Posterior Reversible Encephalopathy Syndrome (PRES) Complicating Newly-Diagnosed Diffuse Large B-Cell Lymphoma

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Clinical Lymphoma, Myeloma & Leukemia, Vol. 14, No. 4, e111-3 © 2014 Published by Elsevier Inc.

Keywords: Capecitabine, Diffuse large B cell lymphoma, Posterior reversible encephalopathy syndrome

Clinical Practice Points

• Patients with posterior reversible encephalopathy syndrome (PRES) might present with altered mental status, headache, nausea, vomiting, seizures, and visual disturbances.
• Posterior reversible encephalopathy syndrome might result from multiple etiologies including uncontrolled hypertension, toxic/metabolic abnormalities, medications, and malignancies.

Introduction

Altered mental status is a common problem among cancer patients with numerous etiologies. Potential causes include direct cancer involvement of the central nervous system, toxic/metabolic encephalopathies, organ dysfunction, and side effects of medications. This case illustrates an uncommon cause of altered mental status in cancer patients: posterior reversible encephalopathy syndrome (PRES).

Case Report

The patient is a 73-year-old right-handed woman with hormone receptor-positive breast cancer diagnosed in 2003. The patient’s breast cancer had been treated with bilateral mastectomy, radiation, and hormonal therapy. Her breast cancer remained in remission and she continued using letrozole.

In 2012, the patient presented with diffuse lymphadenopathy. She went to her local oncologist who presumed the adenopathy to denote metastatic breast cancer. The letrozole was discontinued and the patient was started on capecitabine; no confirmatory biopsy was performed. Approximately 2 weeks after starting capecitabine, she had 2 generalized tonic clonic seizures and was admitted to her local medical center. She also reported visual hallucinations; her uncorrected calcium level was 13.7 mg/dL (albumin level not measured) and was managed with intravenous fluids. A contrast-enhanced magnetic resonance imaging (MRI) scan of the brain showed scattered T2 hyperintense lesions in the subcortical white matter in the posterior distribution, but without any enhancing lesions. A diagnostic lumbar puncture identified no malignant cells in the cerebrospinal fluid. The seizure and white matter changes were attributed to capecitabine, which was discontinued.

The patient was discharged to a local rehabilitation facility, but because of ongoing altered mental status, she was sent to a local hospital where she had not previously been evaluated. Diffuse lymphadenopathy was again identified on examination and a full body positron emission tomography (PET)/computed tomography scan was obtained and showed diffuse fluorodeoxyglucose-avid adenopathy without visceral involvement. A lymph node biopsy was performed showing diffuse large B-cell lymphoma (DLBCL). Laboratory studies showed that the patient was hypercalcemic (corrected calcium 11.5 mg/dL). She was also noted to have labile blood pressure (120-170/80) with frequent episodes of hypertension. She received...
intravenous fluids and zolendronic acid for hypercalcemia, and her mental status improved slightly. Because of the patient’s abnormal mental status and clinical suspicion of central nervous system (CNS) involvement by DLBCL, the patient was transferred to our hospital.

On admission, the patient was observed to have fluctuating mental status with periods of obtundation. Her visual hallucinations persisted. She had a repeat PET study (Fig. 1). An MRI scan showed nonenhancing T2 signal abnormalities in the white matter of the cerebral hemispheres, in a posterior distribution, not significantly changed compared with previous imaging. She was again noted to be hypercalcemic (corrected calcium 11.5 mg/dL), and persistently hypertensive, both of which were managed aggressively. A lumbar puncture was performed, which revealed a cerebrospinal fluid protein level of 32 mg/dL, and a glucose level of 42 mg/dL. Serologies were checked for viral encephalitidies, and were negative for West Nile, Eastern Equine encephalitis, St Louis encephalitis, and LaCrosse viruses. Cytology, flow cytometry, and polymerase chain reaction for clonal immunoglobulin Hv rearrangement were all negative for lymphoma involvement. Based on the imaging and clinical findings, the patient was diagnosed with PRES, occurring in the context of recent capecitabine, DLBCL, and hypercalcemia of malignancy.

She was treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). She tolerated the therapy well and her mental status steadily improved within days of initiation of chemotherapy. She completed 6 full cycles of R-CHOP and achieved a complete remission. Her mental status returned completely to baseline and she had no further seizure activity. Repeat MRI of the patient’s brain performed before the initiation of chemotherapy redemonstrated nonenhancing T2 abnormalities in the periventricular, deep, and subcortical white matter of the cerebral hemispheres, in a predominantly posterior distribution (Fig. 2A, red arrow), not significantly changed (images not shown, but virtually identical in appearance to Fig. 2A). Six months later, repeat MRI scan showed complete resolution of most of the white matter non-enhancing fluid-attenuated inversion recovery T2 signal abnormalities seen previously, with scattered mild residual signal abnormalities being non-specific in etiology but most likely representing underlying chronic microangiopathic ischemic changes (Fig. 2B).

Discussion

We present a case of PRES occurring after initiation of capecitabine in the setting of hypertension, untreated DLBCL, and hypercalcemia of malignancy. PRES is a syndrome characterized clinically by altered mental status, visual hallucinations, headaches, and seizures.1,2 In this case, potential precipitants for PRES include capecitabine, DLBCL, hypertension, and hypercalcemia. There is only 1 case report suggesting an association between capecitabine and PRES,3 but several other reports document an association with 5-fluorouracil, for which capecitabine is a prodrug.4 All such reports have been associated with combination chemotherapy regimens, unlike the association with monotherapy in this case. Toxic encephalopathy and seizures have also been reported with use of capecitabine.5 PRES is usually reversible within 2 weeks of the removal of the drug and the treatment of the underlying disorders. Classic MRI findings include symmetric hyperintense T2 signal involving bilateral occipital and parietal lobes in a subcortical distribution.1 In contrast, CNS lymphoma in immunocompetent patients tends to be uniformly enhancing in contact with the subarachnoid space and without necrosis, and the lesions tend to be solitary.3

The imaging characteristics of PRES include vasogenic edema in the subcortical white matter of the occipital and parietal lobes.6,7 The tendency for PRES to occur in the posterior circulation is believed to be due to impaired autoregulation, because sympathetic
control is more developed in the anterior circulation. PRES can be precipitated by a wide range of systemic insults in the setting of cancer, including chemotherapy, immunosuppressive agents, and toxic metabolic disturbances such as sepsis, renal failure, and hypercalcemia. Underlying diseases such as hypertension and collagen vascular disorders have also been associated. DLBCL and hypercalcemia have previously been described as causing PRES. Hypercalcemia might contribute to the pathogenesis of PRES via inducing cerebrovascular vasospasm, and the mechanism for DLBCL precipitating PRES is unknown.

**Conclusion**

This case illustrates that PRES should be considered in the differential diagnosis of cancer patients presenting with altered mental status, visual hallucinations, and seizures. Successful treatment of the underlying malignancy, and withdrawal of offending agents can lead to complete resolution of this neurologic syndrome.

**Disclosure**

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

**References**