

## Case in Point

# Posterior Reversible Encephalopathy Syndrome as a Complication of Chemotherapy

Igor Sirotkin, MD; Behzad Mowlazadeh, MD; Alexander Sochet, MD; and Bruce Kudryk, MD

Patient presented with seizures soon after starting chemotherapy for large B-cell lymphoma; magnetic resonance imaging confirmed posterior reversible encephalopathy syndrome.

**P**osterior reversible encephalopathy syndrome (PRES) is a neurological disorder that can present with headache, seizure, visual changes, paresis, and altered mental status. On diagnostic imaging, PRES is classically characterized by symmetrical hemispheric edema typically in the parietal and occipital regions.<sup>1</sup>

PRES was first noted to occur in eclampsia, severe hypertension (HTN), and with cyclosporine use in allogeneic bone marrow transplantation and solid organ transplantation.<sup>2-5</sup> Over the years, PRES has been associated with a variety of systemic conditions, including autoimmune diseases, septic shock, and chemotherapy.<sup>6-8</sup> Although awareness of PRES is increasing as a complication of chemotherapy in pediatric oncology, in adult oncology, PRES is still rarely recognized. In this article we present a case report of an older patient who developed PRES after his first cycle of chemotherapy for large B-cell lymphoma.

### INITIAL EXAM

A 60-year-old man was recently diagnosed with large B-cell lymphoma. At that time his first presenting symptoms included shortness of breath, dry cough, and left chest pressure. Computed tomography (CT) and posi-

tron emission tomography imaging demonstrated a large left pleural effusion; multiple enlarged predominantly mediastinal and left axillary lymph nodes; and osseous involvement of multiple ribs, vertebrae, and pelvis. His medical history included controlled type 2 diabetes, HTN, and chronic obstructive pulmonary disease, and no seizure disorder. Before starting chemotherapy his laboratory work was significant for mild renal insufficiency; a creatinine level of 1.58 mg/dL, an estimated glomerular filtration rate of 45 mL/min, and blood pressure (BP) of 127/76.

### TREATMENT

Antineoplastic therapy was started with rituximab 926 mg IV and 5 days later cyclophosphamide 1,500 mg IV, doxorubicin 100 mg IV, vincristine 2 mg IV, prednisone 100 mg by mouth qd (CHOP therapy) days 1 to 5.

Four days after completing the first R-CHOP cycle, the patient complained of a brief episode of visual disturbance lasting less than a minute. He was sent to the emergency department but was asymptomatic and denied any vision complaints or headache.

The next morning he had 2 successive seizure episodes. BP was elevated, 181/112 and 177/114. He became unresponsive, went into respiratory arrest, and later was intubated. His BP gradually normalized in the medical intensive care unit (MICU), and he was able to answer simple yes or no questions. The neurological exam was nonfocal.

A CT revealed 2 focal areas of intraparenchymal hemorrhage, located in the right posterior temporal lobe (Figure 1) and in the right high frontal lobe (Figure 2), and a

**Dr. Sirotkin** is a radiologist, **Dr. Mowlazadeh** is chief of oncology, **Dr. Sochet** is an oncologist, and **Dr. Kudryk** is chief of radiology, all at Bay Pines VA Healthcare System in Bay Pines, Florida. Dr. Sirotkin is a courtesy assistant professor, Dr. Sochet is a clinical assistant professor, and Dr. Kudryk is associate professor, all at the College of Medicine, University of South Florida, Tampa, Florida. Dr. Mowlazadeh is a clinical assistant professor at the Eastern Virginia Medical School, Hampton, Virginia.

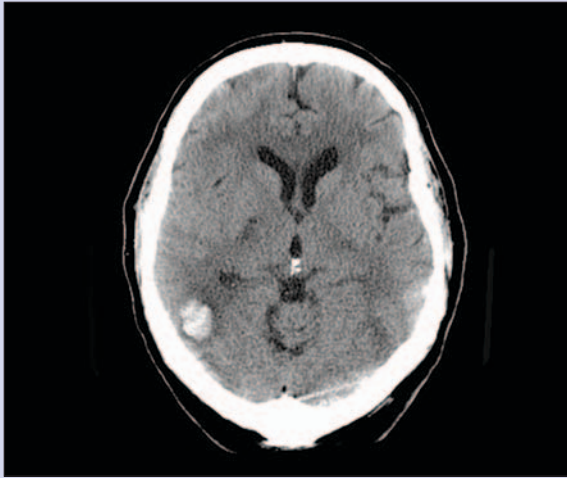


Figure 1. Noncontrast head CT showing a right posterior temporal intra-axial bleed.

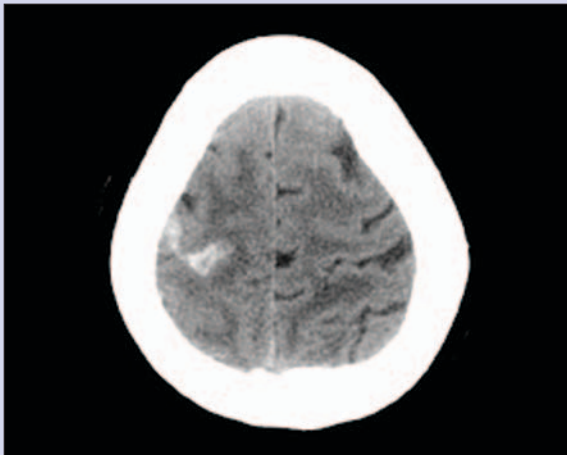


Figure 2. Noncontrast head CT showing a smaller, high, right frontal intra-axial bleed.

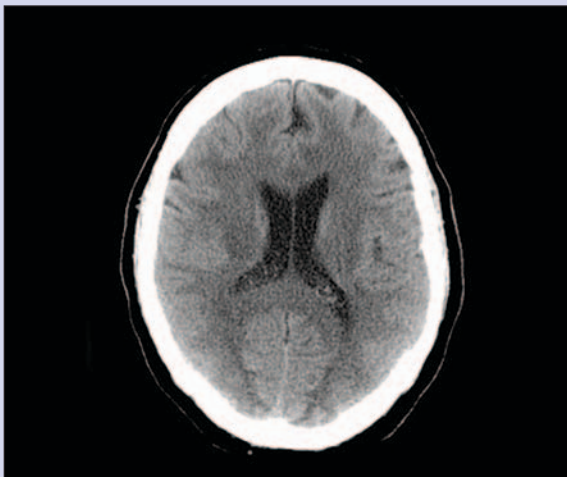


Figure 3. Noncontrast head CT showing bilateral effacement of the cortical sulci posteriorly.

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bilateral effacement of the cortical sulci posteriorly (Figure 3). The differential diagnosis included underlying lymphomatous central nervous system (CNS) involvement and hypertensive hemorrhage.

Later, an MRI revealed diffuse fluid attenuation inversion recovery (FLAIR) signal abnormality in the cortical and subcortical white matter predominantly in the occipital (Figure 4) and high frontal/parietal lobes (Figure 5) and an abnormal FLAIR signal in the cerebellum bilaterally and in the pons (Figure 6). No restricted diffusion existed to suggest an underlying acute infarct. The overall appearance reflected vasogenic edema and was consistent with PRES.

The patient continued to do well clinically and was discharged from the MICU. He went on to receive 4 more cycles of chemotherapy; however, the regimen was changed to the nonvincristine protocol: rituximab, doxorubicin, etoposide, and prednisone (R-AVP).<sup>9</sup> A follow-up MRI of the brain (not shown) obtained 2 months later showed resolution of the vasogenic edema.

### ABOUT THIS CONDITION

PRES manifests as vasogenic edema involving the watershed areas in the brain. PRES affects the cortex as well as the subcortical and deep white matter.<sup>10,11</sup> An MRI is important in excluding underlying cytotoxic edema/infarction by diffusion-weighted imaging as studies have shown that this can develop 11% to 26% of the time.<sup>12,13</sup> PRES can involve the cerebral/cerebellar portions of the brain, basal ganglia, brain stem, and external/internal capsule,<sup>11</sup> and intracranial hemorrhage can occur in 15% of patients.<sup>11,14</sup>

Although HTN is commonly seen, it is absent in 20% to 40% of patients. Moreover, when elevated, BP generally does not exceed the limit of CNS autoregulation (mean arterial pressure > 150-160 mm Hg).<sup>1,15,16</sup>

There are 2 general theories regarding the pathophysiology of PRES. In the first theory, investigators believe that HTN creates a failure of autoregulation and later hyperperfusion/brain edema. In the second theory, investigators see PRES as developing from endothelial dysfunction with subsequent vasoconstriction and hypoperfusion, leading to brain edema and possible ischemia. The presence of HTN in most of the cases and severe HTN in certain animal studies resulting in vasogenic edema and hyperperfusion seem to support the first theory. However, absence of HTN in the smaller percentage of patients and documented hypoperfusion on imaging studies favors the second theory.<sup>17</sup>

The list of medications, including chemotherapy

drugs, that have at times been associated with PRES is growing, including cytarabine, cisplatin, vincristine, cyclosporine, tacrolimus, and high-dose corticosteroids. Notable case reports of PRES following CHOP therapy<sup>9,18,19</sup> include one in which a treatment regimen that avoided cyclophosphamide and vincristine was tried with beneficial results.<sup>9</sup> In the present case report, the use of the R-AVP protocol in place of R-CHOP had similar results. There were no additional episodes of PRES during the next 4 chemotherapy cycles. Unfortunately, despite initial improvement in the lymphadenopathy following the chemotherapy, the patient died of respiratory failure 6 months later.

The etiology and risk factors for developing this condition continue to be controversial as this condition is relatively rare, given the total number of chemotherapy treatments. Immunologic reaction to tumor cells and toxic effect of the chemotherapy on the vascular endothelial cells are hypothesized as possibly being responsible.<sup>17</sup> Treatment involves removal of the offending drug, BP management, and seizure control. Now, increased vigilance in patients with prominent fluid overload, worsening HTN, and renal insufficiency (creatinine > 0.16 mmol/L) seems to be prudent.<sup>9</sup>

### IN SUMMARY

PRES can present with many different systemic conditions, even though it originally was associated with HTN. The etiology of PRES continues to be controversial. Symptoms can be nonspecific but generally include mental status change, visual changes, and seizure. Although MRI helps to confirm the diagnosis, atypical hemorrhage or brain stem involvement may confuse the classic appearance. There are several chemotherapy drugs that have been associated with PRES. Suspecting this condition early when there are neurological changes and the above-mentioned risk factors helps to avoid potential, nonreversible complications. ●

### Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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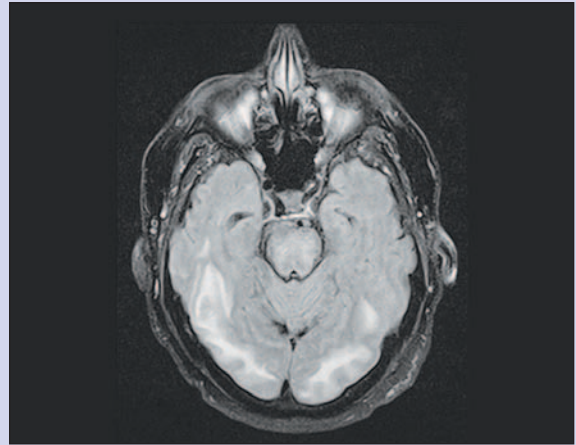


Figure 4. Axial FLAIR MRI of the brain demonstrating abnormal cortical and subcortical white matter signal predominantly in the occipital lobes.

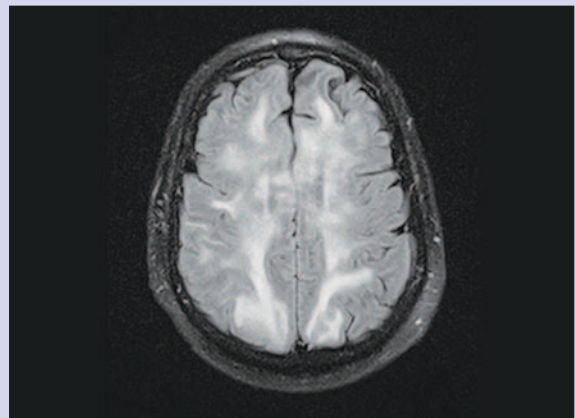


Figure 5. Axial FLAIR MRI brain demonstrating abnormal cortical and subcortical white matter signal in both superior frontal/parietal lobes.

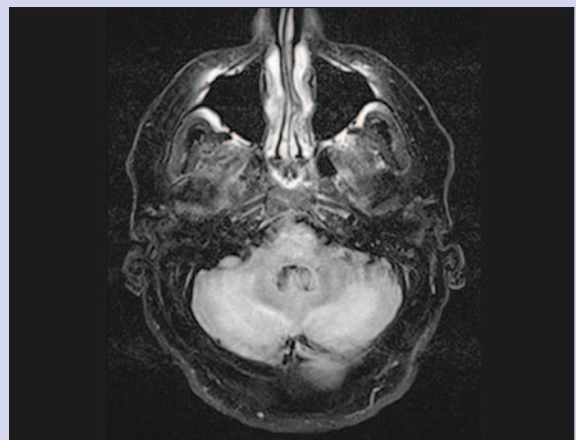


Figure 6. Axial FLAIR MRI brain demonstrating abnormal signal in both cerebellar hemispheres as well as in the pons.

tions—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.

REFERENCES

- Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med*. 1996;334(8):494-500.
- Colosimo C Jr, Fileni A, Moschini M, Guerrini P. CT findings in eclampsia. *Neuroradiology*. 1985;27(4):313-317.
- Weingarten K, Barbut D, Filippi C, Zimmerman RD. Acute hypertensive encephalopathy: Findings on spin-echo and gradient-echo MR imaging. *AJR Am J Roentgenol*. 1994;162(3):665-670.
- Reece DE, Frei-Lahr DA, Shepherd JD, et al. Neurologic complications in allogeneic bone marrow transplant patients receiving cyclosporin. *Bone Marrow Transplant*. 1991;8(5):393-401.
- de Groen PC, Aksamit AJ, Rakela J, Forbes GS, Krom RA. Central nervous system toxicity after liver transplantation: The role of cyclosporine and cholesterol. *N Engl J Med*. 1987;317(14):861-866.
- Kur JK, Esdaile JM. Posterior reversible encephalopathy syndrome: An underrecognized manifestation of systemic lupus erythematosus. *J Rheumatol*. 2006;33(11):2178-2183.
- Bartynski WS, Boardman JF, Zeigler ZR, Shaddock RK, Lister J. Posterior reversible encephalopathy syndrome in infection, sepsis, and shock. *AJNR Am J Neuroradiol*. 2006;27(10):2179-2190.
- Morris EB, Laningham FH, Sandlund IT, Khan RB. Posterior reversible encephalopathy syndrome in children with cancer. *Pediatr Blood Cancer*. 2007;48(2):152-159.
- Haefner MD, Siciliano RD, Widmer LA, Vogel Wigger BM, Frick S. Reversible posterior leukoencephalopathy syndrome after treatment of diffuse large B-cell lymphoma. *Onkologie*. 2007;30(3):138-140.
- Bartynski WS, Grabb BC, Zeigler Z, Lin L, Andrews DF. Watershed imaging features and clinical vascular injury in cyclosporin A neurotoxicity. *J Comput Assist Tomogr*. 1997;21(6):872-880.
- Bartynski WS, Boardman JF. Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. *AJNR Am J Neuroradiol*. 2007;28(7):1320-1327.
- Covarrubias DJ, Luetmer PH, Campeau NG. Posterior reversible encephalopathy syndrome: prognostic utility of quantitative diffusion-weighted MR images. *AJNR Am J Neuroradiol*. 2002;23(6):1038-1048.
- Koch S, Rabinstein A, Falcone S, Forteza A. Diffusion-weighted imaging shows cytotoxic and vasogenic edema in eclampsia. *AJNR Am J Neuroradiol*. 2001;22(6):1068-1070.
- McKinney AM, Short J, Truweit CL, et al. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. *AJR Am J Roentgenol*. 2007;189(4):904-912.
- Kwon S, Koo J, Lee S. Clinical spectrum of reversible posterior leukoencephalopathy syndrome. *Pediatr Neurol*. 2001;24(5):361-364.
- Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson JL Jr. Responses of cerebral arteries and arterioles to acute hypotension and hypertension. *Am J Physiol*. 1978;234(4):H371-H383.
- Bartynski W S. Posterior reversible encephalopathy syndrome, part 2: Controversies surrounding pathophysiology of vasogenic edema. *AJNR Am J Neuroradiol*. 2008;29(6):1043-1049.
- Edwards MJ, Walker R, Vinnicombe S, Barlow C, MacCallum P, Foran JM. Reversible posterior leukoencephalopathy syndrome following CHOP chemotherapy for diffuse large B-cell lymphoma. *Ann Oncol*. 2001;12(9):1327-1329.
- Giménez-Mesa E, Martínez-Salio A, Porta-Etessam J, Berbel García A, Cedena Romero T, Salama Bendoyan P. Reversible posterior leukoencephalopathy in a patient with non-Hodgkin's lymphoma after treatment with CHOP [in Spanish]. *An Med Interna*. 2001;18(11):591-593.

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