Clinical Case Report

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Adrenal relapse of primary central nervous system diffuse large B-cell lymphoma

A case report

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Abstract

Rationale: Primary central nervous system lymphoma (PCNSL) is a rare form of non-Hodgkin lymphoma with a dismal outcome. Most patients relapse in intracranial sites and <5% of patients relapse in extracranial sites. Here, we present the first case of PCNSL with an adrenal relapse.

Patient concerns: A 72-year-old woman, first presented 7 years ago with complaints of headache and dizziness.

Diagnoses: Enhanced magnetic resonance imaging revealed the mass within the splenium of the corpus callosum. On histological examination, there was a diffuse growth pattern of neoplastic cells in the brain biopsy. Immunohistochemistry and flow cytometric analysis demonstrated that the neoplastic cells were of B-cell lineage.

Interventions: The patient underwent methotrexate-based chemotherapy and whole-brain radiotherapy after the initial diagnosis of primary central nervous system-large B-cell lymphoma (CNS-DLBCL).

Outcomes: After 4 years of clinical remission, the patient was diagnosed with endometrial cancer. Interestingly, a radiological study following the treatment of endometrial cancer demonstrated a right adrenal mass, which was suspicious for malignancy. Morphologic examination and immunohistochemistry studies confirmed the diagnosis of diffuse large B-cell lymphoma. A fluorescent in situ hybridization panel for lymphoma showed rearrangement of Immunoglobulin heavy chain (IGH) and B-cell lymphoma 6 (BCL6), respectively, suggesting fusion of BCL6/IGH. Immunoglobulin kappa analysis demonstrated a common origin for the brain and adrenal lesions, which led to the final diagnosis of an adrenal relapse of CNS-DLBCL.

Lessons: PCNSL is a highly infiltrative neoplasm, particularly at relapse. To the best of our knowledge, this is the first case of CNS-DLBCL with adrenal relapse. Considering the poor outcome of CNS-DLBCL, molecular genetic studies should be done to identify a common origin for the primary and secondary lesion.

Abbreviations: CNS = central nervous system, CNS-DLBCL = primary central nervous system-large B-cell lymphoma, CT = computed tomography, CVAD = fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, DLBCL = diffuse large B-cell lymphoma, MRI = magnetic resonance imaging, MTX = methotrexate, NHL = non-Hodgkin lymphoma, PAL = primary adrenal lymphoma, PCNSL = primary central nervous system lymphoma, R-CHOP = rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone, WBRT = whole-brain radiotherapy.

Keywords: central nervous system, differential diagnosis, diffuse large B-cell lymphoma, morphology, prognosis

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1. Introduction

Primary central nervous system lymphoma (PCNSL) is a rare form of non-Hodgkin lymphoma (NHL) comprising 2.2% of all central nervous system (CNS) tumors.[1] Of PCNSL exclusively involving the brain, spinal cord, eyes, meninges, and cranial nerves, 90% to 95% are classified histologically as diffuse large B-cell lymphoma (DLBCL). Clinically, PCNSL commonly presents as a solitary mass and accounts for 3% of all primary brain tumors with a median age at onset of 52 years and a male to female ratio of 1.2 to 1.7:1.[2] Most cases of PCNSLs are sporadic; however, the incidence increases with age. In general, CNS-DLBCL is an aggressive malignancy, with overall long-term survival rates of approximately 20% to 40%.[3] CNS-DLBCL could exhibit unique biological features and characteristic clinical behaviors. Clinical outcomes have improved following the advent of new chemoradiation protocols incorporating high-dose methotrexate (MTX) in the mid-1980s, but disease relapse and adverse neurocognitive sequelae remain major clinical challenges.[3] Herein, we report a very rare case of PCNSL with adrenal relapse after approximately 4 years after the first diagnosis of CNS-DLBCL. To the best of our knowledge, this is the first case of PCNSL with an adrenal relapse.

2. Case presentation

The patient is a 72-year-old woman who first presented in March 2010 with complaints of headache, multiple falls, and "feeling off balance." Magnetic resonance imaging (MRI) findings showed an enhancing mass within the splenium of the corpus callosum measuring 3.2×1.3 cm (Fig. 1A). A stereotactic biopsy was obtained and microscopic examination demonstrated a diffuse growth pattern of neoplastic cells. The neoplastic cells were medium sized to large with irregular nuclear contours and scant cytoplasm (Fig. 2B), which were consistent with lymphoma. Cytological examination of the fluid showed collections of large mononuclear cells, 3 to 4 times the size of mature lymphocytes with high nuclear to cytoplasmic ratio, round nuclei with open chromatin, and 1 or 2 nucleoli. Immunohistochemistry studies demonstrated that the neoplastic tumor cells were diffusely positive for CD45, PAX-5, CD20 (Fig. 2B, inset), MUM-1, BCL-6, and BCL-2, but negative for CK (pan), CD3, CD5, CD30, CD138, CD56, and CD10. Flow cytometric analysis of the cerebrospinal fluid and the vitreous fluid showed an abnormal population of predominantly lambda-restricted medium-sized lymphocytes expressing the B-cell antigens CD19 and CD20. The morphology and immunophenotype support the diagnosis of primary CNS-DLBCL (nongerminal center subtype).

The patient was treated with 9 cycles of high-dose MTX and rituximab from November 2011 to July 2012 and the patient also received whole-brain radiotherapy (WBRT, 23.4 Gy with boost to bilateral orbits 34.2 Gy). Serial MRI monitoring of the brain on April 2016 demonstrated no evidence of progression, which indicated a clinical remission of approximately 4 years. But computed tomography (CT) surveillance imaging suggested the presence of endometrial carcinoma with a right adrenal mass measuring 2.1×1.7 cm, which was suspicious for malignancy (Fig. 1B). Biopsy of right adrenal was performed and the tumor cells were morphologically similar to those present in the patient's previous brain biopsy (Fig. 2A) and shared a similar immunophenotype positive for CD20 (Fig. 2A, inset), c-MYC (Fig. 2C), and cyclin D1 (Fig. 2F), Ki67 staining showed that approximate 80% positive for tumor cells (Fig. 2D). A fluorescent in situ hybridization lymphoma panel was negative for the fusion gene CCND1/IGH, negative for rearrangement of MYC and BCL2, but showed rearrangement of Immunoglobulin heavy chain (IGH) and B-cell lymphoma 6 (BCL6), suggesting fusion of BCL6/IGH. To exclude a possible aggressive variant of mantle cell lymphoma, SOX11 staining was performed, and it was negative in the tumor cells (Fig. 2E). Immunoglobulin kappa analysis in the brain and adrenal tissues demonstrated the same clonal origin (Fig. 3A, B). According to the World Health Organization classification, the lesion was classified as a double-expressor large B-cell lymphoma, which is known to generally have an aggressive clinical course. The patient received a

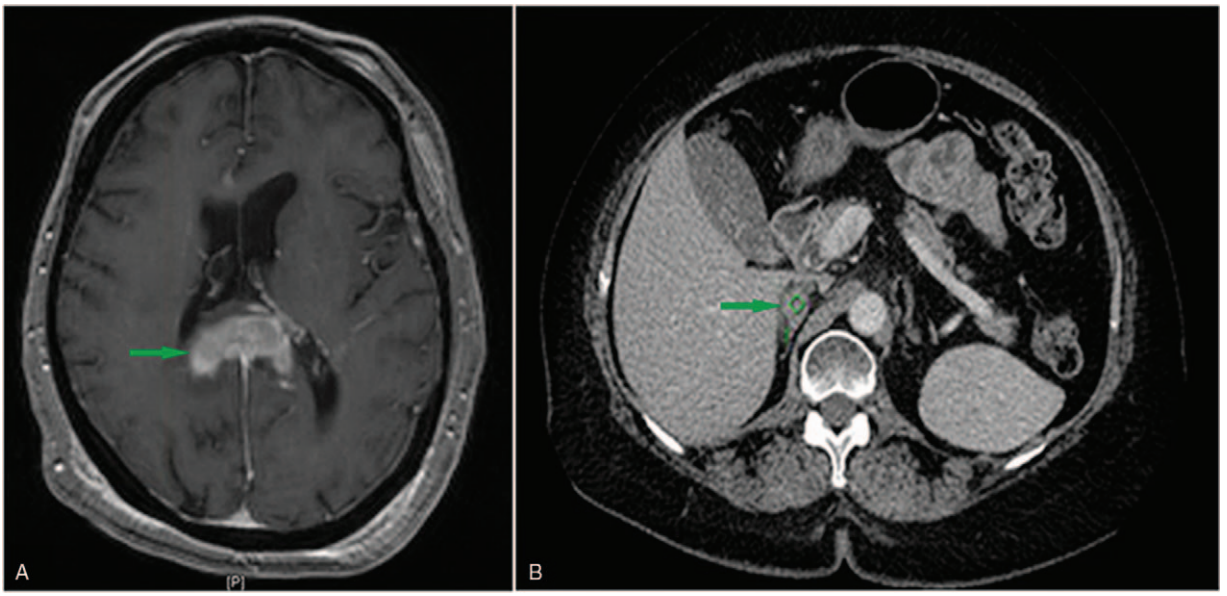

Figure 1. A, Magnetic resonance imaging (MRI) image showed the enhancing mass within the posterior body and splenium of the corpus callosum measuring $3.2 \times 1.4 \times 1.0$ cm, marked with green arrow. B, Computed tomography (CT) image showed the right adrenal nodule measuring 2.1×1.7 cm, marked with green arrow.

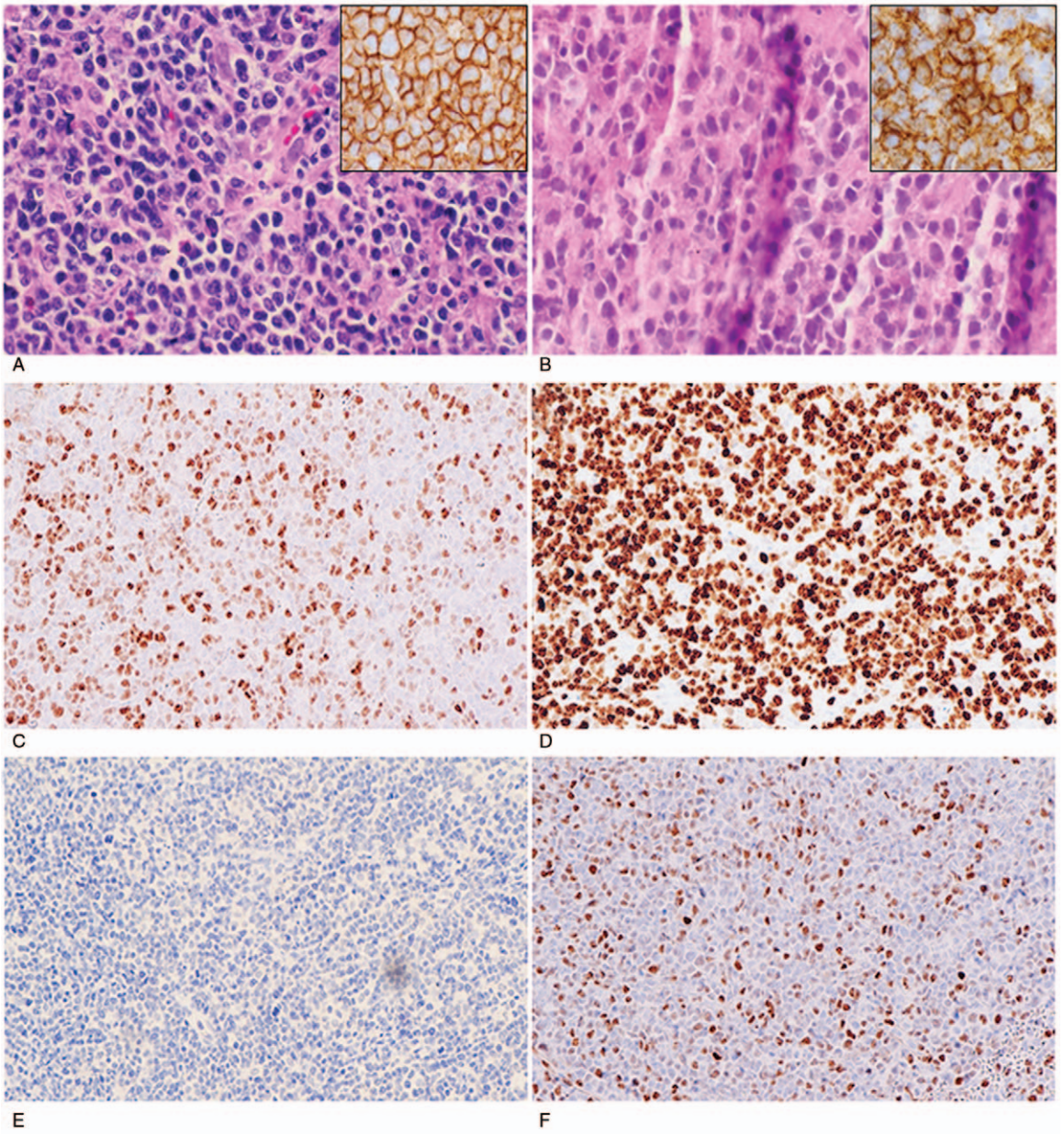

Figure 2. Brain (A) and adrenal (B) tissues were effaced by diffuse growth pattern tumor cells with medium-sized to large and great atypia. The inset figure on the upper left quadrant shows strong positive of CD20 (A and B, 400×). Ki67 staining shows high proliferative index with approximately 90% (C, 200×). MYC staining shows approximate 60% nuclear staining (D, 200×). cyclin-D1 shows approximate 25% nuclear staining (E, 200×). Negative staining for Sox-11 which is helpful to rule out aggressive variant of mantle cell lymphoma (F, 200×).

course of rituximab-hyper CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) on August 2016 and transitioned to R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone) chemotherapy (total cycles = 5) with a subsequent Positron emission tomography (PET) CT scan showing a complete response to therapy after the treatment. The patient complained of visual change in the left eye at a follow-up evaluation 12 months later and a radiological study indicated the presence of an intraocular recurrence.

3. Discussion

PCNSL is characterized by dissemination of aggressive NHL within the brain, cranial nerves, leptomeninges, cerebrospinal fluid, intraocular structures, and spinal cord. Approximately 90% to 95% of PCNSL tumors are large B-cell lymphomas; other less common cell lineages include T-cell (2%), lymphoblastic, Burkitt, and marginal zone lymphoma.[4] It is generally accepted that the radiographic features of PCNSL are similar to gliomas, which commonly present as a solitary mass with vasogenic edema and mass effect. However, PCNSL is a highly infiltrative neoplasm, particularly at relapse, prompting its characteristic "whole-brain disease" descriptor.[5] Attention should be paid to immunosuppressed patients who tend to have a 2-fold frequency of multiple lesions. The best established risk factors for CNS involvement of NHL are acquired or congenital immunodeficiency states. Because of the infiltrative growth pattern, it is almost impossible to completely resect the tumor even it presents

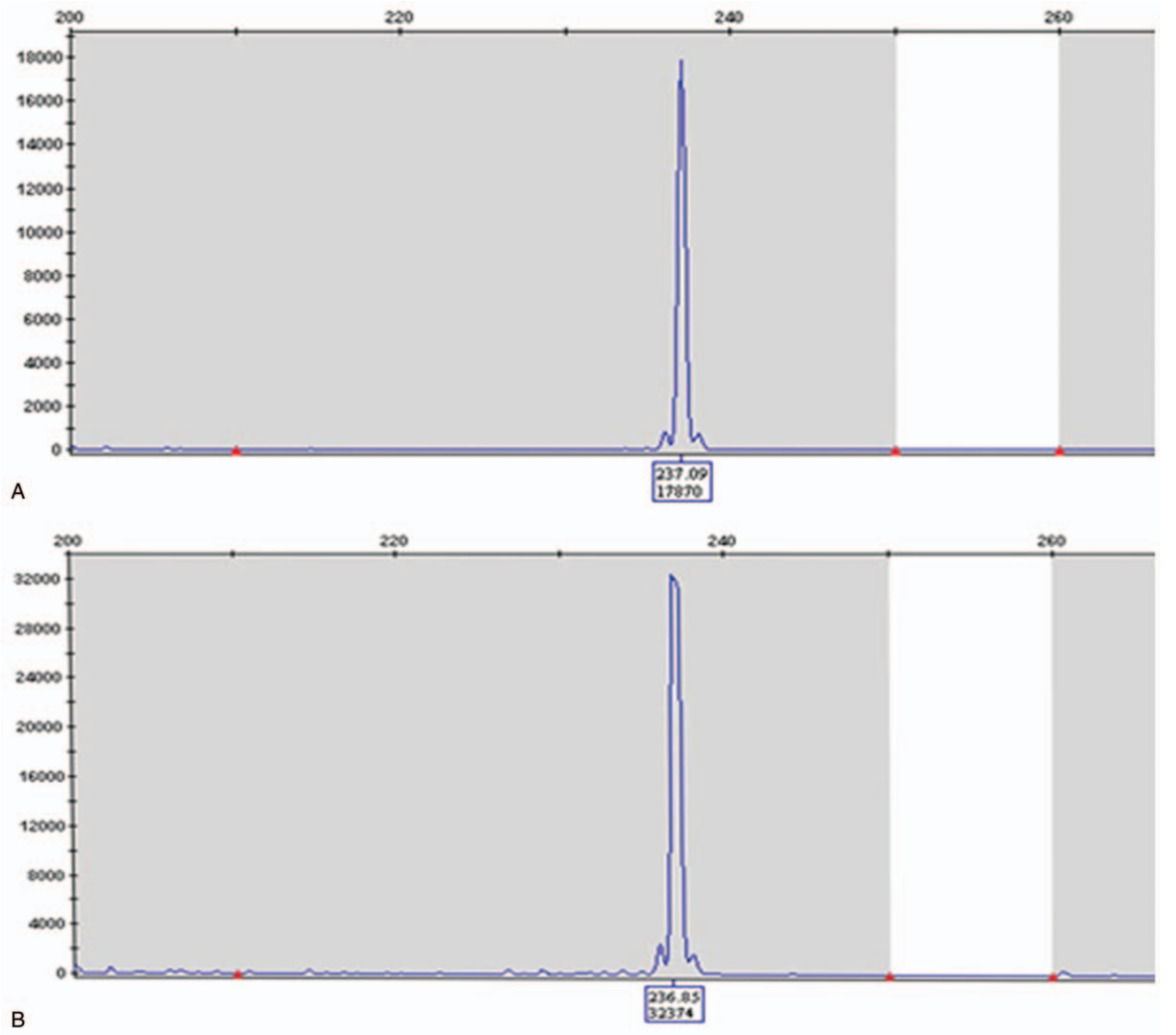

Figure 3. Immunoglobulin kappa analysis in the brain (A) and adrenal (B) tissues demonstrate the same origin.

as a single lesion. For the differential diagnosis, primary brain tumors, such as glioma and meningioma would not be difficult to exclude by morphology or immunohistochemistry. One of the characteristic histological features of PCNSL is that of angiotropism, in which lymphoma cells accumulate around small and medium-sized blood vessels, contributing to disruption of the blood-brain barrier, and enabling their radiographic detection by contrast enhancement.[5]

Data on the relapse of PCNSL are limited and prognosis is poor, with a 2- to 4-month survival.[6] Relapse is seen in 35% to 60% of patients 2 years after the initial diagnosis and in 4% of patients 5 years after the initial diagnosis.[7] Most patients relapse in intracranial sites, but systemic dissemination occurs in 7% to 10% of patients with advanced PCNSL and tends to involve extranodal organs, including the kidneys, skin, and testicles.[7] To the best of our knowledge, this is the first case published in the English literature of CNS-DLBCL with an adrenal relapse. Since the patient had a relatively long clinical remission after her initial chemotherapeutic treatment (4 years), primary adrenal lymphoma (PAL) should be taken into consideration as an important differential diagnosis. In general, PALs are considerably rare, contributing to 3% of all NHLs, and only about 100 cases have been previously reported in the literature. Interestingly, bilateral adrenal glands are involved in 70% of PAL cases.[8] PAL is typically a highly aggressive malignancy[9]; most cases are usually DLBCLs. Age, tumor size, adrenal insufficiency, lactate dehydrogenase level, and performance status of the patient can significantly influence prognosis.[8,10,11] Interestingly, we also note that PAL could relapse with secondary CNS lymphoma, but only 6 cases of PAL relapse with CNS lymphoma have been reported. We still do not know if there is a link between CNS and adrenal lymphoma because of the limited number of cases reported.

The standard management of PCNSL includes surgery, radiotherapy, and chemotherapy. According to the previous case reported, the benefits of surgery are controversial. Bataille et al[12] demonstrated that CNS lymphoma resection provides no survival benefit compared to biopsy alone, and potentially increases the risk of postoperative deficits. Notably, a retrospective analysis of the German PCNSL Study Group-1 Trial provided the first evidence that aggressive resection of CNS lymphoma correlated with improved progression-free survival.[13] Other have suggested that the maximum safe resection of lesions may provide immediate relief of mass effect, facilitate glucocorticoid taper, potentially eliminate drug-resistant tumor clones, and provide substantial clinical benefit without

contributing to neurological deficits, particularly when performed with modern neurosurgical mapping techniques.[14] In our case, the clinicians choose not to use surgery as the primary treatment because they preferred to treat the PCNSL as they do other lymphoid malignancies with aggressive infiltrating patterns, although the imaging study did not show that pattern (infiltration was only seen on histologic examination). The patient received chemotherapy and WBRT.

The standard chemotherapy regimen includes MTX-containing combination chemotherapy and a complete clinical response can be achieved in 30% to 87% of patients. The addition of high-dose cytarabine to MTX seems to increase both response rate and response duration.[15] WBRT is highly effective in the elicitation of immediate responses in CNS lymphoma and therefore brain radiotherapy has historically been of value.[14]

For the therapeutic options in recurrent CNS lymphomas, dose-intensive chemotherapy with autologous stem cell transplant has become an attractive option in the management of relapsed CNS lymphoma.[16–19] Wang et al suggest that the treatment of relapsed CNS lymphomas should depend on whether the primary lymphoma was MTX sensitive or not. The High-Dose Methotrexate (HD-MTX) should be taken into consideration as the treatment for the relapse of lymphoma if the PCNSL is sensitive to HD-MTX.[20–22] While in our case, the patient was not treated with HD-MTX after the relapse in her right adrenal but instead with rituximab-hyper CVAD and R-CHOP, the follow-up information including subsequent visual changes and intraocular recurrence reflect the dismal course of this entity.

4. Conclusions

In conclusion, we described an extremely rare case of a visceral relapse of a primary CNS-DLBCL in the adrenal gland of a 72-year-old patient. Relapse of CNS-DLBCL is almost always confined to the CNS, and systemic relapse is extremely uncommon. Although a few cases of PAL with dissemination to CNS have been reported in the literature, systemic relapse of CNS-DLBCL in the adrenals has not been described. Tissue tropism of the lymphoma cells between CNS and a neuroendocrine organ such as adrenal gland may be an interesting hypothesis, and worth investigating in the future.

Author contributions

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