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## Chemotherapy-associated Posterior Reversible Encephalopathy Syndrome:

### A Case Report and Review of the Literature

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### Abstract

**Introduction:** There are increasing reports of posterior reversible encephalopathy syndrome (PRES) associated with the use of chemotherapeutic agents. Recognition of PRES is crucial given its reversibility with appropriate supportive management. We report a patient presenting with PRES after treatment with Rituximab, Cyclophosphamide, Hydroxydaunorubicin/Adriamycin, Oncovin/Vincristine, Prednisone (R-CHOP) and intrathecal methotrexate. We also perform a systematic review of the literature on chemotherapy-associated PRES.

**Case Report:** A 72-year-old man with recently diagnosed diffuse large B-cell lymphoma became unresponsive 4 days after initiation of R-CHOP and intrathecal methotrexate. Brain magnetic resonance imaging showed interval development of occipital and temporal fluid attenuation inversion recovery hyperintensities consistent with PRES. The patient's blood pressure was aggressively controlled and he received 5 days of high-dose methylprednisone. He subsequently regained consciousness and his mental status gradually improved. Repeat magnetic resonance imaging showed interval resolution of the bilateral fluid attenuation inversion recovery hyperintensities.

**Review Summary:** We performed a systematic review of the literature and included a total of 70 unique cases involving chemotherapy-associated PRES. Platinum-containing drugs, Cyclophosphamide, Hydroxydaunorubicin/Adriamycin, Oncovin/Vincristine, Prednisone/ R-CHOP regimens, and gemcitabine were the agents most commonly used in patients who developed suspected chemo-associated PRES. Median onset of symptoms occurred 8 days after chemotherapy. Hypertension was the most commonly reported risk factor associated with the development of chemotherapy-associated PRES. In most cases, PRES improved with supportive management alone within 2 weeks.

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**Conclusions:** Chemotherapy-associated PRES is an increasingly encountered syndrome. Both neurologists and non-neurologists should be familiar with the most commonly implicated agents, symptoms, risk factors, and clinical course of chemotherapy-associated PRES, given its favorable prognosis with appropriate management.

### Keywords

chemotherapy; posterior reversible encephalopathy syndrome; reversible posterior leukoencephalopathy

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Posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy, is a clinical syndrome characterized by headache, seizures, altered mental status, and visual disturbances. It is often associated with radiographic findings of posterior cerebral white matter edema. First described in 1996 by Hinchey et al,<sup>1</sup> PRES is most commonly associated with hypertensive encephalopathy, eclampsia or preeclampsia, and immunosuppressive therapies such as cyclosporine and tacrolimus. Recently there have been increased reports of PRES associated with chemotherapy. The mechanism of PRES is believed to be related to endothelial dysfunction and failure of cerebral autoregulation, leading to breakdown of the blood-brain barrier (BBB) and resulting cerebral edema.<sup>1,2</sup> In chemotherapy-associated PRES, the cytotoxic effects of treatment may cause direct vascular damage to the BBB. If clinical risk factors for PRES such as acute hypertension, renal dysfunction, or electrolyte imbalances are combined with chemotherapy-related cytotoxic effects, patients may be at higher risk of developing PRES.<sup>3,4</sup>

As use of chemotherapeutic agents increases, the diagnosis of PRES is likely to become more frequent. Prompt recognition of this syndrome is crucial, as PRES is usually reversible with appropriate supportive management.<sup>1</sup> The purpose of this article is to familiarize the physician with the clinical course, outcomes, and risk factors seen with chemotherapy-associated PRES. We report a patient who developed PRES shortly after administration of combination chemotherapy for diffuse large B-cell lymphoma (DLBCL). We then perform a systematic review on chemotherapy-associated PRES in the literature.

## CASE REPORT

A 72-year-old man with recently diagnosed stage IV DLBCL presented to the hospital with 4 weeks of increasing confusion. The family reported the patient was not responding appropriately to questions and had stopped eating and drinking. The patient denied any headaches, visual problems, or seizure-like activity. His past medical history included hypertension, type 2 diabetes mellitus, asthma, and osteoarthritis. His family history was negative for known cancers or neurological disease. He was a former cigarette smoker with a 7 pack year history. He had no history of alcohol or drug abuse. Neurological examination demonstrated no focal deficits. However, the patient was only intermittently oriented to self, time and place, and displayed difficulties with naming, repetition, and following commands. A magnetic resonance imaging (MRI) of the brain showed hyperintensity of the medial temporal lobe and a lumbar puncture demonstrated elevated protein with otherwise negative cytology and no evidence of infection. The patient's confusion persisted despite medical

optimization and a negative infectious disease work-up. There was concern for central involvement of his DLBCL and chemotherapy was initiated.

The patient received one cycle of Rituximab, Cyclophosphamide, Hydroxydaunorubicin/ Adriamycin, Oncovin/Vincristine, Prednisone (R-CHOP) and one dose of intrathecal methotrexate. Three days later he received a second dose of intrathecal methotrexate. The next day the patient was found to be unresponsive, with an episode of right gaze deviation and right upper extremity shaking for 1 to 2 minutes. Repeat neurological examination now showed the patient to be nonverbal and withdrawing only to painful stimuli. His blood pressure was elevated to 200/101. Computed tomography of the head showed no acute intracranial abnormalities accounting for his sudden change in consciousness. His labs and examination were notable for an elevated creatinine to 1.53 (baseline unknown) and significant fluid overload. He was transferred to the intensive care unit where his blood pressure was aggressively controlled. An electroencephalogram showed no evidence of seizure activity, but he was treated with levetiracetam for seizure prophylaxis. A subsequent MRI showed interval development of Fluid attenuation inversion recovery (FLAIR) hyperintensities involving the bilateral occipital and temporal lobes, consistent with PRES (Fig. 1).

The patient remained unresponsive for 1 week despite adequate blood pressure control. The patient then received empirical treatment with a 5-day course of high-dose steroids (methylprednisone 1 g/d). On the last day of treatment a repeat MRI showed interval resolution of the bilateral occipital FLAIR hyperintensities (Figs. 1C, D). The following day the patient regained consciousness and his mental status gradually improved. One month later, the patient was oriented to self and able to answer simple questions and follow commands. He was discharged home.

## DISCUSSION AND RESULTS

We performed a systematic review of the literature to better characterize the clinical course, treatment, and risk factors associated with chemotherapy-associated PRES. The use of targeted therapies, including the VEGF inhibitor bevacizumab, was excluded as this topic has been reviewed elsewhere.<sup>5,6</sup> Search keywords included posterior leukoencephalopathy syndrome and chemotherapy treatments, and were executed in Ovid Medline 1946-, Embase 1947-, and Scopus 1823-. All searches were completed in December 2015 and limited to the English language using database supplied limits. The results were exported to EndNote. A total of 98 unique citations were identified. Additional case reports were identified through article references. Case reports that lacked radiographic data or cited a targeted therapy as a likely inciting cause of PRES were excluded. A total of 70 cases were ultimately included in the review.<sup>4,7-71</sup> To our knowledge, this is the largest systematic review of chemotherapy-associated PRES in the literature.

Table 1 details the clinical characteristics of chemotherapy-associated PRES. Women were more commonly affected than men, accounting for 77% of the cases. Symptoms and radiographic findings were largely consistent with PRES due to other causes.<sup>1,72</sup> Seizures were the most frequent presenting symptom, followed by altered mental status (most

commonly manifesting as decreased consciousness and lethargy), visual changes, headache, and focal neurological deficits. Comatose states, as seen in our patient, were seen in 10 cases (14%), but were generally reversible. Radiographic findings also tended to occur in the posterior distribution, with the occipital lobe implicated in 93% of cases. However, involvement of the frontal lobes, thalamus, cerebellum, and basal ganglia structures were also seen (Table 1). Median blood pressure was 170/92.5, with a median mean arterial pressure (MAP) of 118 mm Hg. This was similar to the median MAP (117 mm Hg) found in a large, retrospective study of 96 patients with all-cause PRES.<sup>72</sup> However, 5 case reports noted a “normal” blood pressure in their patients without providing actual measurements, and were excluded from analysis. Thus, our median MAP was likely an overestimation of systemic blood pressures. Indeed, Liman et al<sup>72</sup> noted a significantly lower MAP in patients with chemotherapy-associated PRES (110 mm Hg) compared with PRES due to other causes (122 mm Hg), which may argue for endothelial dysfunction in precipitating cerebral edema. In our patient and this review, systemic hypertension was an important risk factor associated with the development of PRES, given the elevated median MAP. However, chemotherapy-associated PRES can still develop in the presence of relatively normal blood pressures. Some authors have concluded that a 25% increase of blood pressures from the baseline values will put a patient at risk for chemotherapy-associated PRES.<sup>4</sup>

Table 2 lists the most frequently implicated chemotherapeutic agents. Our patient received R-CHOP and IT-methotrexate, both of which have been implicated in PRES. Interestingly, in our review, the majority (74%) of PRES cases were associated with combination chemotherapy, of which CHOP/R-CHOP was the most frequent. IT-methotrexate was implicated in 5 of the 70 cases (7%). Although IT-methotrexate neurotoxicity has been described in the pediatric population, PRES is relatively rare, and is even less frequently encountered in the adult population.<sup>9</sup> In our review, gemcitabine was the most frequently encountered single chemotherapeutic agent. However, platinum-based drugs were the most commonly encountered agents when accounting for chemotherapy regimens. Given the retrospective nature of this study, it is difficult to ascertain whether the increased frequency of platins reported in PRES is confounded by reporting bias, oncologist practice, or type of cancer being treated. However, platins are known to have neurotoxic side effects, although usually these side effects are restricted to the peripheral nervous system.<sup>73</sup>

The mechanism for chemotherapy-induced PRES is unclear, but it may largely be related to toxic effects of chemotherapeutic agents on endothelial cells, resulting in BBB dysfunction and cerebral vasogenic edema.<sup>74</sup> These toxic effects are likely more potent when combined with systemic risk factors associated with cancer. A study on rats demonstrated that intracarotid injection of cisplatin, the agent most frequently implicated in cases of chemotherapy-induced PRES, increases BBB permeability.<sup>75</sup> Bleomycin has also been shown to have dose-dependent cytotoxicity on endothelial cells in vitro.<sup>76</sup> Chemotherapeutic agents may also lead to immune reactions that increase BBB permeability. Chemotherapies may increase tumor cell recognition by the body’s innate immune system and trigger a complex cascade of endothelial cell activation and cytokine production, ultimately resulting in vascular instability and BBB dysfunction.<sup>77–79</sup> Therefore, both indirect and indirect effects of chemotherapeutic agents may cause BBB dysfunction and result in PRES.

Our patient suffered an acute change in mental status four days after administration of his first dose of R-CHOP and IT methotrexate. In our review, median onset of symptoms occurred 8 days after chemotherapy administration, although often PRES occurred in the second or third cycle of chemotherapy. Two cases reported an onset of PRES 60 days after their last chemotherapy dose.<sup>35,54</sup> Chemotherapy-associated PRES was also largely reversible, and in all nonlethal cases patients showed symptom resolution within two weeks. However, a significant proportion (7% in our study) had fatal outcomes due to neurological and clinical deterioration.<sup>7,10,12,19,21,51,55</sup> Treatment of PRES consists largely of blood pressure control and withdrawal of the inciting factor; however, in some cases, hemorrhagic conversion and infarction can occur.<sup>8,26,51,56,60</sup> Interestingly, the use of high-dose steroids was reported in 9 cases (13%), although outcomes and duration of symptoms were similar to patients treated without high-dose steroids.<sup>8,14,24,27,31,46,47,56,69</sup> In our patient, abrupt neurologic recovery was seen 1 day after pulse steroid conclusion. It is unclear whether or not high-dose steroids have a real impact on the clinical course, given that in most cases the syndrome will resolve on its own with appropriate management.<sup>1</sup> However, there is a theoretical benefit of reducing inflammation and resulting edema, although there are also reported cases of precipitating PRES with initiation of high-dose steroids.<sup>80</sup> The use of steroids in PRES should therefore be exercised with caution, although in the above 9 case reports and our patient, symptoms were not worsened with steroid administration.

Besides hypertension, reported risk factors for PRES include renal dysfunction, fluid overload, and electrolyte imbalances such as hypomagnesemia.<sup>4,81,82</sup> Our patient exhibited an acute kidney injury and marked fluid overload at the time of symptom development. In this review, 8 cases (11%) reported an elevated creatinine, and 6 (9%) reported a below normal magnesium. It is difficult to estimate the true contribution of acute kidney injury and hypomagnesemia in the development of PRES. Therefore, physicians should be vigilant to the possibility of PRES in the presence of these risk factors, and work to correct renal dysfunction and electrolyte imbalances as part of supportive management.

The differential for neurological symptoms in a cancer patient after administration of chemotherapy is broad. However, all physicians should maintain a high clinical suspicion of chemotherapy-associated PRES, as most patients will have a favorable prognosis. Chemotherapy-associated PRES is an increasingly common syndrome during oncologic treatment. Platinum-containing drugs, CHOP/R-CHOP regimens, and gemcitabine are the most frequently implicated agents, although nearly every drug class has been implicated. For the most part, the symptoms, radiographic findings, duration, and outcomes are similar to PRES precipitated by other causes. The onset of symptoms occurs a median of 8 days after chemotherapy administration, but has been reported up to 2 months later. Blood pressures are generally elevated and should be aggressively controlled, although hypertension may be absent in some cases of chemotherapy-associated PRES. High-dose steroids have not been shown to improve outcomes, however they have been used empirically in the management of PRES. Patients typically improve within 2 weeks of symptom onset. Prompt recognition of the syndrome is critical given its reversibility with appropriate management.

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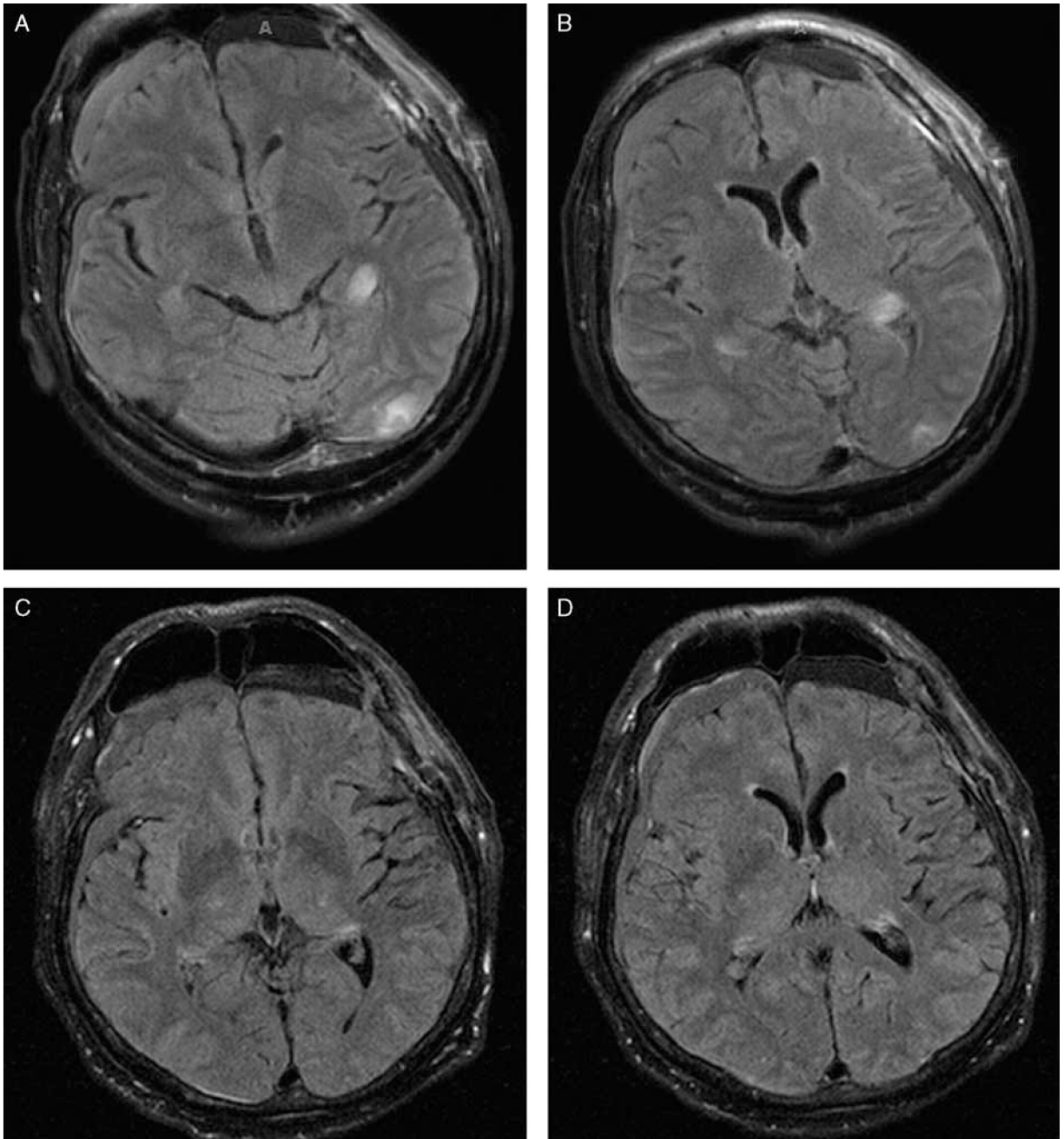
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**FIGURE 1.**

A and B, Magnetic resonance imaging of the brain without contrast demonstrating bilateral occipital FLAIR hyperintensities consistent with posterior reversible encephalopathy syndrome. C and D, Interval resolution of bilateral FLAIR hyperintensities after 11 days.

**TABLE 1.****Clinical and Radiographic Characteristics of Patients With Chemotherapy-associated PRES**

Age (N = 70)	18–79, median: 55
Sex (%)	
Female	77
Male	23
Blood pressure (N = 63) *	106–240/95–124, median: 170/92.5
Days until onset (N = 63) †	1–60, median: 8
Duration(N = 36) ‡	1–14, median: 4
Fatal (%)	7
Symptoms (%)	
Seizure	64
Altered mental status	47
Visual changes	43
Headache	40
Other neurological deficit	19
Coma	14
MRI findings (%)	
Occipital	93
Parietal	57
Frontal	26
Temporal	17

\* Only case reports that included numeric measurements of presenting blood pressures were included.

† Number of days between last administration of implicated chemotherapy and onset of posterior reversible encephalopathy syndrome symptoms.

‡ Duration of symptoms was defined as number of days to significant clinical improvement.

MRI indicates magnetic resonance imaging.

**TABLE 2.**

## Implicated Chemotherapeutic Agents in the Development of Posterior Reversible Encephalopathy Syndrome

Chemotherapeutic Agent	N
Cisplatin, carboplatin, oxaliplatin *	30
CHOP/R-CHOP	14
Daunorubicin	24
Vincristine, vinorelbine, vinflunine, vinblastine, vindesine	21
Cyclophosphamide	16
Gemcitabine	14
Capecitabine, 5-fluorouracil *	13
Cytarabine	9
IT cytarabine	3
Etoposide	8
Methotrexate	7
IT methotrexate	5
Taxane	5
Ifosfamide	3
Bleomycin	2
Lomustin	1
Dacarbazine	1
Irinotecan	1

\* FOLFOX: 7.

CHOP indicates Cyclophosphamide, Hydroxydaunorubicin/Adriamycin, Oncovin/Vincristine, Prednisone; R-CHOP, Rituximab, Cyclophosphamide, Hydroxydaunorubicin/Adriamycin, Oncovin/Vincristine, Prednisone.