Insights in Obstetrics and Gynaecology

Case Report Open Access

Posterior Reversible Encephalopathy Following Primary Debulking Surgery in Ovarian Cancer: Significance of Early Diagnosis and Treatment [Version 1, 2 Approved with Reservations]

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Original Submission

Received: March 06, 2017
Accepted: March 20, 2017
Published: March 25, 2017
Last Updated: May 31, 2017

Open Peer Review Status: Approved with Reservations

How to cite this article: SunayanaSrinivasan, PankajSinghal, SukumarMisra, Jennifer Gibbs. Posterior Reversible Encephalopathy Following Primary Debulking Surgery in Ovarian Cancer: Significance of Early Diagnosis and Treatment [Version 1, 2 Approved with Reservations]. Insights Obstet Gynecol. (2017) 1: 6. 1

Conflicts of Interest: Authors do not have any conflict of interest or any financial disclosures.

Abstract

Background: Posterior reversible encephalopathy (PRES) is a neuroradiological clinical entity with generally good prognosis with early diagnosis and intervention. Various risk factors have been described in literature although the pathophysiology is still not completely understood.

Case: We present a case of a 53-year-old female who underwent primary debulking surgery for ovarian cancer, complicated by immediate postoperative PRES. Although the clinical presentation overlapped with that of posterior stroke and the etiology remained indeterminate, prompt diagnosis and treatment ensued. This resulted in complete recovery with no residual neurological deficits.

Conclusion: Posterior reversible encephalopathy is a challenging diagnostic situation. Patients undergoing major surgical procedures may be subject to autonomic cerebral circulatory alterations described in PRES. Broadening the spectrum of differential diagnosis and maintaining high levels of suspicion in such cases can result in favorable outcomes.

Introduction

Posterior Reversible encephalopathy (PRES) is a clinical entity comprised of predominantly reversible neurological symptoms that arise due to wide array of etiologies. The clinical features usually overlap with other neurological conditions, thus complicating the scenario. Although challenging, early diagnosis is of paramount importance since prognosis is generally good if promptly treated. Various risk factors and causes have been described in literature including hypertension, preeclampsia, and cytotoxic drugs among many others. We present a rare case of PRES that immediately followed primary debulking surgery in a patient diagnosed with ovarian cancer, in the absence of clear risk factors or etiology.

Case

A 53-year-old female presented with an adnexal mass and elevated CA 125 levels. She underwent exploratory laparotomy and radical resection of pelvic malignancy, hysterectomy with resection of parametrial tumor, ureterolysis, bilateral salphigooophorectomy, and radical omentectomy. She also underwent resection of right hemi diaphragm to address the extensive tumor implants which was complicated by a perforation of the diaphragm. The resultant small pneumothorax was promptly corrected with no major consequence. Otherwise she had an uncomplicated intraoperative course. Her blood pressure, accurately monitored through an arterial line was in acceptable range with systolic pressure and diastolic pressure ranging between 100-130 mm Hg and 60-80 mmHg, respectively. No events of arrhythmia was noted. Estimated blood loss was 1200 cc which was rather difficult to accurately assess due to concurrent two liters of ascites. She received 2 units packed red blood cells during surgery and 100 ml of 25% albumin intraoperatively in addition to crystalloids. The patient was then transferred intubated to the intensive care unit. Five hours later she developed deviation of left eye and one episode of generalized tonic clonic seizures. Initial computed tomography (CT) scan was nondiagnostic and she was transferred to a higher-level stroke center for further care. Her blood pressure continued to be in the acceptable range with systolic less than 140 mm Hg. Magnetic resonance imaging (MRI) showed ischemic changes in posterior lobes of the brain, brain stem and thalamus. Despite negative workup for venous thromboembolism elsewhere, a diagnosis of ischemic stroke was considered, secondary to her hypercoagulability status related to ovarian cancer and recent surgery.

Based on expert opinion from neuro-radiologist and the neurology team, an alternative diagnosis of PRES was considered due to the preferential involvement of the posterior circulation and subtle features on imaging. In view of this she was treated with hypertonic saline and nicardipine drip with a systolic blood pressure goal of 110-120. On the third postoperative day, clinical improvement was noted in terms of eye opening to command and slight movements of lower extremity. Within the next few days she showed significant neurological recovery. She regained consciousness along with more robust sensory motor improvement. MRI was repeated which showed marked improvement in her initial findings. This combined with her clinical recovery made PRES the most likely diagnosis. She was eventually discharged home on postoperative day 20. At the time of discharge, she had no residual focal residual deficits.

Discussion

PRES is a reversible neurologic entity that is characterized by a wide spectrum of clinical and radiological features. Typical symptoms include headache, confusion, visual disturbance, altered mental status seizures and are supported by characteristic MRI changes. First described as a separate consortium of syndromes in 1996 by Hinchey et al [1], there has been considerable amount of interest generated regarding PRES in the neuro-clinical world. Although a number of cases have been described in literature and it is being increasingly recognized, the conceptualization of the pathophysiology remains quite a challenge.

The etiologies associated with PRES include hypertension, preeclampsia, immune suppressant drugs, and systemic inflammatory conditions, among others [2]. The most commonly reported causes have been listed in Table 1. However, with progress in understanding the pathology of the condition and improved modalities of diagnosis, more associations are being constantly reported. Constant efforts to comprehend the pathophysiology of this clinical syndrome have led to the proposal of several theories. The commonly accepted theories include; 1) In patients with uncontrolled hypertension, failure in cerebral autoregulation that normally maintains cerebral perfusion has been recognized. This leads to cerebral hyper-

perfusion and consequent increase in osmotic pressure of the cerebral vessels resulting in extravasation of fluids into the interstitial space causing vasogenic edema. 2) Cerebral vasospasm caused by sudden increase in blood pressure, or other circulatory changes caused by unexplained result in ischemia of the glial cells leading to cytotoxic edema. 3) Breakdown of the blood brain barrier by inflammatory cytokines, antibodies, cytotoxic chemotherapeutic drugs which essentially lead to extravasation of fluid in the cerebral white matter. 4) Vasogenic and cytotoxic edema caused by low oncogenic pressure from hypoalbuminemia [3-5].

Table 1: Causes of PRES.

Medications	Chemotherapy	Cytokines and Immunomodulators	Systemic Conditions and others
1. Linezolid 2. Erythropoeitin 3. Cocaine 4. Lysergic acid 5. Carbemezipine 6. Corticosteroids 7. Antiretroviral	1. Cyclosporine 2. Cisplatin 3. Carboplatin 4. Gemcitabine 5. Bevazicumab 6. Methotrexate	1. Rituximab 2. Infliximab 3. Eternacept 4. Tacrolimus 5. Interleukin-2	1. Hypertension 2. Ecclampsia 3. Tumor Lysis syndrome 4. SLE 5. ITP, TTP 6. Blood transfusion 7. IV contrast 8. Renal failure 9. Sepsis

Table 2: Differential diagnosis for patients with symptoms of PRES.

Emergent	Infectious	Inflammatory	Other
1. Ischemia 2. Mass Effect 3. Hemorrhage 4. Seizures 5. Trauma	1. Encephalitis 2. Human Immunodeficiency Virus 3. Progressive Multifocal Encephalopathy 4. Toxoplasmosis 5. Neurosyphillis 6. Septic thromboembolism	1. Systemic Lupus Erythematosus 2. Vasculitis 3. Multiple Sclerosis 4. Scleroderma	1. Toxic white matter demyelination 2. Adreno-leukodystrophy 3. Uremic Encephalopathy

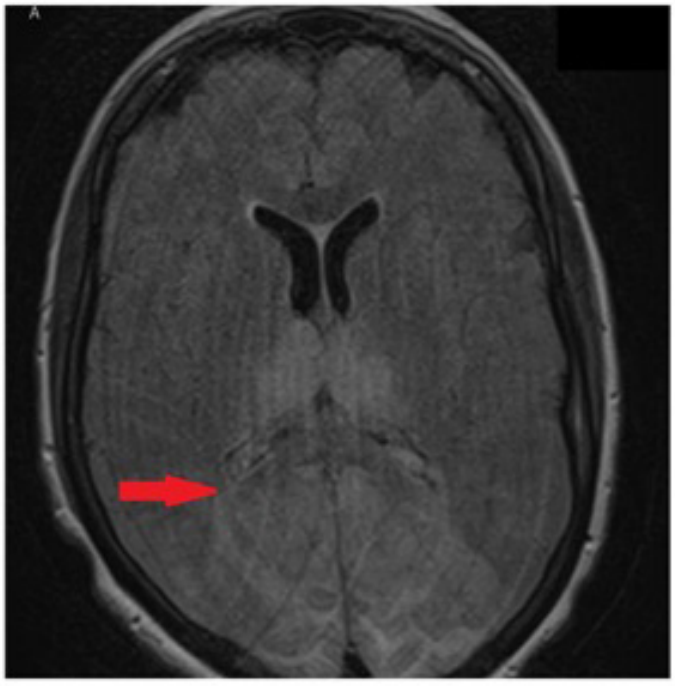

Figure 1: MRI showing increased T2/DWI flair and hyperintense area predominately in occipital lobes, consistent with diagnosis of PRES.

Differential diagnosis includes a wide range of neurological entities including stroke, subarachnoid hemorrhage, cerebral venous thrombosis, infections, as listed in Table 2. Diagnosis is made by maintaining a high degree of clinical suspicion in patients presenting with this spectrum of symptoms, radiological imaging and assessing clinical response to treatment and overall recovery. Characteristic MRI findings incudes abnormally increased T2W/FLAIR signal, thought to be vasogenic edema, primarily within the white matter of the posterior circulation with the parietal or occipital lobes involved in 98% of cases [6]. The lesions can affect the frontal lobes (68%), the temporal lobes (40%) and the cerebellar hemispheres (30%). A bilateral and symmetrical appearance is highly typical although lesions can be asymmetrical. In rarer cases, the lesions can extend to the basal ganglia (14%), the brain stem (13%) and the deep white matter, in particular the splenium of the corpus callosum (10%) [6]. Diffusion-weighted imaging (DWI) can be used when etiology is unclear and typical risk factors are not present [7].

In this case, the distinguishing and interesting feature is that there was no significant or sustained risk factor or clear etiology. Our postulation is that this could have been the result of a multifactorial etiology. Cerebrovascular circulatory changes during extended surgery could have precipitated the event. Although she was given albumin infusion during surgery, it is possible that preexisting decrease in oncotic pressure due to nature of malignancy could have aggravated this condition. Cytotoxic agents released in response to the tumor could also be a potential cause.

Management of PRES revolves around reversing the pathophysiological changes and eliminating the offending agents. Maintaining normal range blood pressure and decreasing cerebral edema are considered treatment goals. Preclusion of further insults to the brain is achieved prevention of seizure activity, intracranial hemorrhage and thrombotic events. Support measures such as intensive care, ventilation and eventually rehabilitation complete the overall scope of treatment. In general, the prognosis is good with complete recovery in most cases. Clinical improvement is usually seen within one week and MRI changes resolve over days to weeks [3,8]. Persistence of symptoms and recurrence of PRES is rare but have been reported [3], thus making close follow up and high clinical suspicion a necessity. Without clear etiology and overlapping clinical features resembling other neurological entities, diagnosis can be quite a perplexing. High degree of suspicion and neuroradiological expertise in diagnosing this entity is extremely imperative. When diagnosed in a timely fashion and appropriate treatment administered, majority of cases show significant recovery.

In our patient, appropriate treatment was instituted with a high suspicion for reversible encephalopathy which resulted in clinical improvement and resolution of MRI changes followed by complete recovery with no neurological deficits. We had a comprehensive counselling session with patient and she was agreeable to chemotherapy fully aware of the association of PRES with chemotherapy and possible recurrence. She has currently completed six cycles of chemotherapy with carboplatin and paclitaxel with remarkable clinical response. Post treatment PET scan was performed and was negative for any persistence of disease.

Conclusion

Posterior Reversible Encephalopathy is an all-encompassing term for a consortium of neurological symptoms and clinical features with several etiologies. As the name suggests, this condition is completely reversible in majority of the cases provided that it is promptly diagnosed and accordingly treated in a timely fashion. The challenge lies in the diagnosis owing to the paucity of incidence and non-specific clinical features. Maintaining a high degree of suspicion, employing sophisticated advancements in MRI imaging and utilizing neuro radiological expertise can help establish an early diagnosis and administer appropriate treatment for satisfactory response and recovery.

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