Case report

Posterior reversible encephalopathy syndrome (PRES) associated with ovarian cancer and voltage-gated potassium channel antibodies: A case report

Laura K. Hadad *, Caroline C. Billingsley

Department of Obstetrics and Gynecology, Division of Gynecology Oncology, University of Cincinnati, 231 Albert Sabin Way, Academic Health Center, PO Box 670526, Cincinnati, OH, 45267-0526, United States

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1. Introduction

Posterior reversible encephalopathy syndrome (PRES) is an encephalopathic condition associated with reversible vasogenic edema. PRES is an increasingly recognized condition of cancer patients undergoing adjuvant therapy. Clinical manifestations include altered mental status, seizures, visual disturbances, and headache. CT and MRI findings include vasogenic edema, typically in the bilateral parieto-occipital regions. MRI shows abnormal T2 signaling, particularly fluid-attenuated inversion recovery (FLAIR) in parieto-occipital regions. The recognized etiologies of PRES include hypertension, cytotoxic drugs, and renal failure. There has been a causative effect noted between chemotherapy drugs such as gemcitabine and cisplatin and the development of PRES. Although PRES is usually reversible, permanent effects on mentation with significant morbidity and mortality can result if the condition is not properly identified and treated.

The mechanism of PRES has not been definitively established but is thought to involve both failure of cerebral autoregulation and endothelial dysfunction. The combination of these factors is hypothesized to lead to disruption of the blood-brain barrier and vasogenic edema. PRES is not typically characterized as a paraneoplastic syndrome, although in a large review malignancies were found in 32% of patients with PRES. Paraneoplastic syndromes are conditions with undetermined causes that are associated with neoplasms and anti-neuronal antibodies. One such anti-neuronal antibody is the voltage-gated potassium channel (VGKC) antibody. In the following case we discuss the etiology of PRES in a patient with ovarian cancer.

2. Case report

A 64-year-old postmenopausal woman presented with a fixed pelvic mass and a normal CA 125 level (12 U/mL, normal 5.5–35 U/mL). She underwent a biopsy of the mass at an outside facility that was reported as a transitional cell ovarian carcinoma. She was treated with neoadjuvant chemotherapy with three cycles of intravenous carboplatin/paclitaxel with stable disease. This was followed by one cycle of carboplatin/gemcitabine with disease progression noted. She then underwent three cycles of cisplatin/gemcitabine with a documented partial response on imaging and reported improvement in her pelvic exam. There was no evidence of tumor lysis syndrome.

She was planned to undergo an interval cytoreduction but experienced a fall due to altered mental status at home leading to a vertebral fracture. She was admitted to the neurology service and diagnosed with PRES based on an MRI of the head which noted no masses, but multiple bilateral, symmetric areas of T2 and FLAIR signal abnormality involving the cerebellar hemispheres, pons, temporal, frontal and parieto-occipital lobes with predominant involvement of the cortical and subcortical zones (Fig. 1). Her symptoms were severe with selective mutism, delirium, confusion and refusal of oral intake. A paraneoplastic panel was negative with the exception of voltage-gated potassium channel antibodies.

The gynecology oncology service was consulted due to a drop in hemoglobin and an enlarging pelvic mass. Surgery was initially deferred given her poor performance status and overall stability of the mass. But, ultimately, her pain increased and her mental status continued to severely decline, and she underwent a radical interval optimal cytoreduction including bilateral salpingo-oophorectomy, tumor

* Corresponding author.
E-mail address: hadadlk@mail.uc.edu (L.K. Hadad).

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patients have a primary immune etiology, described in an abstract by Seby and consistent with posterior reversible encephalopathy syndrome (PRES). Occipital lobes as well as cerebellar hemispheres, as demonstrated on these T2 FLAIR images (a, b, c). T2 hyperintense foci were also noted in the pons (not pictured). Findings were consistent with posterior reversible encephalopathy syndrome (PRES).

A 63 year old female with high grade serous ovarian carcinoma who developed predominantly subcortical and cortical T2 hyperintense foci in the frontal, parietal, temporal, and occipital lobes as well as cerebellar hemispheres, as demonstrated on these T2 FLAIR images (a, b, c). T2 hyperintense foci were also noted in the pons (not pictured). Findings were consistent with posterior reversible encephalopathy syndrome (PRES).

Her postoperative course was prolonged and complicated. She experienced a large retroperitoneal hematoma requiring an ICU admission, wound separation and pelvic fluid collections. She was discharged after several weeks to a nursing facility and continued to suffer from deconditioning and malnutrition. Neurologically she was intact aside from intermittent aphasia. She underwent retreat imaging eight weeks after her cytoreduction and was noted to have extensive recurrent tumor in the pelvis with multiple peritoneal nodules, bladder involvement, increased right ureteral obstruction and several new pulmonary nodules. She was offered chemotherapy versus hospice. She elected hospice and quickly declined from a neurological standpoint, succumbing to her disease within two weeks.

3. Discussion

The present case may provide evidence for a paraneoplastic, autoimmune etiology of PRES associated with neuronal voltage-gated potassium channel (VGKC) antibodies. Evidence for a paraneoplastic etiology of PRES includes the patient’s positive laboratory value for neuronal voltage-gated potassium channel (VGKC) antibodies. Evidence for a paraneoplastic etiology of PRES associated with neuronal voltage-gated potassium channel (VGKC) antibodies. The present case may provide evidence for a paraneoplastic, autoimmune etiology of PRES associated with neuronal voltage-gated potassium channel (VGKC) antibodies.

Neuronal VGKC antibodies are measured on paraneoplastic panels and are associated with various neurological conditions, including limbic encephalitis, Morvan’s disease, and epilepsies. These conditions have variable manifestations on MRI, with many cases having normal-appearing MRIs.

The neurologic effects of VGKC antibodies are broad and include cognitive impairment, seizures, dysautonomia, myoclonus, among other symptoms. It should be noted that the significance of a positive screen for VGKC antibodies is unclear. VGKC antibodies are associated with malignancies, particularly small-cell lung cancer and thymomas.

Paraneoplastic encephalopathies tend to have a poor prognosis. Treatment depends on removal of the tumor and aggressive immunotherapy.

On literature review, a case of PRES was found that was proposed to have a primary immune etiology, described in an abstract by Seby and colleagues. In the described case none of the usual precipitants for PRES were present. The patient’s encephalopathy, seizures, and brain imaging findings resolved after discovery and treatment of squamous cell carcinoma in the lung. A paraneoplastic panel was negative. This reported case may parallel the current case in that both patients’ mental statuses appear to vary based on tumor status. In the previously described case, the patient’s cognition returned to baseline after resection and treatment of the cancer. In the present case, the patient’s mental status returned to baseline after the resection of her ovarian tumor and reduction in pelvic hematoma. In addition, her mentation declined on recurrence and metastasis of the ovarian cancer. It should be recognized that the patient’s worsening mental status late in the course of her disease could have been an effect of the dying process. The authors proposed a primary immune etiology of PRES that may have been paraneoplastic in origin.

The present case has multiple complicating factors, including the patient’s history of hypertension and fluctuating blood pressures throughout her hospitalization. Hypertension is a known precipitant of PRES that may have contributed to her presentation. In addition, the patient’s significant drop in hemoglobin (from 8.0 g/dL to 5.5 g/dL) could have led to decreased cerebral perfusion, contributing to her delirium. Another possible contributing factor is the patient’s history of sepsis early in her hospitalization. Upon treatment, she experienced some improvement in her confusion but ultimately declined again.

Particularly relevant is the patient’s history of gemcitabine chemotherapy. Gemcitabine is known to be a precipitating factor for PRES. This association has been noted in a variety of cancers. In a literature review, gemcitabine was found to be associated with PRES in nonsmall cell lung cancer, immunoglobulin A multiple myeloma, ovarian cancer, pancreatic cancer, gallbladder cancer, and small cell lung cancer.

The onset of PRES following chemotherapy has been reported in cases of ovarian cancer. In a retrospective study of 69 patients with cancer who developed PRES, two patients had primary ovarian cancers, one of whom was treated with chemotherapy. On literature review, a case of PRES in ovarian carcinoma after treatment with bevacizumab was found. Although our patient did not receive bevacizumab, this case provides evidence for drug-precipitated PRES in ovarian cancer. In another case, PRES was reported in a patient with metastatic high-grade serous ovarian cancer who received bevacizumab in combination with gemcitabine. The authors concluded that bevacizumab was the most likely causative agent, but they acknowledge that gemcitabine may have played a role. Gemcitabine-associated neurotoxicity has been noted in a patient with epithelial ovarian carcinoma. In summary, there is evidence of chemotherapy-induced PRES in ovarian cancer.

The majority of previous cases of gemcitabine-associated PRES occurred within two weeks of the most recent cycle of gemcitabine chemotherapy. In the current case, the patient’s PRES did not present until six weeks after her last cycle of cisplatin/gemcitabine. It is possible that this is a later presentation of gemcitabine-associated PRES. The
timing of events and association with tumor status may provide evidence for a paraneoplastic rather than drug-related etiology. It should be noted, however, that gemcitabine could be an alternate explanation for the patient’s PRES.

In summary, in cases of PRES with an associated malignancy, it may be beneficial to do a paraneoplastic workup. It is important to identify PRES early so that it can be treated and its effects reversed. This possible paraneoplastic etiology of PRES is infrequently reported in the literature and may represent a new variation of the disease. Treatment of PRES involves removal of the causative agent, which may differ based on the cause of the PRES. Therefore, recognition of any new etiology of PRES is relevant for management of the condition.

Conflict of interest statement

Neither of the authors has any conflicts of interest to report.

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