

Cyclophosphamide-induced Posterior Reversible Encephalopathy Syndrome in a Patient with Lupus Nephritis

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Posterior reversible encephalopathy syndrome (PRES) is a neurologic condition characterized by vasogenic edema on neuroimaging and is associated with the setting of severe hypertension, eclampsia, autoimmune disease, malignancy, and immunosuppressive drugs. We report on a 42 year-old female systemic lupus erythematosus patient who presented altered consciousness, seizure, and visual disturbance after cyclophosphamide pulse therapy. Magnetic resonance imaging (MRI) showed multi-focal high signal intensity le-

sions in the parieto-occipital cortex bilaterally and in the subcortical white matter. Her condition was improved and her MRI lesions were resolved after aggressive blood pressure control and high-dose steroid treatment. It is possibly the first reported case of PRES in a patient with lupus, treated with cyclophosphamide pulse therapy during a nephritis flare in Korea.

Key Words. Posterior reversible encephalopathy syndrome, Systemic lupus erythematosus, Cyclophosphamide

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a neurologic condition identifiable by characteristic clinical manifestations such as acute headache, altered consciousness, seizure, visual disturbance, and typical magnetic resonance imaging (MRI) features (1). PRES was initially described such as a reversible posterior leukoencephalopathy syndrome (RPLS), reversible posterior cerebral edema syndrome, hyperperfusion encephalopathy and occipital-parietal encephalopathy (1,2). RPLS was a term initially coined by Hinchey et al. when these investigators described 15 patients treated with a reversible syndrome characterized by an acute or subacute onset of altered mental status, headache, seizure, and/or loss of vision associated with white matter changes, mostly in a bilateral parieto-occipital distribution on a MRI (1). These patients had different underlying conditions such as eclampsia, immunosuppressive therapy, organ transplantation, hypertensive encephalopathy and systemic lupus erythematosus (SLE) (1). Then, it has been suggested that PRES does not

implicate a single disease, although the symptoms, signs, and neuroradiologic findings related to PRES do not markedly differ (2).

It can present as a neurological emergency and may lead to permanent brain injury and sequelae without prompt treatment, but with prompt treatment almost always resolves within 2 or 3 weeks. PRES is mainly caused by hypertensive encephalopathy, eclampsia, autoimmune disease, and some immunosuppressive therapies. However, PRES after a cyclophosphamide pulse in a patient with SLE has not been reported in Korea. We describe a patient with SLE on cyclophosphamide therapy that developed acute neurologic changes initially suggesting cerebritis or stroke. These findings were subsequently found to be secondary to PRES. We also discuss the contributing factor, treatment and therapeutic implications for separating PRES from stroke and cerebritis in this report.

Case Report

A 45-year-old woman presented with malaise, fatigue and

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weakness. A chest PA showed interstitial lung disease. Anti-double stranded DNA (anti-dsDNA) was present and anti-nuclear antibodies (ANA) were positive (1 : 320). The laboratory finding showed BUN 41.7 mg/dL, creatinine 2.68 mg/dL. She had thrombocytopenia ($68 \times 10^3/\mu\text{L}$) and massive proteinuria (5.56 g/day), then was diagnosed with systemic lupus erythematosus. She had biopsy-proven diffuse proliferative glomerulonephritis (WHO class III and V) and hypocomplementemia C3: 39 mg/dL (reference 90~180 mg/dL), C4: 5 mg/dL (reference 10~40 mg/dL). Her anti-cardiolipin, anti- β 2 glycoprotein I and lupus anticoagulant antibody were negative and coagulation test was normal. Treatment with monthly cyclophosphamide pulse therapy followed by prednisolone reversed renal failure. On 2 days after 2 cycles of cyclophosphamide when she was being treated with prednisolone 15 mg/day, she complained of nausea, diplopia and motor weakness in the lower part of both legs. However, on the exam of the fundus and lower leg motor functions, there were no significant abnormalities. After 3 days of that time, she suddenly developed hypertension (190/100 mmHg) with vomiting, showed a generalized seizure that lasted for 3 minutes and then was confused and disoriented. The laboratory studies disclosed white blood cell (WBC) $350/\text{mm}^3$, hemoglobin 10.1 g/dL, platelet $70 \times 10^3/\mu\text{L}$, serum albumin 2.9 g/dL, BUN 20.7 mg/dL, creatinine 1.26 mg/dL, ESR 12 mm/hr, C-reactive protein 32.7 mg/L (reference 0~5 mg/L), ANA 1 : 160 positive, anti-dsDNA Ab 5 (reference <4 IU/mL), C3: 91 (90~180 mg/dL), C4: 36 (10~40 mg/dL), and urine protein 1.18 g/day. In peripheral blood smear finding, there was no evidence of microangiopathic hemolytic anemia. Her SLEDAI (SLE dis-

ease activity index) was 14. Heart rate was 112/min and body temperature was normal. The brain computed tomography (CT) scan showed asymmetrical diffuse low density in bilateral parieto-occipital lobes, frontal lobes and basal ganglia (Figure 1). The MRI showed asymmetrical diffuse high signal intensities on T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences, involving the bilateral parieto-occipital lobes, frontal lobes and basal ganglia (Figure 2). The MRI findings were thought to be indicative of vasogenic edema, suggesting possible early Brain blood barrier (BBB)

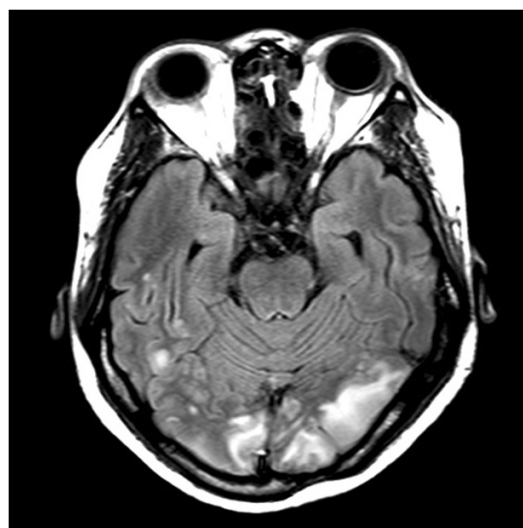


Figure 2. Brain FLAIR MRI imaging showed asymmetrical diffuse high signal intensities lesions in bilateral parieto-occipital lobes.



Figure 1. Brain CT imaging showed asymmetrical diffuse low density lesions in bilateral parieto-occipital lobes.



Figure 3. Follow-up Brain FLAIR MRI after 7 days of imaging showed marked resolution process of the preexisting diffuse high signal intensities lesions.

disruption. The intracranial magnetic resonance angiography (MRA) showed no evidence of significant stenosis or occlusion at carotid bifurcation and intracranial vessels. No thrombosis could be identified in the brain images. Anticonvulsive and antihypertensive medications were given and one more seizure occurred thereafter. Anti-hypertensive therapy normalized her arterial blood pressure. The patient also received intravenous methylprednisolone 500 mg/day over 3 days, followed by prednisolone 60 mg/day. She showed initial improvement of her neurological symptoms on the 3rd day and her consciousness was normal. She fully recovered and was discharged after 20 days and the MRI images also showed marked resolution process (Figure 3).

Discussion

PRES may occur any time in the course of lupus. In a previous series (3), PRES was reported in established cases of SLE with mean disease duration of 61.8 ± 53.6 months. However, in a recent study, it occurred considerably earlier (12.2 ± 13.2 months) in the course of lupus. SLE is known to be aggressive in the early periods of the illness (4). Similarly in our case, the duration is only 2 months and it takes place in the very early periods of the disease.

Headache and seizure are the most common neuropsychiatric manifestations of SLE, which have a variety of etiologies, and PRES should always be a differential diagnosis in acute headache in appropriate clinical settings (5). In view of the diffuse expression of lesions and cortical involvement, the occurrence of seizure and the diffuse edema causing headache is well explained. PRES is associated with diffuse slowing on electroencephalography, consistent with diffuse encephalopathy.

The proposed pathogenic mechanisms of PRES are disordered cerebral autoregulation and endothelial dysfunction (1,6) leading to fluid extravasation into the interstitium at the arterial territory periphery due to overdilatation of these cerebral vessels. The relatively poor sympathetic innervation of the posterior circulation may be related to a predilection for brain edema in this region (7). Because of the heterogeneity of the associations of disorder, the exact pathogenesis in lupus is undetermined, as different mechanisms may etiologically be important in different clinical situations. This is probably the reason for the occurrence of PRES in the setting of normal or mild elevation of blood pressures, where endothelial dysfunction may be due to cytotoxic therapy or vasculitis (8). In the literatures, PRES occurred generally in patients with SLE had high disease activity, so the possibility that high disease activity itself can cause autoimmune or hypoxic endothelial dysfunction in the central nervous system (3).

Severe hypertension and renal failure are known risk factors for the development of PRES (1). However, in our case, we found that severe hypertension is not an invariable association, indicating that it may not be in the extended spectrum of hypertensive encephalopathy that may be seen in SLE with renal involvement. It is interesting that case reports of PRES in normotensive patients with SLE were ascribed to high doses of corticosteroids (1,8) or to cytotoxic therapy with cyclophosphamide (CYC) (9). Occurrence of PRES in normotensives and treatment-naïve patients may explain the endothelial dysfunction due to disease activity playing an important pathogenic role (10).

Our patient was normotensive and receiving 2 cyclic CYC and intermediate dose of corticosteroids when she developed PRES. The use of immunosuppressants is considered one of the risk factors; cyclosporine is one of the most common immunosuppressants associated with PRES and is well studied (11). The mechanism is thought to be mediated through mitochondrial dysfunction (12). High dose of corticosteroids are implicated in the occurrence of PRES by predisposing a patient to hypertension and fluid overload (13). The mechanism of CYC that predisposes a patient to PRES is not clearly known. It can cause water toxicity in the first 2 days after infusion due to an unknown action on renal function that is not explained by the antidiuretic hormone; a similar role may be implicated in PRES in our patient who developed it 2 days after infusion (14). We could not find schistocyte in patient's PBS, then could exclude the possibility of thrombotic thrombocytopenic purpura.

Up to date, very few cases of PRES in patients treated with combination chemotherapy including cyclophosphamide, prednisone, vincristine and adriamycin have been reported and other cases with the combination of hydroxy-chloroquine, steroids and cyclophosphamide or adriamycin, cytarabine have been published as well, but in all cases the authors could not determine which drug (or combination) was the cause (15). In our case, we could not conclude whether cyclophosphamide was the cause of PRES, but it was most likely because our patient recovered from nephritis flare up, had low disease activity scores if seizure was considered to be caused by PRES and was received with intermediate dose of steroid, and her blood pressure was normotensive.

Renal failure with a state of fluid overload is a well-known cause for PRES (1). In the literature review by Leroux et al, 91% of patients had renal involvement, with renal insufficiency in 84% of the cases (6). However, the fact that only one in 13 patients had renal failure in another study emphasizes that disease activity rather than fluid overload could

be responsible for the occurrence of PRES.

In a previous study, the relationship between PRES and the presence of antiphospholipid antibodies difficult to assess. However, 12 of 17 cases tested positive for anticardiolipin antibodies (11), in comparison to 2 of 8 in another study (4). There is need for further study to fully describe the relationship between antiphospholipid antibodies and PRES. In our case, antiphospholipid antibodies of the patient were negative.

MRI predominantly showed transient, white matter hyperintensities on T2-weighted images in PRES (1). Diffusion-weighted images reveal an increased diffusion coefficient indicating vasogenic edema. The advent of MRI has increased the awareness of PRES and gray matter involvement has been shown to be present. The posterior circulation is typically involved, but the anterior circulation may also have affected some patients. In recent years, another magnetic resonance (MR) technique, diffusion-weighted imaging (DWI), has gained importance in the diagnosis of PRES. FLAIR sequences, where the cerebral spinal fluid signal is suppressed, have been shown to be more sensitive in detecting signal changes due to PRES and FLAIR sequences showed cortical edema in 94% of cases (2). In our case, asymmetrical diffuse high signal intensities on T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences, involving the bilateral parieto-occipital lobes, frontal lobes and basal ganglia was found.

The clinical syndrome is further defined by the reversibility of the above described changes. When performed, patients with seizures do not usually undergo a MRI and the decision to pursue a MRI often is based on its availability and on knowledge about the disease. As knowledge about PRES becomes more widespread, there might be increased recognition and reporting of it.

The mainstay of treatment of PRES is supportive care including appropriate control of hypertension and antiepileptics to control seizure. Our patient was treated with high dose corticosteroids because we could not completely rule out the possibility of neuropsychiatric lupus or vasculitis and also with mycophenolate mofetil as required for controlling lupus disease activity.

Although the general recommendation is to withdraw the offending drug, after control of the acute episode was achieved, but patients had no recurrences with reuse of CYC on follow-up (4). This reiterates that multiple etiologies may be responsible for the occurrence of PRES in SLE patients already undergoing treatment with cytotoxic therapy.

PRES is considered benign and a complete recovery can be expected, but residual deficits are not uncommon, as noted in

previous reports, which can include hemiparesis and death (3,4), then prompt diagnosis and treatment should be done.

PRES occurs in young patients with lupus, especially in the early stages of the disease. Many immunosuppressive drugs are implicated with this syndrome, associated with arterial hypertension in almost all cases. Cyclophosphamide is one of the most widely used immunosuppressive drugs in SLE, with many well described secondary effects, and posterior reversible leukoencephalopathy syndrome could be one of them. Management is predominantly symptomatic treatment. Early diagnosis and management is productive. Without any evidence of infections or severe hypertension, cyclophosphamide might well be considered one of the causes of PRES.

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