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Posterior Reversible Encephalopathy Syndrome in Patients With Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. PRES • Reverse posterior leukoencephalopathy syndrome • Encephalopathy • Chemotherapy

Abstract

Background. Posterior reversible encephalopathy syndrome (PRES) is characterized by neurologic symptoms with typical lesions on neuroimaging and may be associated with chemotherapy and immunosuppressive agents used in patients with cancer. We described the spectrum of PRES at a major cancer center.

Methods. We reviewed charts of adults with PRES between 2005 and 2011 at Memorial Sloan Kettering Cancer Center for clinical information and outcome.

Results. We identified 21 women (68%) and 10 men (median cohort age: 58 years). Solid tumors ($n = 22$, 71%) were more common than hematologic ($n = 8$) or primary brain malignancies ($n = 1$). Prior brain irradiation (16%) and central nervous system metastases (10%) were uncommon. There were 55% who received chemotherapy or targeted therapy within the month preceding PRES, including 6 patients who received bevacizumab; PRES followed allogeneic stem cell transplantation in 5 (16%). Presenting symptoms included confusion (71%), seizure (58%), and headache (48%). Maximum systolic and diastolic blood pressures were similar among patients grouped by cancer type, chemotherapy or bevacizumab use, and atypical imaging. Moreover, 37% of patients with both magnetic resonance imaging (MRI) and computed tomography (CT) had normal CT concurrent with PRES on MRI, and 84% returned to neurologic baseline at a median of 7.5 days (range: 1–167 days) from onset. Successful anticonvulsant taper was achieved in 51%. Chemotherapy rechallenge was attempted in 41% without recurrent PRES. Autopsy revealed nonspecific changes isolated to radiographically affected areas in one of two patients.

Conclusion. Recent chemotherapy, particularly bevacizumab, is common in cancer patients with PRES. Clinical and radiographic presentations may vary; MRI appears more sensitive than CT. Anticonvulsant taper and chemotherapy rechallenge is often possible. ***The Oncologist*** 2015;20:806–811

Implications for Practice: Posterior reversible encephalopathy syndrome is characterized by neurologic symptoms with typical lesions on neuroimaging and may be associated with chemotherapy and immunosuppressive agents used in patients with cancer. Clinical and radiographic presentations are protean, and magnetic resonance imaging is more sensitive than computed tomography. Recovery is common, and many patients can be successfully rechallenged with the apparently offending chemotherapy agent or regimen.

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a well-described clinicoradiographic entity of encephalopathy, seizures, and other neurologic symptoms, with characteristic neuroimaging demonstrating lesions with posterior and white matter predominance [1–5]. Variant imaging features such as contrast enhancement, restricted diffusion, and anterior or basal ganglia involvement have been described [6–8]. PRES is typically associated with hypertension, the puerperium, and immunosuppressive agents used in solid organ and hematopoietic stem cell transplants (SCTs) [9–14]. Theories concerning its pathophysiology include overwhelmed cerebral autoregulation allowing breakthrough hyperemia and direct cytotoxic effect on endothelial cells leading to breakdown of the blood-brain barrier (BBB) [15, 16].

Case reports have implicated various chemotherapy agents and other drugs commonly used in patients with cancer [2, 11, 17–21], although no large study has focused on the cancer population. As molecularly targeted therapy becomes more prevalent in oncology, newer agents may become important contributors to this condition [22–30]. We aimed to describe the demographics, clinical course, and outcome of PRES in patients with cancer to better identify potential associations in this vulnerable population.

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Methods

With Institutional Review Board approval, we retrospectively identified adults with cancer who were diagnosed with PRES at Memorial Sloan Kettering Cancer Center (MSKCC) between January 1, 2005, and June 30, 2011. Charts were reviewed and demographic factors were recorded. Tumor types were broadly divided into solid, hematologic, and primary brain groups. Cancer was deemed inactive if most recent relevant testing revealed no evidence of active disease. All chemotherapeutic and biologic targeted agents administered in the month prior to PRES diagnosis were recorded.

We reviewed the initial computed tomography (CT) or magnetic resonance imaging (MRI) scans demonstrating PRES, but also assessed the date of symptom onset based on the reported medical history. We recorded the peak systolic blood pressure (SBP) and diastolic blood pressure (DBP) on the day of symptom onset and at neurologic evaluation.

We defined MRI PRES as primarily subcortical lesions present on standard fluid-attenuated inversion recovery (FLAIR) sequences in the setting of acute neurologic symptoms without radiographic evidence of acute infarct or other processes such as new brain metastases. We defined CT PRES as new hypodensities primarily in the subcortical white matter. We assessed scans for diffusion restriction, contrast enhancement, unilateral disease, and disease affecting the basal ganglia or thalamus.

The approximate date of resolution of presenting symptoms was noted. For cases in which chemotherapy was administered within a month of PRES, subsequent rechallenge with the same agent or regimen was noted. We recorded dates of follow-up imaging and last follow-up or death in all patients.

Survival from PRES was calculated using the Kaplan-Meier method. Differences in median SBP and DBP between groups were assessed using the Wilcoxon rank-sum test. Differences in proportions of various radiographic abnormalities among patients by tumor type and recent chemotherapy administration were assessed using Fisher's exact test.

Results

Baseline Characteristics

We identified 31 patients, of whom 21 (68%) were women, with a median age of 58 years (Table 1). Twenty-four (77%) had active cancer at PRES diagnosis. Among those with inactive cancer, 4 were following SCT and 3 had recent resections of low-stage solid tumors.

Seventeen patients (55%) received chemotherapy or targeted agents in the month preceding PRES (Table 2). Six (35%) of these patients received bevacizumab, either as monotherapy ($n = 1$) or in combination with other agents ($n = 5$). The median number of bevacizumab doses received prior to development of PRES was 8 (range: 1–19). Over the time period studied, 5,052 adult patients received bevacizumab at MSKCC, yielding a minimum incidence of bevacizumab-related PRES of 0.1%. Other common chemotherapies included taxanes (5), platinum derivatives (5), and vinca alkaloids (3). Only three patients received other targeted or biologic agents; two received sunitinib (each in combination with bevacizumab), and one received rituximab.

Table 1. Patient characteristics

Characteristic	Result
Gender, *n* (%)	
Women	21 (68)
Men	10 (32)
Age, median (range)	58 (20–77)
Cancer diagnosis	
Solid tumor, *n* (%)	22 (71)
Lung	4
Ovarian	4
Renal	3
Gastric	3
Other solid	8
Hematologic malignancy	8 (25)
Leukemia	6
Lymphoma	2
Primary brain	1 (3)
Glioblastoma	1
Time to PRES from cancer diagnosis, months, median (IQR)	22 (7–48)
Medical history, *n* (%)	
Hypertension	18 (58)
Hematopoietic stem cell transplant	5 (16)
Brain irradiation	5 (16)
CNS cancer involvement	4 (13)
Cancer inactive	7 (23)

Abbreviations: CNS, central nervous system; IQR, interquartile range; PRES, posterior reversible encephalopathy syndrome.

Table 2. Chemotherapy/targeted therapy within 30 days

Agent	*n* (%)
Any agent	17 (55)
Any cytotoxic agent[a]	13 (42)
Docetaxel	3
Carboplatin	2
Oxaliplatin	2
Vincristine	2
Paclitaxel	2
Irinotecan	2
Any biologic/targeted	7 (23)
Bevacizumab	6
Combination regimen	12 (38)
Carboplatin/paclitaxel	2
Bevacizumab/sunitinib	2

[a]Listed agents may be part of the same combination regimen.

Five patients (three female; four with leukemia, one with lymphoma) had a history of SCT, all allogeneic. PRES occurred a median of 44 days after transplant (range: 5–391 days). Four patients were taking immunosuppressive medications that included tacrolimus ($n = 2$), cyclosporine ($n = 2$), and everolimus ($n = 1$); one patient was not taking any immunosuppressive medication. Over the period of time under study, 745 adult

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patients underwent allogeneic SCT at our institution, yielding a minimum incidence of transplant-related PRES of 0.7%.

Of five patients with prior brain irradiation, three received total body irradiation as part of conditioning for SCT, and two received focal brain radiotherapy, one for glioblastoma and one for brain metastasis. The median time from radiation to PRES was 9 months (range: 1.2–23.5 months).

Clinical Presentation

Symptoms were present for a median of 1 day prior to diagnostic imaging (range: 0–12 days). Notable symptoms included some degree of confusion in 22 patients (71%), headache in 15 (48%), and visual disturbance in 8 (26%). Seizures occurred in 18 patients (58%). Four patients (13%) presented with a severely depressed level of consciousness (Glasgow Coma Scale <8).

Blood pressure data were available for all patients, and the median maximum SBP and DBP on the day of symptom onset were 190 mm Hg (interquartile range [IQR]: 170–200 mm Hg) and 100 mm Hg (IQR: 90–115 mm Hg), respectively. There were no significant differences in maximum blood pressures between patients grouped by sex, tumor type, recent bevacizumab, or recent chemotherapy use. At neurologic evaluation, a median of 1 day (IQR: 0–4 days) after PRES diagnosis, median recorded SBP and DBP were 160 mm Hg (IQR: 140–180 mm Hg) and 90 mm Hg (IQR: 70–100 mm Hg), respectively.

Imaging Characteristics

MRI was obtained in 30 patients, and CT alone was obtained in 1 (Table 3). Classic PRES, as defined by symmetric posterior lesions without enhancement, restricted diffusion, or deep nuclei involvement, was present in only 7 (23%). Of 27 patients who had both MRI and CT, 10 (37%) had a negative head CT concurrent with MRI demonstrating PRES (Fig. 1).

There was no significant difference in maximum SBP or DBP between patients with or without deep gray nuclei involvement or with a diffuse versus posterior predominant PRES. There was no difference between solid and hematologic malignancy groups in proportions of patients with deep gray nuclei involvement or diffuse PRES.

Seizure Management

Eighteen patients (58%) experienced a seizure at presentation. Electroencephalogram was performed in 19 patients and was abnormal in 17 (89%); the majority of abnormalities were limited to generalized slowing (12 patients, 71%), although 5 patients (26%) had epileptogenic discharges present. Twenty-one patients (68%) were treated with antiepileptics at the time of PRES, 18 for seizures and 3 for prophylaxis. After a median follow-up of 4.9 months (range: 0.3–59.6 months), none of the 18 patients with PRES-related seizures experienced a recurrence. Eleven patients (52%) were weaned off antiepileptics between 1 month and 6 months from the onset of PRES.

Management and Outcomes

Twenty-six patients (84%) experienced resolution of their neurologic symptoms a median of 7.5 days (range: 1–167 days) from onset. Four of 5 patients who did not recover to baseline had rapid progression of their underlying cancer as a potential cause of persistent altered mental status. A fifth patient died while intubated for pulmonary-related causes without follow-up neuroimaging.

Follow-up imaging was available for 26 patients (84%), 22 with MRI and 4 with CT only, at a median of 20 days from the original scan (IQR: 9–45 days). Twenty-one patients (81%) had complete resolution of their initial PRES lesions; 5 patients (19%) experienced partial resolution with some persistent FLAIR signal abnormality at the site of the original PRES lesions.

Table 3. Imaging characteristics

Characteristic	*n* (%)
Classic PRES	7 (23)
PRES location	
Posterior	17 (55)
Diffuse	14 (45)
Unilateral PRES	4 (13)
Deep nuclei involvement	7 (23)
Restricted diffusion (DWI)	6 (21)
Contrast enhancement	4 (15)
Intracranial hemorrhage	9 (29)
Intracerebral	4
Subarachnoid	3
Microhemorrhages	2

Abbreviations: DWI, diffusion weighted imaging; PRES, posterior reversible encephalopathy syndrome.

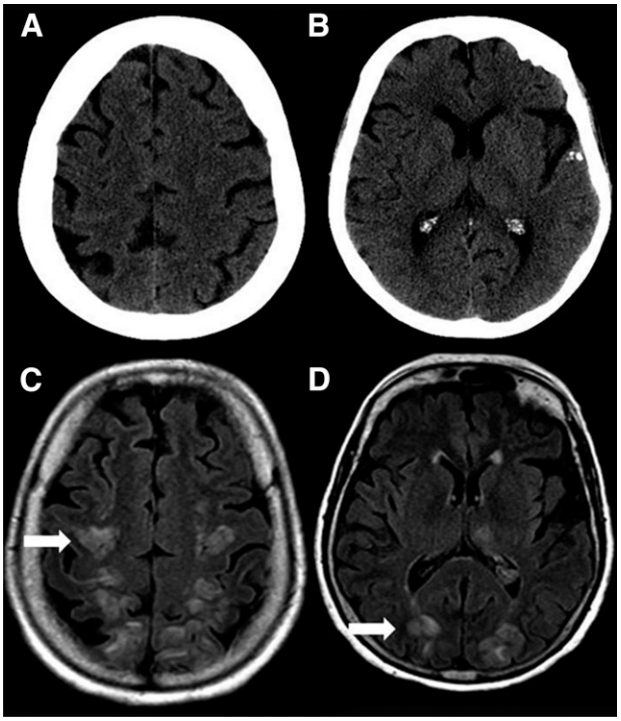

Figure 1. A 73-year-old woman with gastrointestinal stromal tumor developed headaches and confusion in the setting of abdominal pain 4 days following partial gastrectomy. Computed tomography of the head **(A, B)** did not reveal parenchymal abnormality. Subsequent magnetic resonance imaging the next day revealed numerous nonenhancing fluid-attenuated inversion recovery hyperintensities in the posterior white matter consistent with posterior reversible encephalopathy syndrome **(C, D)**. She eventually made a complete neurologic recovery.

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Seven patients (23%) were managed with continuous infusion of an antihypertensive medication, and six required intubation for airway protection. Six patients (19%) died before discharge; none of the deaths were related directly to PRES. Of the 25 patients alive at discharge, 20 (75%) remained on oral antihypertensive medication. Seventeen patients (55%) were discharged home, and 8 (26%) were sent to a hospice or rehabilitation facility. Median length of hospital stay was 19.5 days (IQR: 5–40 days). At a median follow-up of 5 months, 8 patients (26%) were alive; median overall survival from PRES onset for the entire cohort was 5.5 months (95% confidence interval: 2.3–21.6 months).

Of 17 patients who received any chemotherapy, hormonal, or targeted agent within 1 month of PRES, 7 (41%) were rechallenged with the agent in question, and none developed PRES a second time. Two patients (6%) experienced recurrent PRES. One initially developed PRES following administration of carboplatin and paclitaxel with resolution of symptoms and imaging findings. She subsequently was rechallenged with this regimen without recurrence but recurred after receiving pemetrexed 2 years later. Another developed PRES shortly after treatment with rituximab, doxorubicin, vincristine, and cyclophosphamide (RCHOP regimen) and improved clinically and radiographically but recurred in the setting of elevated blood pressures 1 month later without chemotherapy; she later received RCHOP without another episode of PRES. Combination carboplatin and paclitaxel was readministered in two patients; other agents reintroduced included RCHOP, hydroxyurea, leuprolide, combination docetaxel and irinotecan, and sunitinib in one each. No patient who developed PRES while receiving bevacizumab or an immunosuppressant was rechallenged with either agent.

Pathology

Two of the six patients who died underwent an autopsy. A 24-year-old woman who developed PRES following allogeneic SCT for acute myelogenous leukemia died of sepsis 3 months after recovering from PRES; her brain demonstrated only mild and diffuse astrogliosis of the cerebral hemispheric white matter. A 48-year-old man developed PRES following allogeneic transplant for refractory chronic myelogenous leukemia and died 4 months after making a radiographic recovery from PRES. He was imaged with CT only. His brain demonstrated lamellated perivascular mineralizations and small numbers of macrophages associated with scattered blood vessels most prominent in the white matter of brain previously affected by PRES (Fig. 2).

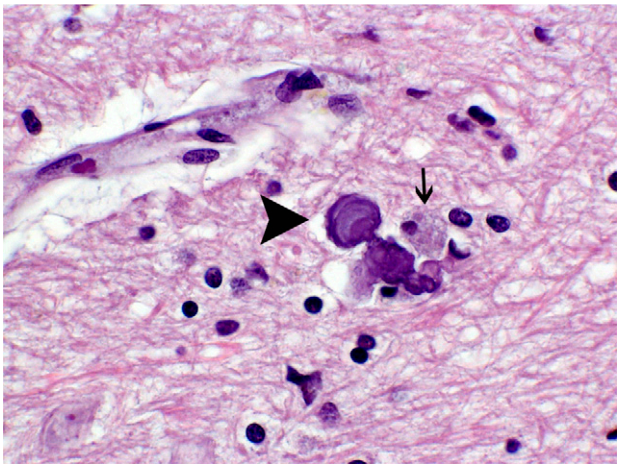

Figure 2. Pathologic examination of postmortem brain tissue from a patient who died 4 months following resolution of posterior reversible encephalopathy syndrome demonstrates lamellated perivascular calcifications (arrowhead) and associated macrophages (arrow) in white matter affected on imaging (hematoxylin and eosin, ×100).

Discussion

We reported the largest study of PRES in cancer patients published to date. PRES was initially described in 1996 in patients with elevated blood pressure or eclampsia or in those receiving immunosuppressive medications [1]. Subsequent reports have implicated a wide variety of putative etiologies and have attempted to correlate PRES etiology with clinical presentation [31, 32] or lesion location [5, 6, 8]. The absence of a unified method of radiographic assessment, objective disease definition, or means to definitively link potentially causative risk factors to the syndrome have led to conflicting or inconsistent results [33]. Prior studies of PRES have included a minority of patients with chemotherapy as a presumed cause [4, 5, 32], have focused on stem cell transplant recipients [9, 10, 13, 14], or have been small series limited to childhood cancers [2, 11, 12]. No prior study has examined this syndrome specifically in adult cancer patients.

Our patients were predominantly women, consistent with a number of prior series [5, 6, 8, 31]. In a series of 302 patients with neurologic complications, including PRES associated with allogeneic SCT, female gender was an independent multivariate risk factor [13]. The reasons for the predilection in women are unclear, although a gender-related limit to cerebral vessel autoregulatory ability may be responsible.

There was no significant association between degree of SBP or DBP elevation with PRES location, tumor type, or recent administration of chemotherapy or bevacizumab. A retrospective study of 96 patients with PRES demonstrated that those who received recent chemotherapy ($n = 16$) or immunosuppressive medications ($n = 22$) had significantly lower mean arterial pressure (MAP) than those with PRES from other etiologies [5]. Other studies found no significant correlation between extent or location of PRES involvement and SBP [8, 31]. These seemingly contradictory findings may reflect different study definitions because MAP may reflect a more sensitive and specific physiologic metric of blood pressure than specific systolic or diastolic values. MAP may also reflect differences in blood pressure at syndrome onset compared with blood pressure at diagnosis. As observed in our cohort, blood pressure had substantially improved, and normalized in some patients, by the time of neurologic evaluation. These findings, along with the frequent discrepancy between normal head CT and MRI demonstrating PRES, highlight the need for high clinical suspicion and the importance of MRI to establish the diagnosis.

Few patients in our series had received prior brain radiotherapy or had central nervous system involvement with their cancer. Although total body irradiation conditioning was identified as an independent predictor of neurologic toxicity, including PRES following allogeneic SCT [13], few reports have

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associated brain radiation with PRES. The paucity of patients with brain tumors among our population suggests that neither the intrinsic perturbation of the BBB by a malignancy nor the radiotherapy used to treat such tumors represents a significant risk factor for PRES.

Our 0.7% incidence of PRES in post-SCT patients was far below that reported by other series devoted exclusively to SCT patients. Studies of neurologic complications in allogeneic SCT cohorts have yielded rates of PRES of 6%–7% [10, 13]. A study of PRES related to tacrolimus use in post-SCT patients reported an incidence of 1.6%, save for a rate of 7.7% in the cord-blood transplant cohort [34]. Possible explanations for the lower rate observed in our patients include incomplete ascertainment due to the retrospective nature of our study or possibly the increased use at our institution of T-cell depleted transplants, minimizing the use of immunosuppressants.

Chemotherapy as a potential risk factor for PRES has been described primarily in case reports. More than one-half of our patients had received chemotherapy or targeted therapy in the month preceding PRES, and more than one-third had received combination therapy. Bevacizumab use in the month prior to PRES was relatively common, almost always in combination with cytotoxic chemotherapy, consistent with prior reports implicating this agent [22, 26, 30]. In a study of more than 10,000 patients treated with bevacizumab, only 2 (0.02%) developed PRES in contrast to our 0.1% incidence [30]. Interestingly, we detected no significant difference between peak blood pressures in the patients receiving bevacizumab compared with the remainder of the cohort, despite this agent's well-described propensity for causing hypertension; however, small sample size may have limited this analysis. Notably, no patient receiving bevacizumab for a malignant glioma developed PRES, despite the frequent use of bevacizumab in this population. Sunitinib was used in two of our patients, both combined with bevacizumab, also consistent with prior reports [24]; other targeted biologic agents were not overrepresented in our study.

Repeated administration of potentially offending agents was attempted in several patients without recurrent PRES. Successful chemotherapy rechallenge with cisplatin following PRES has been reported [21], as has one case of successful reintroduction of bevacizumab [27]. Our data suggest that judicious chemotherapy re-exposure may be safe if accompanied by vigilant clinical monitoring and blood pressure control.

In contrast to the pediatric literature, in which death and permanent neurologic deficits including epilepsy have been reported in 12%–33% of children with PRES [2, 11, 12], the majority of our patients were successfully weaned off antiepileptics, similar to prior reports in adults [35]. Our data support the suggestion that antiepileptics may be safely tapered in patients who have recovered clinically and radiographically from PRES.

Pathologic examination of affected brain in PRES is rare. Prior case reports have demonstrated direct [36] and indirect [37] evidence of demyelination on pathologic material obtained during the PRES episode, whereas others have revealed nonspecific changes such as astrogliosis [38]. Similarly, the postmortem examination months after resolution of symptoms demonstrated nonspecific findings in two of our patients. It is notable that one case demonstrated pathologic abnormalities limited to the brain region affected on CT, although MRI was never obtained in this patient. Nonetheless, the pathologic findings suggest that PRES may lead to chronic brain abnormalities outlasting imaging and clinical features. Notably, neither patient had received brain irradiation at any point in the disease course to potentially explain the observed pathologic changes.

Limitations of our study include failure to identify subclinical or inadequately imaged patients and any MSKCC patients whose PRES was diagnosed and treated at an outside hospital. Our effort to link specific chemotherapy use with PRES is limited by the difficulties inherent in establishing clear causality between potential inciting factors and the syndrome and by our small study population. It is admittedly difficult to establish a firm causative connection between chemotherapy or targeted therapy agents and observed toxicities such as PRES, particularly when a window of 1 month between treatment and development of symptoms is used. Nonetheless, many of these medications may have an extended biological effect by virtue of their pharmacokinetic properties, and the authors decided in favor of overinclusion to better describe potential toxicities as completely as possible. Finally, given that PRES is defined by clinical and radiographic criteria, it is possible that the syndrome may reflect a continuum of loosely related entities of varied pathophysiology.

Author Contributions

Conception/Design: Samuel Singer, Christian Grommes, Lisa M. DeAngelis
Provision of study material or patients: Samuel Singer, Christian Grommes, Lisa M. DeAngelis
Collection and/or assembly of data: Samuel Singer, Christian Grommes, Anne S. Reiner, Lisa M. DeAngelis
Data analysis and interpretation: Samuel Singer, Christian Grommes, Marc K. Rosenblum, Lisa M. DeAngelis
Manuscript writing: Samuel Singer, Lisa M. DeAngelis
Final approval of manuscript: Samuel Singer, Christian Grommes, Anne S. Reiner, Marc K. Rosenblum, Lisa M. DeAngelis

Disclosures

The authors indicated no financial relationships.

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