification × 200. (B) Lymphoma cells showed medium-to-large sized nuclei, typically with small nucleoli (*white arrow*) and nuclear fission (*black arrow*). HE stain. Original magnification × 400. (C) Immunohistochemistry (IHC) staining demonstrated extensive membranous expression of the B-cell antigen CD20 (*brown*). Original magnification × 200. (D) *In situ* hybridization (ISH) staining for EBV-encoded RNA (EBER) showed strong positivity within the tumor cells (*brown*). Original magnification × 200.

Table 1

Summary of the case reports of PCNSL in patients with SLE.

				Radiographic findings						
Study	**Age/ Sex**	**Duration of SLE**	**SLE therapy**	**No. of lesions**	**Size of the largest lesion**	**Location**	**T1WI**	**T2WI**	**Postcontrast**	**FLAIR**
Dasgupta et al[3]	58/F	1 y	MMF for 1 y	2	3 cm	Both basal ganglia	–	–	Peripheral enhancement	–
Finelli et al[4]	42/F	13 y	AZA for 6 y, CTX for 1 y, and MMF for 6 y, consecutively	Multiple	Not mentioned	Pons and cerebellum	–	–	Ring-enhancing lesions	Edema of pons and cerebellum
Tsang et al[5]	43/F	16 y	MMF for 2 y and AZA for 6 y, consecutively	1	1.5 cm x 1.4 cm x 1.6 cm	Right frontal lobe	Isointense to grey matter	Isointense to grey matter	Rim enhancement	–
Balci et al[2]	56/F	6 y	MMF for 2 y	1	4.7 cm x 5.7 cm	Left parietal lobe	Isointense with mild hyperintensity in the border	–	Ring-like enhancement	Diffuse vasogenic edema surrounding the lesion
Biasiotta et al[6]	67/F	30 y	Intermittent prednisone treatment	1	1 cm	Hypothalamus	–	–	Homogeneous hyperintensity	–
Tse et al[7]	28/F	Not mentioned	MMF for 11 y	1	3.9 cm x 6.4 cm x 4.7 cm	Left frontal lobe	Lesion discovered by CT scan had thin contrast-enhancing rims and nonenhancing central areas with perifocal edema.			
Woolf et al[8]	54/F	21 years	AZA for 9 mo	Multiple	Not mentioned	Right temporal and parietal lobes	CT scan showed homogeneously enhancing lesion.			

AZA = azathioprine, CT = computed tomography, CYC = cyclophosphamide, FLAIR = fluid-attenuated inversion recovery, MMF = mycophenolate mofetil, PCNSL = primary central nervous system lymphoma, SLE = systemic lupus erythematosus, T1WI = T1-weighted image, T2WI = T2-weighted image.

SLE per se is a disease of immune disorder. Chronic inflammatory state, activation of oncogenes, and impairment of immunosurveillance promote the development of malignancy.[6] The risk of NHL increases in patients with SLE. DLBCL is the most frequent, accounting for nearly 90% of the cases.[7] Besides, the increasing risk of lymphoma could be partially attributed to antirheumatic therapy. It is reported that the incidence of central nervous system (CNS) post-transplant lymphoproliferative disease was the highest in renal transplant patients who took MMF.[8] All the lupus patients who were reported to develop PCNSL had taken MMF. Time interval from the initial use of MMF to the onset of PCNSL varied from 1 year to 11 years. Different from previous reports, the patient in our case also took MTX and CsA. The use of azathioprine (AZA), cyclophosphamide (CYC), and MTX has been reported to increase hematological cancer risk in SLE.[9] In particular, most cases of MTX-associated lymphoma are B-cell lymphoma with extranodal involvement.[10] Therefore, the development of PCNSL in the present case could be cocktail effect of the use of multiple immunosuppressant. The causal relationship needs to be evidenced with further research.

Our report reinforced the disparity in radiographic manifestation of PCNSL in immunodeficiency patients. MRI of PCNSL in immunocompetent patients usually displays hypointensity signal in T2-weighted image (T2WI) and homogeneous postcontrast enhancement in T1WI, which is different from that of glioma. However, 5 of 7 reviewed cases and our patient showed ring-like enhancing lesions, suggesting that noncanonical manifestation of PCNSL was relatively common in patients with SLE. PCNSL in immunocompromised hosts contains blood products or necrosis, so it may present heterogeneous contrast enhancement. It is also reported that morphological differentiation between PCNSL and glioma by MRI is difficult. Lesion of PCNSL can locate supra- or infra-tentoria, involve basal ganglia or cerebral cortex, and infiltrate diffusely.[11] In our case, 2 lesions in the right hemisphere were considered as glioma and ischemic stroke before surgery, respectively. PET-CT demonstrated an increasing uptake within the lesion located in the right parietal lobe and SUVmax was moderately elevated. Taking histopathological findings into consideration, we speculate that both lesions in the right hemisphere were lymphoma-related.

Chemotherapy is the primary treatment for PCNSL. However, recent research suggested subtotal or gross resection in combination with chemotherapy may prolong progression-free survival.[12] Surgery is considered in the case of large, compressive lesion.[13] Compared with previous reports, the tumor volume in our case was the largest with remarkable midline shift, which made surgery necessary.

This report highlights the possibility of PCNSL in lupus patients treated with combined immunosuppressant. Strict vigilance must be maintained against the differential diagnosis with glioma.

Author contributions

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Writing – review & editing: Lei Su.

References

[1] Villano JL, Koshy M, Shaikh H, et al. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. Br J Cancer 2011;105:1414–8.
[2] Balci MA, Pamuk GE, Unlu E, et al. Development of primary central nervous system lymphoma in a systemic lupus erythematosus patient after treatment with mycophenolate mofetil and review of the literature. Lupus 2017;26:1224–7.
[3] Vernino S, Salomao DR, Habermann TM, et al. Primary CNS lymphoma complicating treatment of myasthenia gravis with mycophenolate mofetil. Neurology 2005;65:639–41.
[4] Podolsky DK, Gonzalez RG, Hasserjian RP. Case records of the Massachusetts General Hospital (Case 8-2006). N Engl J Med 2006;354:1178–84.
[5] Fukushima M, Katayama Y, Yokose N, et al. Primary central nervous system malignant lymphoma in a patient with rheumatoid arthritis receiving low-dose methotrexate treatment. Br J Neurosurg 2013;27:824–6.
[6] Wang HL, Zhou YM, Zhu GZ, et al. Malignancy as a comorbidity in rheumatic diseases: a retrospective hospital-based study. Clin Rheumatol 2018;37:81–5.
[7] Bernatsky S, Ramsey-Goldman R, Labrecque J, et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. J Autoimmun 2013;42:130–5.
[8] Crane GM, Powell H, Kostadinov R, et al. Primary CNS lymphoproliferative disease, mycophenolate and calcineurin inhibitor usage. Oncotarget 2015;6:33849–66.
[9] Bernatsky S, Boivin JF, Joseph L, et al. The relationship between cancer and medication exposures in systemic lupus erythematosus: a case-cohort study. Ann Rheum Dis 2008;67:74–9.
[10] Georgescu L, Quinn GC, Schwartzman S, et al. Lymphoma in patients with rheumatoid arthritis: association with the disease state or methotrexate treatment. Semin Arthritis Rheum 1997;26:794–804.
[11] Malikova H, Koubska E, Weichet J, et al. Can morphological MRI differentiate between primary central nervous system lymphoma and glioblastoma? Cancer Imaging 2016;16:40.
[12] Weller M, Martus P, Roth P, et al. German PCNSL Study GroupGerman PCNSL Study Group. Surgery for primary CNS lymphoma? Challenging a paradigm. Neuro Oncol 2012;14:1481–4.
[13] Hoang-Xuan K, Bessell E, Bromberg J, et al. Diagnosis and treatment of primary CNS lymphoma in immunocopetent patients: guidelines from the European Association for Neuro-Oncology. Lancet Oncol 2015;16:e322–32.