Dexamethasone-associated posterior reversible encephalopathy syndrome

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Posterter reversible encephalopathy syndrome (PRES) can be correlated with medical illness, hypertension, and treatment with medications that cause immunosuppression. This syndrome was first described by Hinchey and colleagues in 1996.1 PRES is not necessarily confined to the posterior white matter of the brain as the name indicates, but can be located in the frontal lobes, basal ganglia, cortex, and brain stem. Manifestations of this syndrome include seizures, headache, visual loss, altered mental status, visual changes, and radiologic alterations, and are easily detected on magnetic-resonance imaging (MRI) of the brain.1-4,6

Case presentation and summary

A 55-year-old white woman with a history of a poorly differentiated neuroendocrine tumor of the esophagus after resection 4 weeks earlier was readmitted to our institution because of intractable nausea and vomiting. She had received her first adjuvant chemotherapy of etoposide 100 mg/m² daily for 3 days, and cisplatin 45 mg/m² on days 2 and 3 as a continuous intravenous infusion 6 days before her re-admission and had been discharged after tolerating the chemotherapy well. After returning home, she experienced nausea and vomiting that was persistent and unrelieved with her home antiemetic regimen of prochlorperazine 10 mg orally every 6 hours as needed and she was readmitted 48 hours after chemotherapy for the intractable nausea and vomiting.

The patient underwent an acute abdominal series that did not show any obstruction or cause for the intractable nausea and vomiting. During her re-admission, her medications included atorvastatin 5 mg orally daily, Maalox 10 ml orally every 4 hours as required, benzonatate 200 mg every 8 hours as required for cough, dexamethasone 4 mg IV push twice daily for nausea and vomiting, ferrous sulfate 75 mg orally daily, fluconazole 200 mg IV daily, guaifenesin 100 mg orally every 4 hours as required for cough, levothyroxine 0.088 mg orally daily, and pantoprazole 40 mg IV twice daily. The patient’s oral intake was limited and she was started on IV fluids.

On day 8 of the hospital admission, the patient developed an acute change in her mental status. She was awake but disoriented and aware only of place. She was verbally combative, which was outside of her normal behavior according to her husband. The patient did not complain of headache, visual disturbance, or experience a seizure. Her vital signs and results for complete blood count with differential and complete metabolic panel were within normal limits. A computed-tomography (CT) scan of the head showed hypodensities in the bilateral occipital lobes and an MRI was recommended. The MRI revealed vasogenic edema in the bilateral occipital lobes involving white matter, consistent with PRES. Dexamethasone was identified as a possible cause and rapidly tapered. Within 24 hours of discontinuation, the patient’s mental status had markedly improved and agitation and combative ness had ceased.

The probability for this adverse effect to be caused by dexamethasone was evaluated by the Naranjo Adverse Drug Reaction Probability Scale.7 There were positively scoring answers including previous reports of this reaction (+2), a temporal relationship between initiation of the drug and initiation of symptoms (+2), the abatement of symptoms following discontinuation (+1), there were no other causative agents (+2), the reaction was less severe when the dose was decreased (+1), and objective evidence of an MRI confirmed reaction (+1). The final score was concluded to be 9, which was indicative of a “definite” relationship.

Discussion

The underlying pathology and a thorough understanding of the cause of PRES remains elusive, but the most customary explanation is that quickly developing hypertension leads to an interruption
in cerebral autoregulation. This loss of control, most notably found in the posterior cerebrum, precipitates a forced hyperperfusion, which leads to fluid and protein extravasation that produces focal vasogenic edema.\(^1\,^5\,^6\) Another theory proposes that vasospasm with subsequent ischemia may be responsible.\(^9\,^10\) Alternative explanations include development associated with preeclampsia, eclampsia, and sepsis which implicates endothelial dysfunction as a possible causative process, endothelial injury from pre-transplantation conditioning regimens or graft-versus-host effects.\(^11\,^12\,^14\) Nonetheless, the precise cause of PRES remains unproven, although there are associations with eclampsia, preeclampsia, sepsis, corticosteroids, cyclosporine, tacrolimus, autoimmune disease, medical-renal disease, and severe hypertension. Some findings have also suggested an association with hypomagnesemia, hypercholesterolemia, and antigenic mismatch in allogeneic bone marrow transplantation.\(^10,\,11,\,13\)

Dexamethasone is a long-acting systemic corticosteroid with varied uses in many areas of medicine. It is a potent anti-inflammatory with documented use in the treatment of pain; and it is also used in the treatment of multiples sclerosis to decrease cerebral and airway edema and to relieve acute exacerbations of the disease. In the oncology setting, dexamethasone is used as an adjunctive treatment of malignancies and as an antiemetic given with moderately to highly emetogenic chemotherapy. When used short term, dexamethasone is generally well tolerated, with the most common adverse effects being appetite stimulation, hyperglycemia, and mood alterations including euphoria, agitation, and insomnia. Long-term or chronic dexamethasone use is not routinely recommended and can affect many organ systems including cardiovascular, neuromuscular, and skeletal, as well as endocrine and metabolic. It can have immunosuppressive properties in high doses.\(^15\) Dexamethasone has been rarely associated with the development of PRES.\(^16\,^17\)

The first case of PRES related to dexamethasone was described in a 48-year-old woman who was receiving dexamethasone in preparation for external-beam radiation for the treatment of brain metastases. After 5 days in the hospital, she became disoriented and agitated. On day 6 of her hospitalization, she became obtunded. The patient was also found to be hypertensive with a blood pressure of 190/100 mmHg and had a pulse of 160 beats a minute. She also presented with anisocoria and sluggish pupillary reflexes. The patient’s laboratory studies, a CT scan, and 2 lumbar punctures did not reveal abnormality. The results of an MRI of the brain were consistent with PRES.\(^16\)

The second case involved a normotensive 32-year-old woman with advanced mesothelioma. The patient developed PRES with use of dexamethasone for nausea control after administration of cisplatin and pemetrexed. Symptoms included new-onset seizures and cognitive impairment. Again, the results of an MRI of the brain were consistent with PRES. Chemotherapy was withheld and dexamethasone tapered. The patient returned to baseline with resolution of MRI abnormalities after the discontinuation of dexamethasone and chemotherapy.\(^17\)

**Conclusion**

Posterior reversible encephalopathy syndrome is known to be associated with many medications and disease states, although the precise cause and pathology is unclear. Dexamethasone-related PRES remains rare; and as far we know, only a few cases have been reported in the literature. Our case report re-emphasizes the need for providers to be aware of medication-related radiologic disorders and the importance of promptly identifying the causative process.

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**References**