Gemcitabine Associated With Posterior Reversible Encephalopathy Syndrome (PRES): A Case Report and Review of the Literature

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Introduction

Posterior reversible encephalopathy (PRES) is a clinical radiographic syndrome that is often characterized by headaches, altered consciousness, visual disturbances, and seizures in association with typical radiologic findings of vasogenic edema involving bilateral parietal-occipital lobes.[1] However, the syndrome is not always reversible, and it is often not confined to either the white matter or the posterior regions of the brain. The pathogenesis remains unclear but is usually associated with hypertensive encephalopathy, eclampsia, renal failure, general anesthesia, and several immunosuppressants.[2,3] Chemotherapy agents (eg, cisplatin,[4] cytarabine,[5] and gemcitabine[6] [Gemzar, Eli Lilly]) and targeted therapies (including rituximab[7] [Rituxan, Genentech/Biogen Idec Pharmaceuticals] and bevacizumab[8] [Avastin, Genentech]) have been shown to cause PRES. After reviewing the literature, there are 5 cases in which gemcitabine was reported to cause PRES, usually when combined with other chemotherapy, primarily cisplatin. In this case, we describe a patient who developed PRES and occlusion of the celiac artery, renal vein, and splenic vein while receiving single-agent gemcitabine for metastatic breast cancer.

Case Report

A 57-year-old woman was diagnosed with breast cancer via localized excisional biopsy in September 2008. Pathology revealed invasive ductal carcinoma that was well-differentiated and had a low nuclear grade with lobular features. It measured 1.8 cm in greatest dimension, and was estrogen receptor (ER) 90% positive, progesterone receptor (PR) 40% positive, and human epidermal growth factor receptor (HER)-2/neu negative with positive margins. A positron emission tomography (PET)/computed tomography (CT) scan revealed extensive osseous lesions consistent with malignancy. She was started on anastrozole (Arimidex, AstraZeneca) 1 mg daily and zoledronic acid 4 mg once monthly in November 2008. Anastrozole was discontinued in June 2009 due to disease progression, and the patient's treatment was changed to capecitabine (Xeloda, Roche). In September 2010, a PET scan revealed disease progression; her chemotherapy was changed to gemcitabine (1,250 mg/m^2 on days 1 and 8 of a 21-day cycle). She received gemcitabine (2,260 mg total dose) first on October 27, and then on November 4, 17, and 24.

The patient presented to the emergency room 5 days after the last dose of gemcitabine. She complained of severe abdominal pain, nausea, vomiting, and anorexia that had persisted for 3 days. Other symptoms included mild headache and visual blurriness. At the time of presentation, her blood pressure was 226/78 mmHg; there was no history of hypertension, and her blood pressure had been normal during previous clinic visits (systolic blood pressure [SBP], 120–140 mmHg). The patient developed right gaze preference, which was followed by a witnessed, generalized tonic-clonic seizure. She was given lorazepam followed by a loading dose of fosphenytoin, with resolution of symptoms. CT without contrast of the brain was normal; CT with contrast of the abdomen and pelvis revealed thrombosis of the celiac artery, left renal vein, and splenic vein. She was given intravenous metoprolol in the emergency room, and her blood pressure improved.

The patient was admitted into the intensive care unit. She was evaluated by neurology professionals, and an electroencephalogram (EEG) revealed diffuse slowing with no epileptiform activity. The patient was

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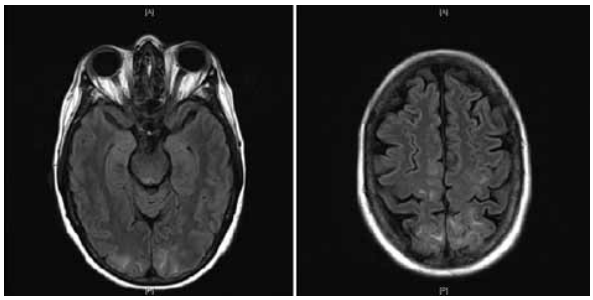

Figure 1. Magnetic resonance imaging (MRI) on presentation. Flair images revealing white matter increased signal intensity compatible with edema seen symmetrically in the posterior brain involving the occipital lobes extending into parietal lobes bilaterally.

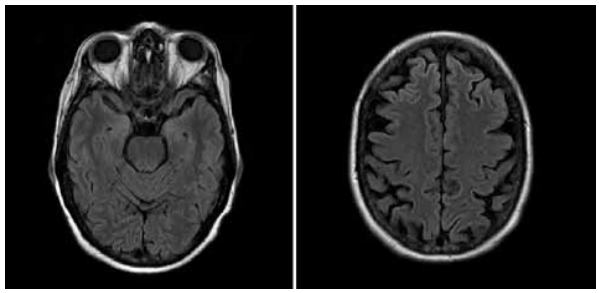

Figure 2. Magnetic resonance imaging (MRI) 2 months after original. Resolution of white matter increased signal intensity.

continued on maintenance phenytoin and had no seizure recurrence. A brain magnetic resonance imaging (MRI) revealed white matter increased signal intensity on T2-weighted images involving the occipital lobes, extending into parietal lobes bilaterally, and thalamus (Figure 1). The clinical radiographic syndrome was consistent with PRES. While in the intensive care unit, she was started on enoxaparin for the treatment of celiac artery, left renal vein, and splenic vein thrombosis. She developed progressive decline in her platelet count, to as low as 58,000 µL. Heparin-induced thrombocytopenia antibody was negative, and serotonin release assay was also negative. Peripheral smear did not reveal any schistocytes to suggest thrombotic thrombocytopenic purpura. Her thrombocytopenia gradually improved and was thought to be secondary to gemcitabine.

The patient was transferred out of the intensive care unit 2 days later. She was continued on metoprolol for her initial elevated blood pressure; with resolution of PRES, her blood pressure normalized and she did not require therapy. Treatment with phenytoin was changed to levetiracetam. The patient was discharged from the hospital 10 days later. Since gemcitabine was the most likely culprit causing PRES, it was discontinued. At the time of follow-up, she was started on treatment with vinorelbine for breast cancer. A repeat MRI 2 months later revealed complete resolution of the white matter changes (Figure 2). The patient was weaned off of levetiracetam and did not have any recurrence of symptoms. At present, she is tolerating therapy and doing well.

Discussion

PRES was first described by Hinchey and associates in 1996, after observing a series of patients who presented with headaches, altered mental status, seizures, visual loss, and radiologic findings of reversible symmetric posterior cerebral white-matter abnormalities on MRI.[1] Hinchey hypothesized that these patients had reversible posterior leukoencephalopathy syndrome (RPLS). The pathogenesis remains unclear, but is usually associated with hypertensive encephalopathy, eclampsia, renal failure, general anesthesia, immunosuppressants, and chemotherapeutic agents.[2-8]

Several antineoplastic agents have been implicated as potentially PRES-inducing, including cytotoxic and targeted agents.[1-11] A clear explanation of the mechanisms by which antineoplastic agents cause PRES has been difficult to establish, and precise mechanisms may be highly variable, depending on the specific agent. Hinchey and colleagues proposed that the mechanisms responsible for PRES include disordered cerebral regulation and endothelial dysfunction.[1] When the upper limit of cerebral autoregulation is exceeded, brain hypoperfusion occurs, which may lead to breakdown of the blood brain barrier and allow for extravasation of fluid and blood products into the brain parenchyma.[12] In severe cases, autoregulation may lead to reactive focal vasoconstriction, resulting in cerebral infarction.[13] Endothelial dysfunction has been implicated in PRES, especially with cytotoxic drugs. These drugs may have direct toxicity on vascular endothelium, leading to capillary leakage and blood-brain barrier disruption that may trigger vasogenic edema.[4]

Russell and coworkers first described the association between gemcitabine and PRES in 2001.[9] Similarly, Larsen and Hansen reported 3 cases of separate malignancies in which gemcitabine was administered with cisplatin and/or paclitaxel.[10] Central nervous system symptoms developed in all 3 patients, and radiographic evidence of leukoencephalopathy was present in 1 patient after gemcitabine was re-administered.[10] Rajasekhar and coauthors reported PRES that was associated with the use of gemcitabine combined with erlotinib.[11] Among the recent literature describing cases of PRES after administration of gemcitabine and cisplatin[6] or carboplatin,[14] 2 additional cases have reported PRES associated with gemcitabine-based combination regimens. As depicted in Table 1,

Table 1. Gemcitabine-Containing Regimens Associated With PRES Reported in the Literature

Author	Patient Age (years); Sex	Malignancy	Chemotherapy	Gemcitabine Dosing	Timing of PRES
Russell et al[9]	55; Female	Stage IV NSCLCA and IgA MM	Gemcitabine and erythropoietin	940–1,640 mg/m^2	3 days after 5 doses over 2 months
Larsen and Hansen[10*]	63; Female	Stage III ovarian	Gemcitabine, cisplatin, and paclitaxel	1,000 mg/m^2 Day 1, Day 8	2 days after 3rd cycle
Rajasekhar and George[11]	65; Female	Stage III pancreatic	Gemcitabine and erlotinib	1,000 mg/m^2 Day 1, Day 15 of 28-day cycle	10 days after 3rd cycle
Kwon et al[6]	58; Female	Stage IV gallbladder	Gemcitabine and cisplatin	1,200 mg/m^2 Day 1, Day 8 of 21-day cycle	14 days after 3rd cycle
Bhatt et al[14]	45; Female	Small-cell lung	Gemcitabine and carboplatin	1,250 mg/m^2	Hours after 2 doses over 4 weeks

*Of note, Larsen and Hansen reported 3 cases of PRES, but only 1 patient had PRES that was confirmed radiographically.
IgA MM=immunoglobulin A multiple myeloma; NSCLCA=non-small cell lung cancer; PRES=posterior reversible encephalopathy syndrome.

PRES occurred with different gemcitabine-containing regimens. In all of the reported cases, the symptoms occurred after more than 1 dose of gemcitabine.

Neurologic toxicities associated with gemcitabine are uncommon; somnolence and peripheral neuropathy have been reported in very few patients. However, as depicted in this case and other reports, PRES is a clinical entity that can develop after gemcitabine administration. Although PRES is a reversible process in the majority of cases, failure to recognize the syndrome and correct the underlying cause can result in severe central nervous system injury or death. Thus, increasing awareness of PRES is essential in patients who undergo chemotherapy with these agents.

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Review

Posterior Reversible Encephalopathy Syndrome

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Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiologic entity characterized by headaches, seizures, altered mental status, and visual disturbance that is associated with white matter vasogenic edema predominantly affecting the occipital and parietal lobes of the brain. This edema is potentially reversible in totality, but in some cases, it can persist without recovery.[1]

PRES has gained substantial recognition since its initial description by Hinchey and associates in 1996.[1] Over the last few years, this syndrome was also referred to as reversible occipitoparietal encephalopathy, hyperperfusion encephalopathy, hypertensive encephalopathy, posterior leukoencephalopathy, reversible posterior cerebral edema syndrome, and potentially reversible encephalopathy. Casey and colleagues proposed the term "posterior reversible encephalopathy syndrome" in 2000.[2]

The cause of PRES is not yet understood. Autoregulatory failure with resultant vasodilatation, as seen in hypertensive encephalopathy, is often cited as the underlying mechanism.[3,4] PRES is commonly seen in the setting of hypertension, likely due to a breakdown of autoregulation. The autoregulation is an intrinsic function of the vasculature of the brain, designed to maintain a stable blood flow independent of the variation of blood pressure. In animal models, when a severe increase in blood pressure beyond the upper limit of autoregulation was caused, arteriolar dilation, injury to the capillary bed, vasogenic edema, and vessel injury with altered artery morphology often occurred.[5] The upper limits of autoregulation vary among individuals. These limits primarily depend on the capillary hydrostatic pressure, under the influence of the systolic blood pressure, the integrity of the blood-brain barrier, and other situations (various disease and neurotoxic medications).[6]

The most common neuroimaging presentation of PRES is the parieto-occipital subcortical T2 hyperintensity without enhancement; however, other structures such as the brain stem, cerebellum, and frontal and temporal lobes may also be involved, and although the abnormality primarily affects the subcortical white matter, the cortex and basal ganglia may also be affected. The edema usually reverses completely.[7,8] In a review of 53 cases of PRES, Liman and coworkers found the total reversibility of the edema in 58% of the cases, and a partial reversibility in 26% of the cases.[9]

Numerous factors can trigger PRES; acute elevation of blood pressure, abnormal renal function, and immunosuppressive therapy are the most common.[1] Other possible etiologies are eclampsia,[10-12] transplantation,[13] neoplasia and chemotherapy,[8] and acute or chronic renal disease.[14] In general, cases of PRES are associated with higher levels of blood pressure or with renal disorder.[1,8-10]

Truong and associates described a very interesting case of a 57-year-old woman with metastatic breast cancer who presented with clinical signs of PRES (headache, nausea, visual disturbance, and seizure) associated with hypertension 5 days after the use of gemcitabine.[15] In acute brain magnetic resonance imaging (MRI; T2) an increased signal in occipital and parietal lobes was identified. The patient received another MRI 2 months later, which revealed the reversibility of the lesions.

In a previous report, our group described a case of a 74-year-old woman who received adjuvant gemcitabine (1,000 mg/m^2 on days 1, 8, and 15 of each 28-day cycle) as monotherapy for stage IIa pancreatic adenocarcinoma. During this treatment, she developed a tonic-clonic seizure and visual blurring; a brain MRI (T2 and fluid-attenuated inversion recovery image sequences) revealed a subcortical T2 hyperintensity in both occipital and temporal lobes. In this report, we demonstrated that gemcitabine was associated with PRES, independent of other drugs.[8]

No single antineoplastic class or agent has been consistently associated with PRES, although some chemotherapeutic agents may cause direct central nervous system microvascular injury.[16] PRES is more likely to be encountered after high-dose multidrug cancer therapy, typically in hematopoietic malignancies.[17,18]

The precise cause of PRES remains enigmatic, and the optimal treatment has yet to be established. However, immediate treatment of severe hypertension, seizures, and withdrawal of causative agents have been the primary strategies for treating PRES. If not recognized and treated promptly and appropriately, this syndrome can progress to ischemia and hemorrhage, with permanent deficits. Therefore, continuing to recognize and study PRES is of crucial importance for physicians and researchers.

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