Case Report

# Posterior reversible encephalopathy syndrome in non-Hodgkin's lymphoma: Not necessarily reversible!

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## ABSTRACT

Posterior reversible encephalopathy syndrome (PRES) is a rare clinicoradiological entity that is an increasingly recognized complication of pediatric cancer treatment. However, there have been very few reports of PRES in association with non- Hodgkin's lymphoma (NHL) and reported incidence is only 0.06%. The available literature and case reports on PRES were studied in depth, and the important conclusions were taken into account for writing athe review. We describe a case of PRES in a boy of 15 years with NHL on cyclophosphamide, doxorubicin, vincristine and prednisolone combination chemotherapy who presented with generalized seizures and reversible blindness. Magnetic resonance imaging of the brain revealed characteristic findings of the syndrome establishing the diagnosis. However, despite transient improvement of the symptoms, the patient succumbed to respiratory failure. The authors conclude that PRES is a rare entity especially in NHL patients that must be recognized early and should be managed aggressively as it may prove to be fatal also.

**Key words:** Cyclophosphamide, doxorubicin, vincristine and prednisolone chemotherapy, non-Hodgkin's lymphoma, posterior reversible encephalopathy syndrome, reversible blindness

## INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiological entity that was first described by Hinchey *et al*. in 1996.[1] It is characterized predominantly by white matter edema affecting the occipital and posterior parietal lobes of the brain. The precise incidence of the syndrome is unknown. PRES can develop in association with a wide array of conditions. Table 1 lists some of the common etiologies of PRES. Exposure to toxic agents is the most common association with PRES reported in up to 61% of the cases.[2] Hypertension is the second most common condition present in up to 72% of cases.[3] Infections have been reported in up to 24% of cases.[4] Non-Hodgkin's lymphoma (NHL) is a rare association with this syndrome. In an online data of 10,092 NHL patients, only 6 (0.06%) had PRES.[5] It has been reported from age 4 to 90 years, although most cases occur in young to middle-aged adults. There is a marked female predominance. PRES is now the accepted term but has been challenged recently based on the risk of neurological impairment and up to 15% mortality rate. We describe a case of PRES in a boy of 15 years with NHL on chemotherapy that ended with fatal outcome and provide a review of available literature.

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## CASE REPORT

A 15-year-old boy diagnosed with NHL (diffuse large B-cell lymphoma- Figure 1) Stage IIIB at presentation was on cyclophosphamide, doxorubicin, vincristine, and prednisolone combination chemotherapy. He had cervical, mediastinal and abdominal lymphadenopathy. After 10 days of receiving fourth cycle of chemotherapy, he complained of an episode of seizure followed by sudden loss of vision bilaterally. Also, the patient appeared confused.

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**Table 1: List of drugs and other causes of PRES**

| |
|---|
| Cytotoxic agents |
| Alkylating agents |
| Cisplatin |
| Oxaliplatin |
| Carboplatin |
| Anti-metabolites |
| Gemcitabine |
| Cytarabine |
| Methotrexate |
| Mitotic inhibitors |
| Vincristine |
| Irinotecan |
| Others |
| L-asparaginase |
| Bevacizumab |
| Immunomodulatory cytokines |
| Interferon-alpha |
| Monoclonal antibodies |
| Rituximab |
| Immunosuppressive agents |
| Anti-calcineurin agents |
| Cyclosporine A |
| Sirolimus |
| High-dose corticosteroid therapy |
| Other agents |
| Granulocyte-stimulating factor |
| Linezolid |
| Erythropoietin |
| Hypertension |
| Hypertensive encephalopathy |
| Eclampsia |
| Renal failure with hypertension |
| Other reported causes |
| Collagen vascular disorders |
| Systemic lupus erythematosus |
| Polyarteritis nodosa |
| Behçet's syndrome |
| Thrombotic-thrombocytopenic purpura |
| Acquired immunodeficiency syndrome |
| Acute intermittent porphyria |
| Following organ transplantation |

PRES: Posterior reversible encephalopathy syndrome

On ophthalmoscopic examination, patient's visual acuity was limited to light perception while the lens and media were clear. Optic disc was normal. Magnetic resonance imaging (MRI) of the brain was done and it revealed altered signal intensity of cortex and subcortical white matter in bilateral posterior parietal, occipital region and bilateral frontal region appearing hyperintense on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images and hypointense on T1-weighted images. [Figure 2] Restricted diffusion was not seen. These radiological features suggested diagnosis of advanced posterior reversible encephalopathy syndrome. Cerebrospinal fluid analysis showed normal protein and glucose concentrations, no malignant cells were seen. HIV 1 and 2 serology was negative. Serum magnesium level was in normal limit. The patient's visual acuity recovered to normal and also there were no further seizure episodes while the patient was kept on phenytoin and mannitol. However, the patient developed increasing respiratory distress and expired even on intensive care unit (ICU) admission and intubation.

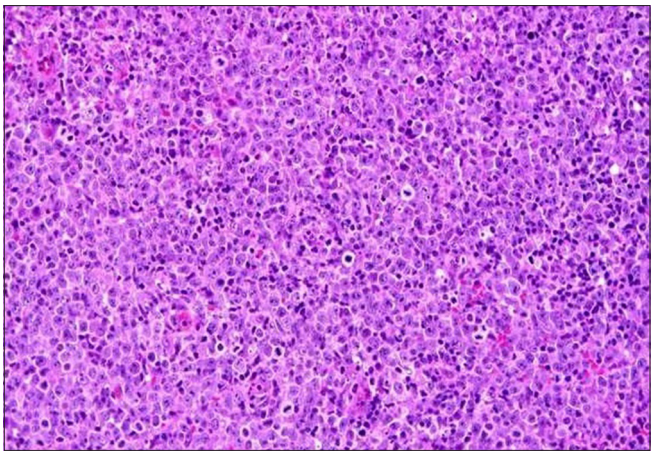

**Figure 1:** Photomicrograph of biopsy from cervical lymph node showing diffuse replacement of lymph node architecture by lymphocytes

## DISCUSSION

One of the hypotheses to explain the pathogenesis of PRES, is an excess of the auto regulatory capacity of the brain by a sudden rise of the blood pressure, leading to disruption of the blood-brain barrier, followed by vasogenic edema.[1] Cerebral white matter is predominantly involved as this region is more susceptible to vasogenic edema compared with the more tightly packed cortex.[1] The pathophysiology of PRES in patients with cytotoxic drugs is also uncertain. In relation to cyclosporin, Truwit *et al*. have suggested that an acute toxic insult of undetermined origin produced by these pharmacological agents results in axonal swelling and increased water content in the white matter.[6]

The clinical presentation of PRES consists of consciousness impairment, seizures, headaches, visual abnormalities, nausea/vomiting and focal neurological deficits. Consciousness impairment may range in severity from confusion, somnolence, and lethargy to encephalopathy or coma. Seizure occurs in up to 92% of cases and are usually generalized.[3] Visual abnormalities range from blurred vision, visual neglect, homonymous hemianopia, visual hallucinations and cortical blindness.[1] Our patient had an episode of seizure followed by transient blindness and confusion.

Magnetic resonance imaging is superior to computed tomography (CT) for the diagnosis of PRES. CT finding is often normal or nonspecific.[7] Hypodensities in a suggestive topographic distribution suggest PRES. Proton-density and T2-weighted images show regions of high signal indicating edema. FLAIR has been shown to improve the diagnosis of PRES and the detection of subcortical and cortical lesions in PRES. T1-weighted images show low-intensity foci. Of 67 patients who had both CT and MRI at least 2 days after the clinical onset of PRES, 22

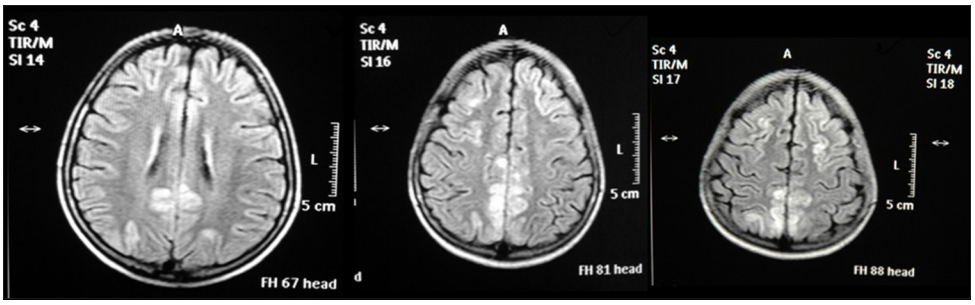


**Figure 2:** Magnetic resonance imaging showing altered signal intensity of cortex and subcortical white matter in bilateral posterior parietal, occipital region and bilateral frontal region appearing hyperintense on T2-weighted and fluid-attenuated inversion recovery images and hypointense on T1-weighted images

had both investigations on the same day and of these, only 7 (32%) had contributive CT findings. Interestingly, the proportion of patients with contributive CT findings was 74% on day 2, suggesting that repeated CT scanning may be helpful when MRI is unavailable.[8] Bartynski *et al*. described four radiological patterns in the study of 136 patients.[7] [Figure 3]. Holohemispheric watershed pattern was found in 23% [Figure 3a] and characterized by confluent vasogenic edema extending through the frontal, parietal and occipital lobes. Superior frontal sulcus pattern was reported in 27% [Figure 3b] and had the patchy edema in the frontal lobes along the superior frontal sulci. In 22% patients, dominant parietal-occipital pattern [Figure 3c] was found. This was previously thought to be typical of PRES; the posterior part of the parietal and occipital lobes is predominantly involved. 28% patients had partial or asymmetric expression of the primary patterns [Figure 3d].

Patients with PRES require the symptomatic measures usually taken in the ICU. The need for upper airway protection should be evaluated continuously in patients with marked consciousness impairment or seizure activity. Hypoglycemia should be looked for routinely and corrected. If the glucose is given, 100 mg of thiamine should be administered concomitantly. Patients should be routinely evaluated for hyperthermia and metabolic disturbances, in particular hypomagnesemia, which require prompt correction. Antiepileptic treatment should be initiated on an emergency basis and according to current guidelines. Control of hypertensive emergency, if present, is an important part of the symptomatic management. The aim is not to normalize the blood pressure but rather to decrease the mean arterial pressure by 20-25% within the first 2 h and to bring the blood pressure down to 160/100 mmHg within the first 6 h.[9] Overzealous blood pressure reduction can aggravate the cerebral perfusion pressure alterations and promote ischemia. Intravenous antihypertensive drugs include labetalol, nicardipine, or fenoldopam.

As the name of this syndrome suggests, appropriate treatment is expected to ensure a full recovery. However, permanent complications and fatal cases have been

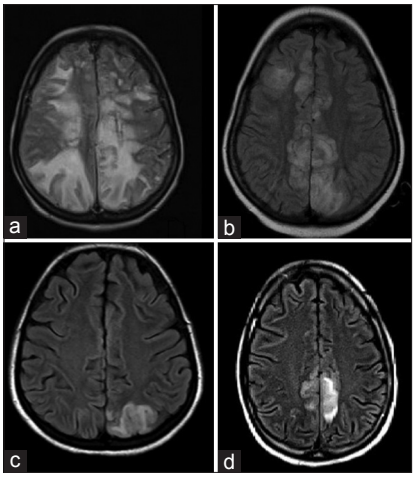


**Figure 3:** Four main magnetic resonance imaging patterns of posterior reversible encephalopathy syndrome. (a) Holohemispheric watershed pattern. Fluid-attenuated inversion recovery (FLAIR) sequences showing bilateral vasogenic edema in a linear pattern involving the white matter of the cerebellum and brainstem, (b) superior frontal sulcus pattern. FLAIR sequences are showing bilateral vasogenic edema in a nonconfluent pattern involving the frontal sulcus area, (c) dominant parietal-occipital pattern. FLAIR sequences showing bilateral vasogenic edema in the white matter of the occipital and parietal lobes, (d) partial expression of the three primary patterns

reported[10] as in our case, leading some authors to suggest that a better name may be "potentially reversible encephalopathy syndrome."[9] Radiological recovery occurs in 49-75%.[1] Time taken for resolution of the initial radiologic abnormalities varies from 5 days to 17 months.[1] Permanent neurological abnormalities are related to ischemia and/or bleeding. Recurrences have been reported in 6% of cases. Death has been reported in up to 15% of patients.

## CONCLUSION

An early etiologic diagnosis allows prompt correction of the cause of PRES. Patients may require blood pressure control, withdrawal of cancer chemotherapy or immunosuppressive agents, cesarean section, dialysis, or other interventions. Prompt correction of the cause is crucial to decrease the risk of ischemia or bleeding and therefore to avoid permanent disability or death.

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