Clinical Case Report

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# A case report of posterior reversible encephalopathy syndrome in a patient receiving gemcitabine and cisplatin

Hannah Cherniawsky, MD, BMedSci[a,*], Neesha Merchant, MD[b], Micheal Sawyer, MD, BSc Phm[b], Maria Ho, MD[b]

**Abstract**

**Rationale:** Posterior reversible encephalopathy syndrome (PRES) is a subacute syndrome causing characteristic neurologic and radiologic findings. PRES is predominantly caused by malignant hypertension though it has been associated with immunosuppressive treatments such as chemotherapy.

**Patient Concerns:** We describe a case of a 58 year old female who developed fluctuant level of consciousness, agitation.

**Diagnosis:** MRI findings were in keeping with posterior reversible encephalopathy syndrome following cycle 6 of palliative gemcitabine and cisplatin therapy for metastatic cholangiocarcinoma.

**Interventions:** The patient was managed with magnesium supplementation for hypomagnesemia and amlodipine.

**Outcomes:** The patient's level of consciousness returned to normal though she had residual neurologic deficits impairing her ability to drive and impacting her balance.

**Conclusions:** Cisplatin is a documented causative agent of PRES though gemcitabine is rarely associated with the syndrome. Combination cisplatin and gemcitabine therapy causing radiologically proven PRES has been documented in only 3 previous case reports. Gemcitabine's poor blood-brain barrier penetration makes it an unlikely culprit of central nervous system (CNS) toxicities. Our case and previous reports suggest higher doses may contribute to CNS toxicities such as PRES. Additionally, an emerging trend of hypomagnesemia associated with PRES has been documented inside and outside the context of malignancy and suggests a possible target for treatment and prevention warranting further investigation.

**Abbreviations:** CA 19-9 = carbohydrate antigen 19-9, CNS = central nervous system, ER = Emergency Room, FDG = Fluorodeoxyglucose, GCS = Glasgow Coma Scale, MRI = magnetic resonance imaging, PE = Pulmonary embolism, PRES = Posterior reversible encephalopathy syndrome.

**Keywords:** cisplatin, gemcitabine, posterior reversible encephalopathy

## 1. Introduction

Posterior reversible encephalopathy syndrome (PRES) is a syndrome characterized by subacute neurologic and radiographic findings.[1–4,9–12,15] It occurs due to a number of causes, predominantly malignant hypertension, eclampsia, and medical treatments such as immunosuppressive therapy. Patients often present with headaches, seizures, visual changes, or altered mental status hours to months after the inciting insult.[9–12,15,17]

Diagnosis of PRES relies on history, clinical examination, and radiologic findings of symmetric bilateral hyper-intensities on T2-weighted magnetic resonance imagings (MRIs) representing vasogenic edema.[1,4,9,15] This edema most commonly affects the posterior occipital and parietal lobes but may be seen throughout the frontal and temporal lobes, cerebellum, or brainstem.[12,15]

PRES's pathogenesis remains unclear though its association with malignant hypertension, renal dysfunction, and now immunosuppressant use is well documented.[2,4,9–13,15] Management of PRES includes removal of any offending agents, blood pressure, and seizure management.[1] Current hypothesis proposes dysfunctional cerebral vascular auto-regulation leading to a cascade of arteriolar vasodilation, capillary damage, and subsequent cortical and subcortical vasogenic edema as a possible mechanism.[2,3,7,9–11,13] It has also been proposed that cytotoxic edema due to chemotherapy induced tumor destruction and subsequent dysfunctional cerebrovascular auto-regulation may play an additional role.[1,2,9]

Cisplatin has been a documented culprit of PRES; however, gemcitabine remains a rare causative agent.[2,3,8–10,12,15,16] We will explore the relation of combination cisplatin and gemcitabine therapy and PRES through the following case.

## 2. Case report

MR is a 58-year-old woman with medical history of depression and smoking who was diagnosed with cholangiocarcinoma in fall

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[a] Department of Internal Medicine, University of Alberta, Edmonton, Alberta, [b] Cross Cancer Institute, Edmonton, Alberta, Canada.

[*] Correspondence: Hannah Cherniawsky, Department of Internal Medicine, University of Alberta Hospital, Edmonton, Alberta, Canada (e-mail: hchernia@ualberta.ca).



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of 2012. She was initially treated surgically with partial hepatectomy and total extra-hepatic bile duct removal followed by several biliary reconstructions. Pathology showed a cholangiocarcinoma T2bN0M0.

After 18 months of remission, MR experienced increasing abdominal pain accompanied by rising carbohydrate antigen 19-9 levels prompting a Positron emission tomography/computed tomography (CT) scan which demonstrated Fluorodeoxyglucose-avid peri-portal and para-aortic lymphadenopathy. She was started on palliative cisplatin and gemcitabine chemotherapy. Cisplatin was not administered in cycle 1 due to a reduced Eastern cooperative oncology group status of 2. MR tolerated cycle 1 of gemcitabine monotherapy without complications. Cisplatin was subsequently added during cycle 2 of chemotherapy dosed at 34 mg (20 mg/m$^2$) IV on days 1 and 8 of cycles 2 to 6. Gemcitabine was dosed at 1700 mg (1000 mg/m$^2$) IV on days 1 and 8 of all cycles.

MR had no complications in cycles 1 to 5 and tolerated chemotherapy quite well. However, 24 h after day 1 of chemotherapy cycle 6, she became increasingly somnolent which worsened over 3 days and prompted her presentation to emergency medical services. At presentation in the Emergency Room, she was agitated and confused with a fluctuant Glasgow Coma Scale (GCS) of 9 to 12. She had no new medications, infectious prodrome, or trauma prior to admission. Vital signs were stable and within normal limits with no tachycardia, fever, or hypertension. Her neurologic examination was without focal deficits and she had no neck stiffness. Cardiac, respiratory, and abdominal examinations were also unremarkable. MR's laboratories indicated hypokalemia (2.6 mmol/L) and hypomagnesemia (0.49 mmol/L). All other laboratories, chest X-ray and head CT were unremarkable (Fig. 1).

MR was started on empiric antibiotics and antivirals (ampicillin, ceftriaxone, vancomycin, and acyclovir) after a lumbar puncture was performed. The lumbar puncture results eventually returned negative for viral or bacterial pathogens. MRI of the head revealed bilateral cortical and subcortical edema in the posterior regions of the occipital, parietal, and frontal lobes confirming the PRES diagnosis (Fig. 2).

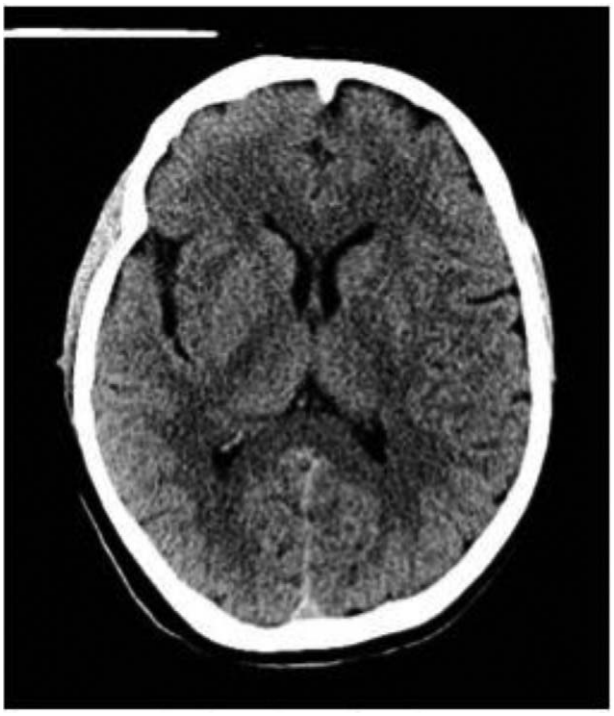

**Figure 1.** Computed tomography imaging of patient MR showing no abnormalities.

During her weeklong admission, MR was given amlodipine for blood pressure management and further chemotherapy was held. Her mental status cleared and she was discharged within 1 week of presentation on amlodipine 10 mg PO daily. She continued to experience residual visual changes and loss of balance compromising her ability to drive. She was able to ambulate and carry out all her activities of daily living. MR did not pursue any further chemotherapy and passed away peacefully surrounded by family in fall of 2015. Her family consented to publication of her presentation on her behalf.

## 3. Discussion

PRES is a rare but treatable complication of chemotherapy first described by Hinchey et al in 1996. There have been 3 published case reports of radiologically proven PRES in patients receiving combination gemcitabine and cisplatin chemotherapy alone despite its widespread use (Table 1).[7,8,11,16] Case reports of PRES induced by gemcitabine with other platinum analogs have also been described as have reports of PRES induced by gemcitabine alone (Table 1).[21–23] Connolly et al[16] described a patient undergoing treatment for nonsmall cell lung cancer with cisplatin 80 mg/m$^2$ and gemcitabine 1000 mg/m$^2$ (days unspecified) presenting with seizures, hypertension (184/92 mm Hg), and MRI indicating subcortical occipito-parietal T2 hyperintensities consistent with PRES. The patient had normal magnesium levels though IV $MgSO_4$ was used as a blood pressure control agent with improvement in the patient's condition. Maeda et al[7] described a patient with urethral carcinoma presenting with GCS of 4 and MRI findings consistent with PRES who was being treated with cisplatin 56 mg/m$^2$ day 1 and gemcitabine 1000 mg/m$^2$ days 1, 8, and 15. In comparison to the previous case study, Maeda et al's patient was normotensive and magnesium levels were unreported.[7]

Though peripheral neurotoxicity and somnolence are known complications of gemcitabine, it is historical described as having poor blood–brain barrier penetration making it an unlikely culprit of central nervous system (CNS) toxicity.[2,3,5,6,9] Two case reports have described PRES related to gemcitabine monotherapy (Table 1). Han and Findlay[23] first described a case on PRES in a patient on gemcitabine monotherapy, 1000 mg/m$^2$ days 1, 8, and 15 of a 21-day cycle, while Stukov et al[6] documented effects of gemcitabine in intracranial tumors which may be dose-dependent.[9] As such, higher doses of gemcitabine may contribute to its ability to induce PRES though this was not the case in our patient and requires further investigation. Conversely, PRES is a rare but well-documented complication of cisplatin chemotherapy.[3,10] Cisplatin boasts poor blood–brain barrier penetration though it is known to rarely cause severe CNS toxicity by way of seizures, hemiparesis, cortical blindness, or coma.[20] The greater association of cisplatin with CNS toxicity as compared to gemcitabine may account for the increased frequency of PRES associated with cisplatin therapy.

MRI is the modality of choice for diagnosis of PRES and reveals bilateral subcortical white matter changes in the posterior aspect of the brain suggestive of edema though expansion to adjacent subcortical and brainstem structures may be present. Singer et al[14] described large discrepancies between CT and

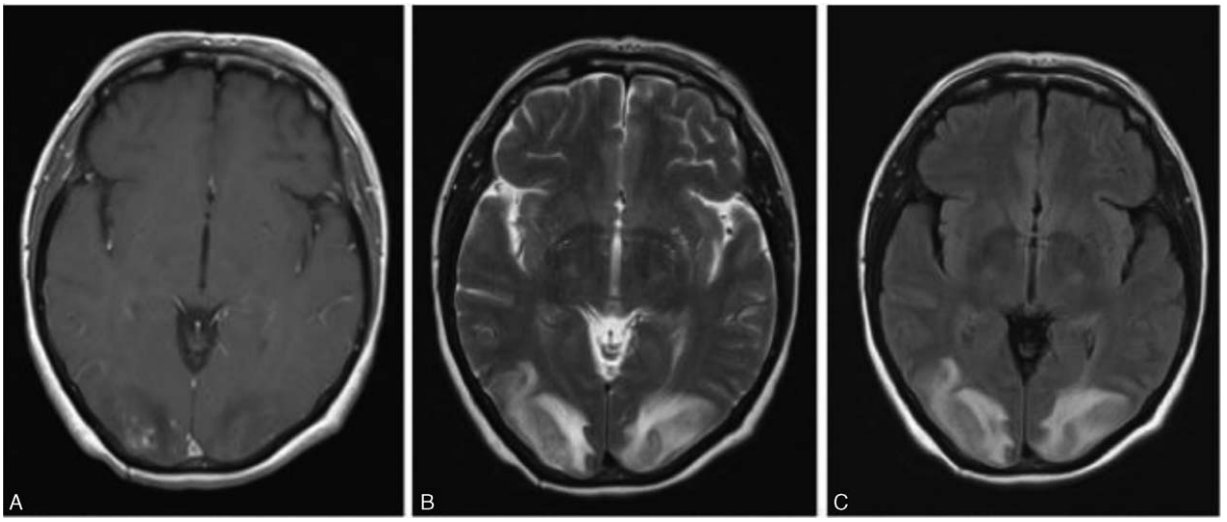


**Figure 2.** (A) T1-weighted MRI of patient MR reveals minimal abnormality. (B) T2-weighted MRI reveals bilateral symmetric hyper-intensities in the posterior occipital lobe consistent with vasogenic edema of PRES. (C) FLAIR sequence again reveals bilateral symmetric hyper-intensities of the posterior occipital lobe consistent with PRES. MRI = magnetic resonance imaging, PRES = Posterior reversible encephalopathy syndrome.

MRI in patients with PRES noting that of their 31 patients diagnosed with chemotherapy induced PRES, 37% had normal CT imaging. Though CT imaging is critical to rule out other life-threatening diagnoses, it cannot reliably assess for the presence or absence of PRES. As such, we recommend urgent MRI for further diagnostic evaluation of patients presenting with symptoms of PRES in whom CT imaging returns normal or nondiagnostic.

Hypertension is present in 53% of patients diagnosed with PRES and remains one of the main targets of treatment.[1] Chemotherapy-induced PRES is no exception to this association.[9–11,16,17] Several theories attempt to explain the pathogenesis of PRES as it relates to both hypertension and chemotherapy. The vasogenic theory suggests that elevated mean arterial pressure overcomes cerebral auto-regulation leading to

**Table 1**

**Previous case reports of PRES in patients treated with gemcitabine, and cisplatin combination chemotherapy or gemcitabine monotherapy.**

| Author | Malignancy | Cycle length, d | Cisplatin dose | Gemcitabine dose | BP | Magnesium | Outcome |
|---|---|---|---|---|---|---|---|
| Connolly et al[16] | Nonsmall cell lung cancer<br>Cycle 2 | NA | 80 mg/m$^2$<br>Days unspecified | 1000 mg/m$^2$<br>Days unspecified | 184/92 | Within normal limits | Improved with IV phenytoin. Blood pressure controlled with IV labetalol, hydralazine, and magnesium sulfate |
| Maeda et al[7] | Urethral carcinoma<br>Cycle 3 | 28 | 56 mg/m$^2$<br>Day 1 | 1000 mg/m$^2$<br>Days 1, 8, and 15 | Normotensive | NA | Treated with sedation, antiepileptics and cerebroprotective. Recovered most higher level mental function. Died of PE during hospitalization |
| Kwon et al[11] | Gallbladder cancer<br>Cycle 3 | 21 | 60 mg/m$^2$<br>Day 1 | 1200 mg/m$^2$<br>Days 1 and 8 | 170/90 | NA | Treated with IV phenytoin. Cognition improved over 10 d. Died of cancer progression 1 mo later |
| Han and Findlay[23] | Pancreatic adenocarcinoma<br>Cycle 2 | 21 | | 1000 mg/m$^2$<br>Days 1, 8, and 15 | 240/120 | NA | Treated with IV phenytoin and diazepam; complete recovery |
| Marrone et al[9] | Pancreatic adenocarcinoma<br>Cycle 1 | 28 | | 1000 mg/m$^2$<br>Days 1, 8, and 15 | 170/90 | NA | Treated with IV phenytoin; complete recovery in 10 d |

BP = blood pressure, NA = not available, PE = Pulmonary embolism.

elevated hydrostatic pressures within the cerebral vasculature, dysfunctional tight junctions, and subsequent edema.[1] The greater sensitivity of posterior vessels to hypertensive damage explains the posterior location of PRES.[1] However, this theory does not account for normotensive patients presenting with PRES such as our patient and that described by Maeda et al.[7] The cytotoxic theory suggests that chemotherapy causes release of chemokines into the bloodstream leading to dysfunctional endothelium and cerebral edema. However, molecules responsible for this effect and predisposition of posterior circulation to such dysfunction are not yet known.[1,22]

Though the population of study is small, an emerging trend of hypomagnesemia at presentation has also been noted in previous case reports of PRES inside and outside the context of malignancy.[2,10,11,18,19,22] Hypomagnesemia is known to be associated with primary hypertension though these features are not mutually present in all patients with PRES.[18,19,22] Boulos et al[18] described a case of a normotensive patient presenting with PRES attributable to severe hypomagnesemia (0.15 mmol/L). They illustrate hypertension and hypomagnesemia as independent agents in the pathogenesis of PRES as was the case with our patient.[19] Much like the case described by Connolly et al,[16] Boulos et al[18] utilized supplemental magnesium as treatment with excellent results. The prevalence of hypomagnesemia in patients with PRES is an area that warrants further investigation and may implicate magnesium levels in the prevention, early detection, and treatment of chemotherapy-induced PRES by treatment of hypertension and stabilization of the vascular endothelium.[16,18]

## 4. Conclusion

Given its life-altering and life-threatening outcomes, PRES should be considered in all patients undergoing chemotherapy presenting with characteristic neurologic findings. The classical history and physical examination findings in the setting of chemotherapy should lead the clinician toward a diagnosis of PRES. Differential diagnosis of stroke, brain metastasis, meningeal bleeds, and metabolic derangements of infectious etiologies can generally be assessed with use of routine laboratories and CT scan. With a negative workup we recommend consideration of prompt MRI to assess for this serious and treatable diagnosis.

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