Case Report

# Posterior Reversible Encephalopathy Syndrome (PRES) After Treatment With Oxaliplatin and 5-Fluorouracil

Nicholas Truman,[1] Daniel Nethercott[2]

## Clinical Practice Points

- Posterior reversible encephalopathy syndrome (PRES) is a rare disease with a diverse range of precipitants.
- PRES can occur after exposure to chemotherapy agents and should be considered in patients presenting with otherwise unexplained neurological symptoms.
- Magnetic resonance imaging is required to confirm the diagnosis.
- Recovery can be rapid and complete, warranting full supportive care regardless of a context of otherwise palliative treatment.

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## Introduction

Posterior reversible encephalopathy syndrome (PRES) is a rare disease with a diverse range of precipitants. The cause is not well understood. We report a case of PRES that occurred soon after exposure to oxaliplatin and 5-fluorouracil, in which the patient presented with mild symptoms and normal blood pressure, but progressed to a severe condition with associated hypertension. The patient required treatment on the intensive care unit but made a fast and remarkable recovery. We remind clinicians of the possibility of this rare syndrome in patients exposed to chemotherapeutic agents and question the role of hypertension in the etiology.

## Case Report

A 73-year-old woman with a past history of metastatic cecal carcinoma (pelvic and peritoneal disease) had received palliative chemotherapy with oxaliplatin and 5-fluorouracil. Corticosteroids were not included in the therapy. Her third cycle of treatment had been given 4 days before she presented with symptoms of severe occipital headache. A full neurologic examination was normal. There were no abnormal findings on examination of other body systems and she was normotensive (noninvasive blood pressure measurement of 125/75 mm Hg). Levels of serum urea, creatinine, electrolytes (including magnesium), liver enzymes, and C-reactive protein, as well as clotting times and a full blood count were all within normal limits. A computed tomographic scan of her head was normal. After 48 hours of observation (including repeated measurements of blood pressure, which was within normal limits), her symptoms resolved and she was discharged home, only to present again after a further 48 hours with similar symptoms.

All previous tests including computed tomography were repeated, and results were again normal. The only physical sign to have changed on readmission was her blood pressure, which was elevated at 198/105 mm Hg. Later that day the patient suffered a series of tonic-clonic seizures, which responded partially to treatment with intravenous boluses of diazepam but then required an infusion of phenytoin. In a brief period between seizures, the patient was found to have left-sided hemiparesis. A third computed tomographic scan was obtained, which was also normal. Intubation and ventilation on the intensive care unit were undertaken, along with empirical treatment for meningitis/encephalitis. Subsequent analysis of her cerebrospinal fluid showed normal biochemical parameters and proved negative for bacterial culture and viral polymerase chain reaction testing. The elevated blood pressure was successfully managed by titrated intravenous sedation with propofol and remifentanil. After sedation was discontinued the following day, the patient was successfully extubated and found to have complete resolution of her symptoms. Her blood pressure was normal.

Magnetic resonance images were obtained and showed a bilateral cortical and subcortical deep white matter high-signal change in the

[1]Northwest Deanery, United Kingdom
[2]Bolton Foundation NHS Trust, United Kingdom

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Address for correspondence: Daniel Nethercott, FRCA, FFICM, Department of Anaesthesia and Critical Care, Royal Bolton Hospital, Farnworth, Bolton, BL4 0JR, UK
E-mail contact: daniel.nethercott@boltonft.nhs.uk


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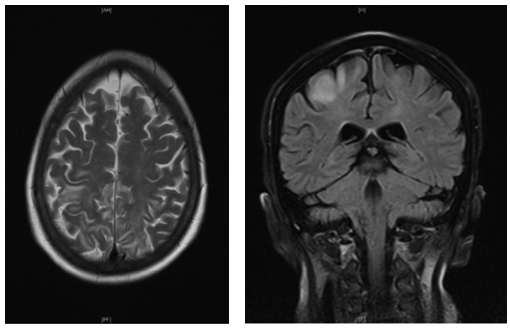
**Figure 1** T2/FLAIR Magnetic Resonance Images Showing Bilateral Cortical and Right Parietal Signal Change



occipital/parietal lobes consistent with posterior reversible encephalopathy syndrome (Figure 1).

The patient was discharged from the hospital 10 days later; she was asymptomatic and had normal functional status.

## Discussion

In 1996, Hinchey et al described a "reversible posterior leukoencephalopathy syndrome" that presented with headache, altered mental function, seizures, and loss of vision associated with imaging studies showing changes in the white matter of the brain supplied by the posterior cerebral vessels.[1] Of the 15 patients described, 4 had hypertensive encephalopathy associated with renal disease, 8 were receiving immunosuppressive therapies (after transplantation or for malignancy), and 4 had eclampsia. Once the hypertension had been treated or the immunosuppressive drugs reduced, neurologic deficits resolved within 2 weeks. Another case series of posterior reversible encephalopathy syndrome (PRES) identified 36 patients with presenting features of seizures, encephalopathy, visual disturbance, and headache.[2] Comorbidities included hypertension, renal disease, malignancy, and previous solid organ transplantation. Lumbar puncture was performed in 18 of these patients and showed normal values for protein and white blood cell counts. Clinical symptoms resolved after an average of 5 days. Generally, the prognosis for PRES is good. Another series reported good long-term outcomes and a recurrence rate of only 8%.[3] However the word *reversible* in the name of this syndrome is not always reassuring.[4,5] Patients have also been described with brainstem lesions and minimal supratentorial involvement,[6] although edema is often widespread and commonly predominates in the parietal and occipital regions.

The pathophysiology of PRES is not fully understood and there are 2 conflicting hypotheses.[7,8] An early theory suggested a progression from cerebral vasoconstriction to hypoperfusion and then to ischemia. Later theories cite a common pathway of failed autoregulation of the cerebral circulation with hyperperfusion and edema. Moderate to severe hypertension is seen in 50% to 70% of all cases, and abnormal vasomotor reactivity of cerebral vessels has been shown to coincide with the clinical course of the disease.[9]

Our patient presented with severe headache but no abnormal physical signs and normal blood pressure. Hypertension was seen only as the disease progressed to its more serious manifestations (seizures and hemiparesis), which suggests that the hypertension was not causative but rather a secondary phenomenon due to the neuropathologic condition already present. An acute hypertensive response to intracerebral hemorrhage is well recognized and is presumed to be an autoregulatory phenomenon to protect threatened central nervous tissue.[10] Given the temporal relationship between the treatment with oxaliplatin and 5-fluorouracil, the exposure to either (or both) of these drugs seems the most likely trigger for the development of PRES in this case.

Neurologic complications of chemotherapeutic drugs are relatively common,[11] and although several compounds have been proposed as neuroprotective agents, few have shown efficacy.[12] Encephalopathy associated with 5-fluorouracil does not commonly fit the pattern of PRES. It can be associated with elevated serum ammonia and lactate[13] levels and can occur with normal magnetic resonance images.[14,15] The general neurotoxicity of 5-fluorouracil is reported to be dose related[16]; however low doses have been implicated in cases of PRES.[17]

We have found 4 other cases of PRES associated with oxaliplatin[18-21] and 1 other case similar to ours after treatment with both oxaliplatin and 5-fluorouracil.[22]

## Conclusion

Although posterior reversible encephalopathy syndrome is apparently rare, it is likely to be underdiagnosed given the wide clinical spectrum of disease, varying precipitants, and the requirement for magnetic resonance imaging for diagnosis. It should be considered in any patient showing unexplained neurologic disease after exposure to chemotherapy, seizures being the most common manifestation.[3] The cause could only partially be explained by macrocirculatory changes, such as systemic hypertension, which may not be causative.

## Disclosure

The authors have stated that they have no conflicts of interest.

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