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Posterior Reversible Encephalopathy Syndrome (PRES) Complicated by Subarachnoid Hemorrhage Induced by Chemotherapy: A Rare Case and Literature Review

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Abstract

Posterior Reversible Encephalopathy Syndrome (PRES) is a rare neurological entity characterized by vasogenic cerebral edema, often triggered by hypertension, renal failure, preeclampsia, certain immunosuppressive drugs, or chemotherapeutic agents. We report the case of a 68-year-old woman with multifocal metastatic intrahepatic cholangiocarcinoma who developed PRES complicated by subarachnoid hemorrhage following the administration of the third cycle of FOLFOX chemotherapy. The clinical picture included headaches, visual disturbances, and recurrent generalized tonic-clonic seizures. Brain magnetic resonance imaging (MRI) confirmed the diagnosis by showing bilateral and symmetrical T2/FLAIR hyperintensities predominantly in the parieto-occipital regions, consistent with vasogenic edema, associated with minimal leptomeningeal bleeding signs. Management consisted of immediate discontinuation of chemotherapy, strict blood pressure control, and anticonvulsant therapy, leading to a rapidly favorable outcome. This case highlights the rarity of oxaliplatin as a causative agent and the importance of heightened clinical vigilance for any acute neurological symptom in a patient undergoing chemotherapy, to enable early management and improve prognosis.

Keywords

Posterior Reversible Encephalopathy Syndrome (PRES), Oxaliplatin, FOLFOX, Subarachnoid Hemorrhage, Chemotherapy,

Neurological Complications

1. Introduction

Posterior Reversible Encephalopathy Syndrome (PRES) is a rare but potentially serious neurological condition characterized by vasogenic edema of the cerebral white matter. It manifests with a constellation of symptoms including headaches, visual disturbances, seizures, and altered consciousness [1]. Magnetic resonance imaging (MRI) is essential for diagnosis, revealing characteristic hyperintensity on T2 and FLAIR sequences, predominantly affecting the parieto-occipital regions, although other brain structures can be involved [2].

This syndrome is often associated with underlying conditions such as acute hypertension, renal failure, preeclampsia, immunosuppression, or exposure to certain pharmacological agents, including chemotherapy [3]. Among these agents, cisplatin is most frequently implicated, followed by cytarabine, methotrexate, and 5-fluorouracil [4]. The involvement of oxaliplatin, although widely used in digestive cancers, remains exceptional and poorly documented [5].

We report here the case of a patient who presented with PRES complicated by subarachnoid hemorrhage, occurring in the context of FOLFOX chemotherapy for multifocal intrahepatic cholangiocarcinoma.

2. Case Report

2.1. Initial Clinical Data

A 68-year-old woman has been followed since 2017 for non-resectable multifocal intrahepatic cholangiocarcinoma, with hepatic and peritoneal metastases. Her medical history includes hypertension, an old cardiac murmur, shingles (2017), an allergy to corticosteroids (flushing), an adenoidectomy, and the excision of a benign cervical polyp. The initial workup did not reveal a DPD deficiency.

The patient successively underwent radioembolization, chemotherapy with gemzar-cisplatin, then reduced-dose gemcitabine monotherapy due to neutropenia. Liver thermo-ablation followed by biopsy was performed in 2019, and then the patient was enrolled in an immunotherapy trial (MS 200647-0047), which was discontinued due to tumor progression. A FOLFOX regimen was initiated in December 2019. Two cycles had been administered before the neurological event occurred.

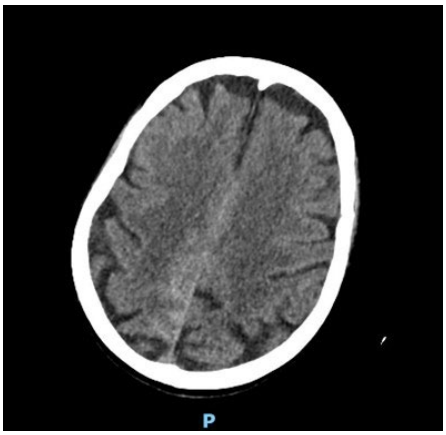
2.2. Acute Episode

On January 10, 2020, during the administration of the third cycle of FOLFOX, the patient presented with headaches and visual disturbances such as phosphenes. Moderate hypertension was noted, leading to the administration of nicardipine (20 mg). At the end of the infusion, she experienced a brief generalized tonic-clonic seizure. Upon the arrival of the resuscitation team, she was in a post-ictal

state, with a blood pressure of 170/70 mmHg, altered vigilance, no focal motor deficit, but complaining of sudden blindness. A second seizure occurred one hour later, justifying the administration of levetiracetam (2500 mg) and transfer for imaging. A third seizure occurred during the CT scan, subsiding after administration of clonazepam (1 mg).

2.3. Brain Imaging

The initial CT scan (Figure 1) revealed right occipital cortical hyperdensity associated with hyperdensity of the adjacent sulci, suggesting cortical or leptomeningeal hemorrhage, as well as edema of the underlying white matter.



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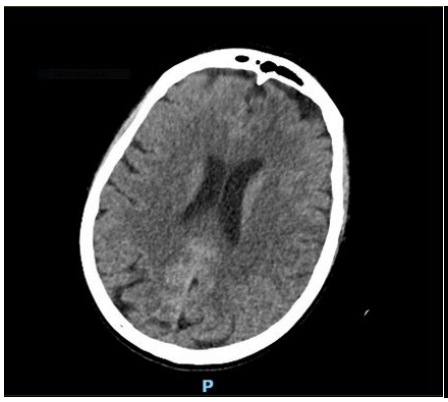

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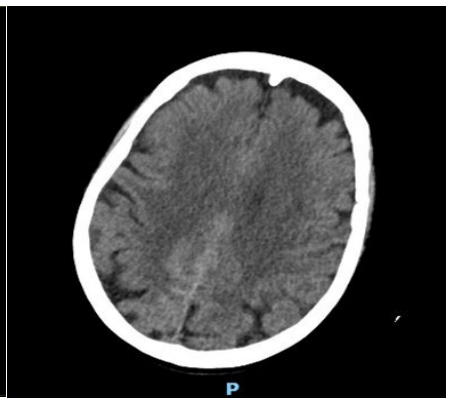
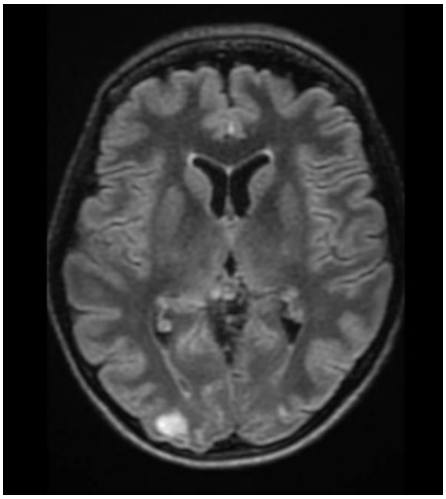


(c)

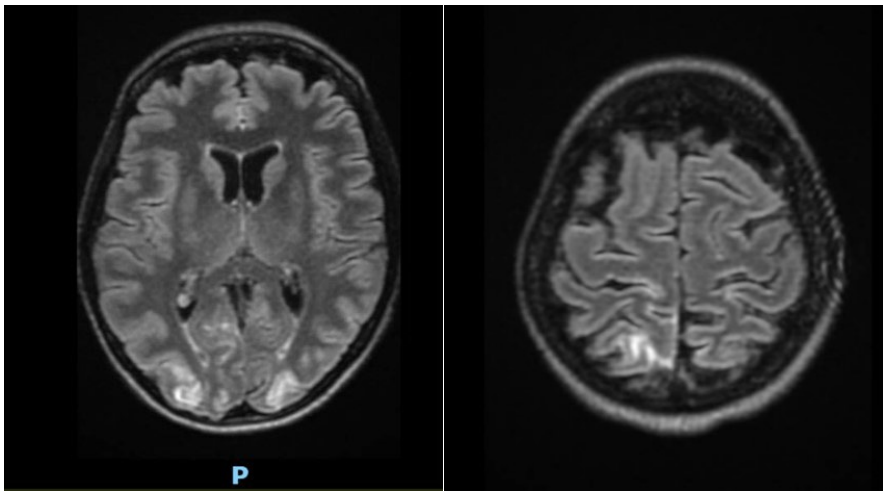
Figure 1. Non-contrast Brain CT Scan. (a)-(c) images showing right occipital cortical hyperdensity (arrows) and adjacent sulci, compatible with hemorrhage, associated with underlying edema.

The emergency brain MRI (Figure 2) confirmed a typical PRES picture, showing bilateral and symmetrical T2 and FLAIR hyperintensities involving the parieto-occipital regions, with cortical and U-fiber involvement. These abnormalities were compatible with vasogenic edema. Also noted were cortical signal abnormalities, focal meningeal and cortical contrast enhancement, and scant lep-

tomeningeal hemorrhage. MR angiography showed no focal vascular abnormality.



(a)



(b) (c)

Figure 2. Brain MRI.

2.4. Differential Diagnosis

Given the sudden onset of neurological disorders, several diagnoses had to be considered: ischemic stroke, severe hypoglycemia, brain metastasis, or meningeal infiltration. The temporal link to chemotherapy infusion directed suspicion towards drug toxicity, including PRES. Rarer conditions were ruled out based on imaging and context, pointing towards a toxic PRES.

2.5. Management in Intensive Care

Upon admission to the ICU, the patient had a Glasgow Coma Scale score of 3, tachycardia at 112/min, blood pressure at 161/77 mmHg. Treatment consisted of strict blood pressure control, anticonvulsant therapy (levetiracetam then sedation

with propofol), close monitoring, and immediate discontinuation of FOLFOX chemotherapy. The overall picture was compatible with PRES syndrome, most likely induced by oxaliplatin and/or 5-FU.

2.6. Outcome and Follow-Up

The patient was seen one month later in oncology consultation. No new neurological episodes had occurred and the patient tolerated capecitabine (Xeloda) well.

3. Discussion

PRES is a rare disease associated with severe morbidity. The diagnosis of PRES is made when a patient presents with (sub)acute encephalopathy and typical MRI imaging patterns, in the presence of one of many triggering factors and in the absence of underlying infectious, metabolic, or malignant causes of encephalopathy (Table 1) [6]. The onset of clinical symptoms is acute to subacute and includes: encephalopathy (incidence 50% - 80%), seizures (60% - 75%), headaches (50%), visual disturbances (33%), focal neurological deficit (10% - 15%), and status epilepticus (5% - 15%) [7].

Table 1. Triggering factors for PRES.

Category	Examples/Medications/Diseases
Hypertensive encephalopathy	
Eclampsia	
Immunosuppressive therapy	Cyclosporine, Tacrolimus
Renal failure	
Acute intermittent porphyria	
Cytotoxic drugs Chemotherapy	Oxaliplatin, 5-fluorouracil, Irinotecan, Paclitaxel, Gemcitabine, Bevacizumab, Sorafenib, Regorafenib, Sunitinib, Pazopanib
Sepsis	
Autoimmune / Systemic diseases	Systemic lupus erythematosus, Thrombotic thrombocytopenic purpura, Hypothyroidism, Scleroderma, Crohn's disease, Ulcerative colitis, Primary sclerosing cholangitis, Rheumatoid arthritis, Sjögren syndrome, Polyarteritis nodosa, Granulomatosis with polyangiitis, Neuromyelitis optica

Symmetrical focal edematous areas in the brain constitute the typical patterns on CT or MRI, predominantly affecting the parietal and occipital lobes [8]. T2/FLAIR sequences are more sensitive than CT for detecting PRES, due to their high sensitivity for cortico-subcortical edema, which is the main characteristic of PRES [9].

The exact pathophysiology of PRES remains unknown, but the two most accepted theories are the vasogenic theory and the cytotoxic theory. According to the vasogenic theory, an elevation in blood pressure beyond the brain vessels' autoregulatory capacity (mean arterial pressure > 150 - 160 mmHg) leads to focal transudation of fluid and petechial hemorrhages, due to disruption of the endothelial junctions of the blood-brain barrier, with a predilection for white matter [1] [7] [10]. The cytotoxic theory suggests that a sudden and severe elevation in blood pressure can cause cerebral vasospasm, leading to local ischemia, cytotoxic edema, and secondarily, extracellular edema [10]. Neither theory accounts for all cases, as PRES has been described in patients with normal or low blood pressure, particularly in the context of sepsis [10].

The association of PRES with chemotherapeutic agents is documented, but its mechanism remains poorly understood. Direct endothelial toxicity is suspected, disrupting the blood-brain barrier, which overwhelms cerebral autoregulation, leading to breakthrough hyperemia, producing direct cytotoxic effects causing PRES [11] [12].

Although exposure to toxic agents is common in patients who develop PRES, it is rare for oxaliplatin to be associated with it [13]. A thorough review of the literature found that 10 cases of PRES have been associated with oxaliplatin alone or in combination with other drugs like 5-fluorouracil (5-FU) and bevacizumab. The first case was reported by Skelton *et al.* [14] of a 19-year-old woman with metastatic rectal adenocarcinoma, receiving modified FOLFOX (oxaliplatin/5-FU) who subsequently developed seizures and altered mental status, later confirming PRES. Since then, nine other cases have been reported in different parts of the world, identifying oxaliplatin or a combination of oxaliplatin with 5-FU or bevacizumab as a possible cause related to the development of PRES in these patients [14]-[16].

In the absence of specific treatment, management is primarily symptomatic, based on blood pressure control and treatment of seizures if present [2]. The precipitating cause must be removed or treated. In patients undergoing anti-VEGF therapy, it is particularly important to anticipate and treat hypertension.

The prognosis of PRES is generally favorable, with complete recovery within one to two weeks, sometimes extending over several weeks, as observed in our case [2] [17]. Even with early diagnosis and rapid intervention, a low risk (10% - 20%) of persistent neurological symptoms remains [2]. Recurrence is rare if the cause is identified and blood pressure is properly controlled. Reintroduction of chemotherapy or targeted oncological treatments can be considered under close monitoring and rigorous blood pressure control [17] [18].

The main objective of these observations is to increase clinicians' vigilance when a patient with (sub)acute encephalopathy is receiving chemotherapy or targeted oncological treatment.

4. Conclusion

This case illustrates the occurrence of Posterior Reversible Encephalopathy Syn-

drome (PRES) complicated by subarachnoid hemorrhage, occurring in a strongly suggestive temporal context of imputability to FOLFOX chemotherapy. The particularity of this observation lies in its association with oxaliplatin. The rapidly favorable outcome after discontinuation of the implicated treatment strengthens the etiological hypothesis. This clinical picture, although rare, underscores the importance of increased vigilance by clinicians regarding any acute neurological symptom—headaches, visual disturbances, seizures, or altered consciousness—in a patient undergoing common chemotherapy regimens like FOLFOX. Early diagnosis and appropriate management usually allow for complete recovery without necessarily compromising the oncological outcome.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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