# Reversible Posterior Leukoencephalopathy Syndrome in a Patient with Relapsed Hodgkin's Disease: A Case Report

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Reversible posterior leukoencephalopathy syndrome (RPLS) is a distinctive clinicoradiological entity that's characterized by headache, confusion, seizure and frequent visual disturbances. It is associated with certain neuro-radiological findings, and predominantly white matter abnormalities of the parieto-occipital lobes. RPLS has been identified mostly in patients with malignant hypertension, pre-eclampsia and renal insufficiency and in those patients who are using immunosuppressive agents or cytotoxic drugs. We report here on a case of RPLS in a patient who was undergoing chemotherapy. A 49-year-old woman presented with abrupt mental changes and visual disturbances five days after the administration of a chemotherapeutic agent. MRI showed hyper-intense signals on the magnetic resonance (MR) diffusion images in the bilateral temporal, parietal and occipital lobes. The clinical manifestations completely resolved after one week of treatment that consisted of blood pressure control, a negative intake-output balance and the best supportive care. These radiological changes and the reversible clinical manifestations were consistent with RPLS. ***(Korean J Hematol 2009;44:177-181.)***

**Key Words:** Posterior leukoencephalopathy syndrome, Hodgkin disease, ESHAP regimen

## INTRODUCTION

Cancer patients are at high risk of complications during chemotherapy, including changes in mental state. Common causes of acute mental changes in cancer patients are infections, embolic events, the toxicity of anti-neoplastic agents and central nervous system (CNS) malignancies. Chemotherapeutic agents can induce CNS toxicities, and secondary CNS involvement may be a cause of mental changes in patients undergoing treatment for systemic malignant lymphoma. In addition, complications due to cerebrovascular accidents are not rare in elderly patients with poor performance statuses.

Reversible posterior leukoencephalopathy syndrome (RPLS) is a characterized disease that shows diverse symptoms including neurologic abnormalities such as altered mental function, loss of vision, stupor, and seizures. Patients commonly exhibit changes in brain images, including bilateral white matter abnormalities in the posterior regions of the cerebral hemispheres. The pre-

접수 : 2009년 4월 20일, 수정 : 2009년 9월 11일
승인 : 2009년 9월 11일
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viously mentioned complications should be differentiated with RPLS because it is amenable to treatment and reversible. Here we report a case of RPLS in a patient undergoing chemotherapy.

## CASE REPORT

In February 1995, a 49-year-old woman was diagnosed with Hodgkin's lymphoma after biopsy of the right neck lymph node. At that time, the stage was IIA and the subtype was mixed cellularity. First-line chemotherapy was initiated with a CVPP regimen (cyclophosphamide, vinblastine, procarbazine and prednisone). During the first-line chemotherapy, there were no specific complications except the post-herpetic neuralgia by herpes zoster virus infection.

After 4 cycles of first-line chemotherapy, the patient followed the second-line chemotherapy with an ABVD regimen (adriamycin, bleomycin, vinblastine and dacarbazine) because of the appearance of a new lesion. At the end of the fifth cycle of ABVD chemotherapy, she dropped out of the chemotherapy because of intolerance and noncompliance. Since then, she had visited clinics solely for supportive care every other year.

In April 2008, the patient visited our hospital for pruritus and palpable lymph nodes on the both inguinal and axillary areas. For identification of relapse, we started imaging studies. CT scan showed multiple lymph node enlargements on the neck, chest and abdomen and a PET scan image revealed a conglomerated hyper-metabolic lesions on the right supraclavicular, axilla, paratracheal, mediastinal, aortocaval and ilio-inguinal lymphatic channel. A biopsy was performed on the axillary area and the pathologic finding was compatible with mixed cellularity. She was diagnosed with the relapsed Hodgkin's lymphoma. The patient was admitted for a third line of chemotherapy with an ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) regimen in May 2008. On the $5^{th}$ day of chemotherapy, the patient complained of dyspnea and generalized weakness. Her body weight gained 7 kg during chemotherapy. So a loop diuretic agent was given to control balance of volume between intake and output but it was not successful. The next day, the patient developed a mental disturbance suddenly. She disrobed herself and was unable to recognize her family or medical personals. Her blood pressure was 140/80 mmHg (normally 110/ 70 mmHg), heart rate 90/min and body temperature 36.1°C. The patient didn't gazed into the right side on a visual field exam, she diagnosed as Rt. homonymous hemianopsia. The patient had become lethargic and unresponsive to verbal stimuli and her motor grade was decreased to 3 or less. She had a brief seizure which was subsided after treating her with intravenous lorazepam 2 mg. She was transferred to the medical intensive care unit and immediately performed intubation. And then supportive care was given.

Laboratory findings showed mild leukocytosis $12.2\times10^3/\mu L$ (97.8% neutrophils), hemoglobin 10.5 g/dL, platelets 372,000/$\mu$L, serum creatinine 0.79 mg/dL, BUN 29.1 mg/dL, serum sodium 138 mEq/L, and serum potassium 2.7 mEq/L. A chest x-ray showed mild congestion with increased vascular marking. Cardiac wall motion was normal on an echocardiogram. There was no abnormal waveform on electroencephalogram. MR diffusion was taken, and the apparent diffusion coefficient (ADC) signal decreased in the Lt. occipital area (ADC reduction) (Fig. 1). Diffusion weighted imaging (DWI) and a fluid-attenuated inversion-recovery MR (FLAIR) image showed hyperintensity in the occipital white matter (Fig. 2).

After five days in the intensive care unit, the patient was stabilized and transferred to the general ward. Visual problems were improved gradually over the one week and motor strength was returned to previous levels. She received the second cycle of a new chemotherapy with no relapse of RPLS. After the second cycle of chemotherapy,

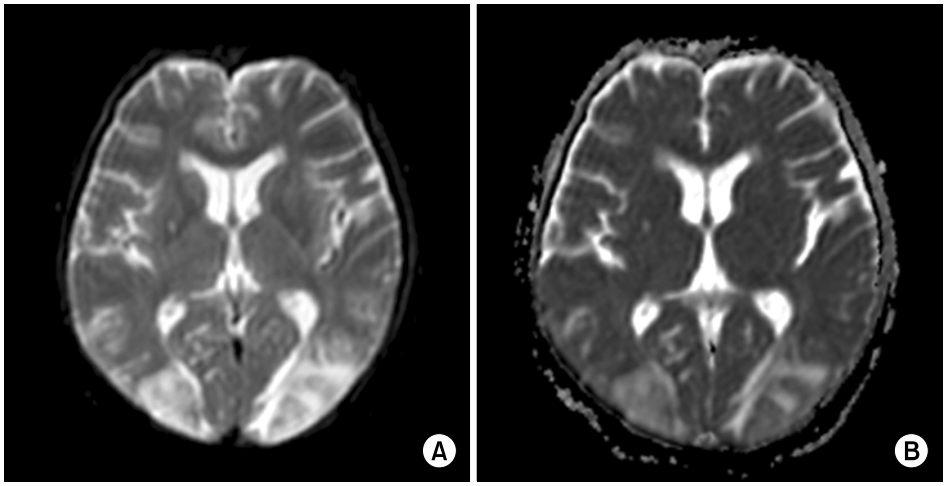


**Fig. 1.** MR diffusion. (A) TRACE map, diffusion high signal intensity on temporal, parietal, and some occipital gyruses. (B) Apparent diffusion coefficient (ADC) map, focal restricted diffusion on area of left parietal occipital and right parietal.

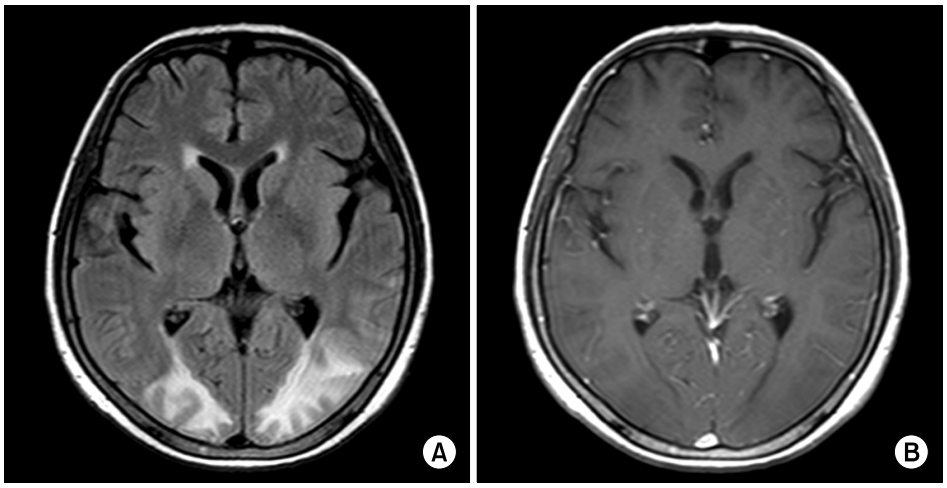


**Fig. 2.** MRI. (A) Fluid-attenuated inversion-recovery (FLAIR), white hyperintensity in the occipital white matter. (B) Gadolinium enhanced image, no enhanced area on same area.

partial remission was observed.

## DISCUSSION

Reversible posterior leukoencephalopathy syndrome (RPLS) was first reported by Hinchey et al.[1] RPLS is characterized by headaches, visual disturbances, altered mental function and seizures. Common image findings of RPLS include bilateral white-matter abnormalities in the posterior regions of the cerebral hemispheres (leukoencephalopathy). Most patients recover quickly and permanent disability and fatality do rarely occur.[2] The underlying conditions of RPLS are diverse (e.g. use of immunosuppressive therapy, eclampsia, acute hypertensive encephalopathy, and renal diseases such as lupus nephritis or acute glomerulonephritis).[1] Characteristic neuroimaging is due to vasogenic edemas dominating the white mater of the posterior cerebral area.[1,3] The changes are well visualized on T2 weighted MR scanning and are best visualized via fluid-attenuated inversion recovery (FLAIR) sequences.[4] The mechanism of edema is thought to be associated with a brain-capillary leak syndrome related to hypertension and fluid retention.[1] Cerebral white matter is composed of myelinated-fiber tracts in a cellular matrix of glial cells, arterioles, and capillaries that makes the region susceptible to the accumulation of fluid in the extra-cellular spaces.[1] The theory is still controversial though, sudden elevations in systemic blood pressure may

induce dysfunction of the autoregulatory capability of the brain vasculature.[1,3] The posterior hemispheres receive less sympathetic innervations than the carotid system, which explains the predilection of RPLS on posterior area.[5]

Common conditions associated with RPLS are malignant hypertension, eclampsia, renal failure and the use of immunosuppressive agents (e.g. cyclosporine), which are frequently used during hematopoietic stem cell transplantation (HSCT). In pediatrics, RPLS is the most common severe neurological complication during HSCT.[6] In adult areas, RPLS is rare but there have been reports that patients treated with cyclosporine and other immunosuppressants had shown changes in neuroimages similar to leukoencephalopathy. Some had suggested the direct effect of cyclosporine on the CNS as a possible explanation of perturbation of the brain blood barrier.[7] Initial symptoms may include confusion, short-term memory loss, gait abnormalities, and seizures that generally begin within 1～3 months of treatment. Leukoencephalopathy can emerge early and vascular disease may be part of the spectrum of global treatment-related neurotoxicity.[8] RPLS may be caused by various anti-neoplastic treatments, and the reported number of cases has recently increased.[9] Anti-neoplastic agents known to be associated with RPLS include cisplatin, cytarabine, adriamycin, ifosfamide, etoposide, interferon-$\alpha$, MTX, melphalan, rituximab, and bevacizumab.[4] Intravenous high dose MTX also has a strong tendency to cause leukoencephalopathy when combined with cranial radiation therapy.[10,11] Combined therapies are associated with more frequent and more rapid presentation than those using only a single agent.[12]

In our specific case, the patient showed acute mental change, magnetic resonance imaging (MRI) showed hyper-intense signals on T2 weighted images and fluid attenuated inversion recovery (FLAIR) images of bilateral temporal, parietal, and occipital lobes. Blood pressure was poorly controlled during chemotherapy and the probable cause of hypertension is the fluid retention due to overhydration. However, initially the body weight was unresponsive to the diuretics. Treatment was consisted with the controlling the blood pressure and seizure, and reaching a negative intake-output balance with fluid restriction. One week later after supportive care, her clinical manifestations were completely resolved. The recovery of radiological changes and clinical manifestations are consistent with RPLS.

Until now, adult cases of chemotherapy related RPLS were rare in Korea and reported cases abroad showed relatively poor outcomes, high mortality and slow recovery. On the other hand, our case followed a typical course of RPLS and there were no sequelae. In that aspect, we think our case is unique.

Based on our experience, we suggest that RPLS should be differentiated from other toxicities related to the chemotherapy because it is preventable with early detection, controlling blood pressure, and supportive care. Medical oncologist should include RPLS in the differential diagnosis of acute neurological changes during chemotherapy and be aware of its early signs and symptoms when the symptoms are not explained by other medical conditions and especially when the patient is treated with a high risk chemotherapeutic agents and large volumes of fluid.

## 요 약

가역성후백질뇌병증은 두통, 혼수, 발작 그리고 흔히 시력변화를 동반하는 질환이다. 이 질환은 주로 두정엽과 후두엽의 백질에 주로 이상을 보이는 신경 영상학적 소견과 연관이 있으며 악성고혈압, 전자간증, 신기능부전 환자나 면역억제제를 투여 받는 환자에서 주로 발병한다고 알려져 있다. 우리는 항암치료를 받은 환자에서 발생한 가역성후백질뇌병증 한 예를 보고 하고자 한다. 49세 여자 환자가 항암치료 시작 5일째 발생한 급작스런 의식의 변화와 시력의 장애를 보였고 자기 공명 영상 상에서 양측성 측두엽, 두정엽, 후두엽에 고강도 신호영상이 보였다. 혈압의

조절과 수액불균형의 교정 등 보전적 치료 후 환자의 임상 증상은 호전되었다. 영상의학적인 변화양상과 가역적 임상증상이 가역성후백질뇌병증에 합당한 소견이라 할 수 있었다.

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