Neurological Case Reports

Case Report
Published: 08 Feb, 2023

Oxaliplatin-Induced Status Epilepticus in the Absence of Posterior Reversible Encephalopathy Syndrome: A Case Report

Tedjasukmana R[1], Sudoyo AW[2] and Widjaja P[3]*

[1]*Department of Neurology, Medistra Hospital, Krida Wacana Christian University, Indonesia*

[2]*Department of Internal Medicine, Medistra Hospital, University of Indonesia, Indonesia*

[3]*Deparment of Radiology, Medistra Hospital, Jakarta, Indonesia*

Abstract

Background: Oxaliplatin is a chemotherapeutic agent that consists of a platinum compound that inhibits DNA synthesis. Widely used for various cancers, this drug can have neurological, gastrointestinal or hematological side effects. The most common neurological adverse effect of this drug is peripheral sensory neuropathy. Although quite rare, there have been several reports of seizures associated with the chemotherapy-related toxicity of oxaliplatin. Generally, these patients showed concomitant blood pressure elevation and Posterior Reversible Encephalopathy Syndrome (PRES) on Brain Magnetic Resonance Imaging (MRI). However, there was a report of one patient who did not show evidence of PRES.

Case Report: We report a second case of oxaliplatin-induced status epilepticus in the absence of PRES. The patient was a 74-year-old Indonesian woman diagnosed with colorectal cancer. In this patient seizures occurred a few days after the first cycle of treatment. Her blood pressure remained normal and her brain MRI showed no sign of metastasis or PRES. She became conscious with no neurological sequelae 4 days after her seizures.

Conclusion: These cases challenge the notion that oxaliplatin-induced seizures are caused by PRES. Perhaps there are other unknown mechanisms involved. The risk of seizures induced by oxaliplatin is low. However, physicians need to be aware of this risk and inform their patients accordingly.

Keywords: Chemotherapy-related toxicity; Oxaliplatin; Posterior reversible encephalopathy syndrome; Seizures

OPEN ACCESS

Correspondence:
Rimawati Tedjasukmana, Department of Neurology, Sleep and Snoring Clinic, Medistra Hospital, Krida Wacana Christian University, Jl. Kelapa Nias I. PA4 no 1, Jakarta 14250, Indonesia, E-mail: rima.tedja@gmail.com/rimawati.tedjasukmana@ukrida.ac.id

Received Date: *12 Jan 2023*
Accepted Date: *03 Feb 2023*
Published Date: *08 Feb 2023*

Citation:
Tedjasukmana R, Sudoyo AW, Widjaja P. Oxaliplatin-Induced Status Epilepticus in the Absence of Posterior Reversible Encephalopathy Syndrome: A Case Report. Neurol Case Rep. 2023; 6(1): 1036.

Abbreviations

CT scan: Computerized Tomography scan; EEG: Electroencephalography; IV: Intravenous; mg: milligram; MRI: Magnetic Resonance Imaging; PET scan: Positron Emission Tomography scan; PRES: Posterior Reversible Encephalopathy Syndrome; t.i.d: Three Times A Day

Introduction

Oxaliplatin is a chemotherapeutic agent that consists of a platinum compound that inhibits DNA synthesis. Widely used as part of chemotherapy regimens against various cancers notably colorectal cancers this drug has been used since the late 1990s and has few adverse effects. The side effects of this drug are mostly gastrointestinal and hematological, and are commonly found with other cytostatic drugs. A more common side effect is acute peripheral sensory neuropathy, characterized by distal paresthesia or dysesthesia, that often occurs immediately after infusion; it is often reversible but can continue as a chronic condition lasting for years [1]. Although quite rare, there have been several reports of seizures associated with the chemotherapy-related toxicity of oxaliplatin [2-4]. Generally, these patients also concomitant Posterior Reversible Encephalopathy Syndrome (PRES) on brain Magnetic Resonance Imaging (MRIs) [2,5].

PRES occurs very rarely, and patients present with acute or subacute encephalopathy and typical imaging patterns on brain MRI [2]. Patients generally come plain of headaches, altered mental status, seizures and visual loss. Because of the frequent concomitant occurrence of typical PRES on imaging and seizures, it was surmised that oxaliplatin chemotherapy-related toxicity associated PRES was

the cause of seizures in these patients [3]. However, there was only one known case report of seizures following oxaliplatin therapy without the presence of PRES [4]. This contradicted the notion that PRES caused the seizures in these patients. We present a second case of seizures induced by oxaliplatin treatment in the absence of PRES.

Case Presentation

A 74-year-old Indonesian woman of ethnic Chinese descent was admitted to our hospital for the first regimen of her cancer chemotherapy. She was previously diagnosed with stage 3 colorectal cancer (stage T3N3Mx). She underwent laparotomy 4 months earlier. Her biopsy showed adenocarcinoma. The patient was allergic to contrast material, so a CT scan was not performed, and postoperative imaging studies had to rely on Positron Emission Tomography (PET) scan which was within normal limits. On admittance, the patient was alert with normal vital signs. Her blood pressure was 103/95 mmHg, pulse rate 70 times/min, respiration rate 20 times/min, and body temperature 36C. Her body weight was 54 kg, height 154 cm, body mass index 22.78 kg/m^2. She was administered oxaliplatin 127 mg, folinic acid 600 mg, 5-fluorouracyl 600 mg bolus and 3,600 mg in 46 h.

The next day, the patient had nausea and vomiting. On the morning of the third day, the patient became confused and disoriented. Later, she became unconscious, conjugate gaze deviation to the right was seen, and her extremities were spastic with subtle twitching in her right leg. Her vital signs remained normal. She continued in this condition for more than an hour. After a neurological examination, we concluded that she had generalized status epilepticus. She was administered diazepam 5 mg intravenously, which stopped her seizure. Next, we administered 20 mg/kg body weight bolus of phenytoin followed by maintenance phenytoin 100 mg IV t.i.d. The patient was still unresponsive one day after the seizures, and she became delirious for 2 days. Neurological examination showed mild right-sided hemiparesis. Her vital signs remained normal during this time. She was conscious 4 days after status epilepticus, and her motor functions were normal. There were no more seizures before she was discharged (Figure 1).

Her laboratory results were within normal limits, except for mild hyponatremia. The complete blood count, liver enzymes, serum urea and creatinine were normal; of her serum electrolytes, only the sodium level was slightly low (133 mEq/L). After her seizure, we conducted brain CT scan the same day and brain MRI and Electroencephalography (EEG) the next day. A non-enhanced axial CT scan of the brain shows some multifocal hypodense lesions in both deep white matter in the frontoparietal regions associated with periventricular white matter abnormalities due to perfusion disturbances, with no evidence of any posterior hypodensity abnormality or space-occupying lesion, and a normal ventricle system. Her brain MRI did not show any metastatic lesions, or PRES. Non-enhanced brain MRI in axial T1WI, T2WI and T2 Flair demonstrate multiple subcortical and deep white matter lesions in both frontoparietal regions (Figure 2). EEG recorded one day after status epilepticus showed background rhythm slowing of 5 Hz to 6 Hz and intermittent high-voltage generalized paroxysmal 1.5 Hz to 2 Hz spike-slow wave complexes (Figure 3).

Discussion

Oxaliplatin has a broad spectrum of antineoplastic activity and is used in various cancers, especially colorectal cancer. In these patients, the addition of oxaliplatin to first-line fluorouracil/folinic acid therapy significantly increased the treatment efficacy compared with fluorouracil/folinic acid therapy alone. Adverse effects of this drug can be neurological, gastrointestinal or hematological. Gastrointestinal and hematological toxicities occur frequently but are generally mild to moderate in intensity. Neurological toxicity is usually a reversible peripheral sensory neuropathy [1]. Although very rare, there have been several reports of seizures induced by oxaliplatin [2-4]. Oxaliplatin is a platinum-derived drug that poorly penetrates the blood-brain barrier. However, in combination with other leucotoxic agents, it may cause endothelial injury and weakness of the cerebral endothelial wall through vasogenic oedema [2].

This patient's presentation was not typical for oxaliplatin-induced seizures. Generally, patients present with symptoms of PRES, which is characterized by a variety of neurological symptoms, usually associated with elevated arterial blood pressure [6]. Oxaliplatin has rarely been associated with PRES, and only 11 cases have been reported worldwide [7]. Some of these patients were treated with a combination of oxaliplatin and 5-fluorouracyl [8-12], and other patients were treated in combination with capecitabine [5,7,13-15], or bevacizumab [13,16]. All of these patients were diagnosed with colorectal cancer; they showed a variety of neurological symptoms

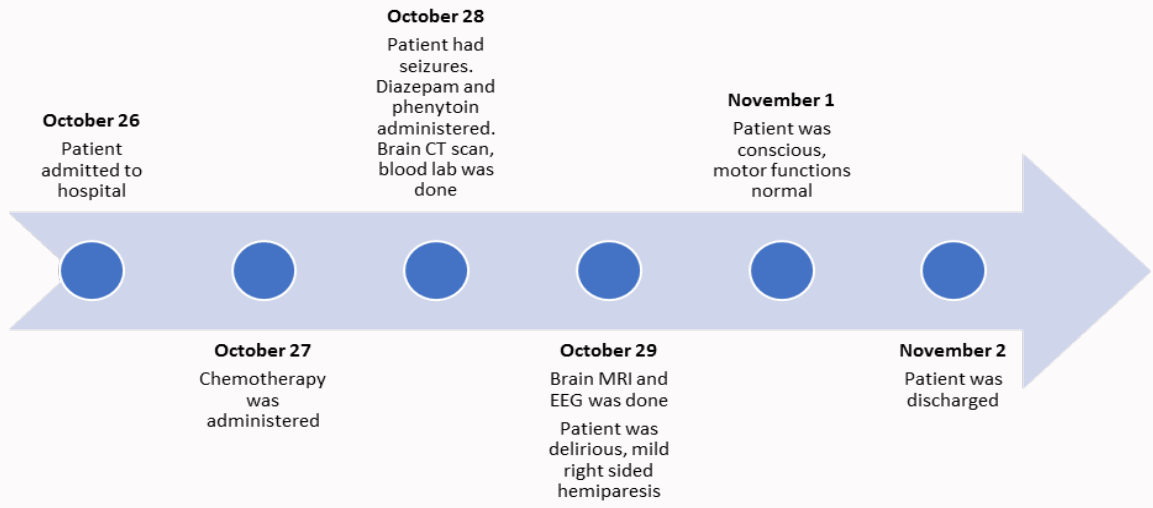

Figure 1: Timeline of disease progression.

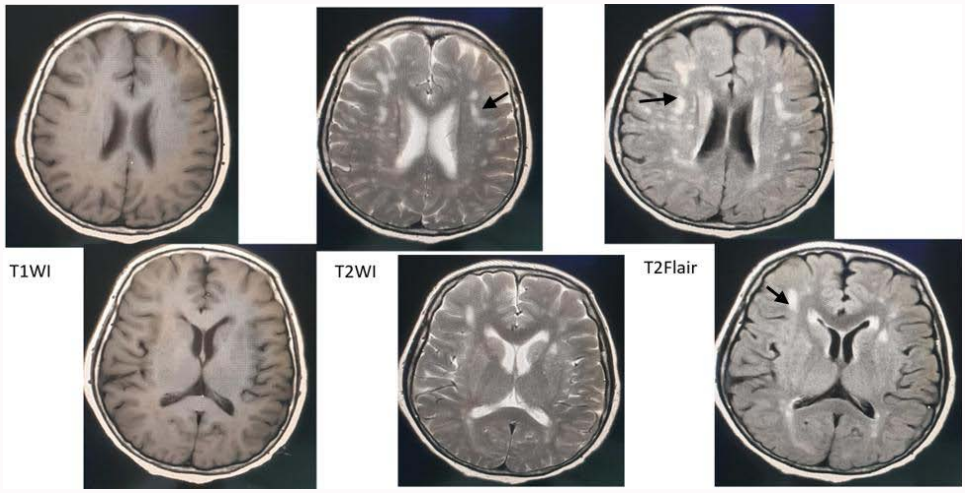

Figure 2: Non-enhanced Brain MRI in axial T1WI, T2WI and T2 Flair demonstrate multiple subcortical and deep white matter lesions in both frontoparietal regions (black arrows), no abnormality seen in the posterior parietal regions, no evidence of acute infarction or any space occupying lesions. No sign of PRES or metastatic lesions was seen.

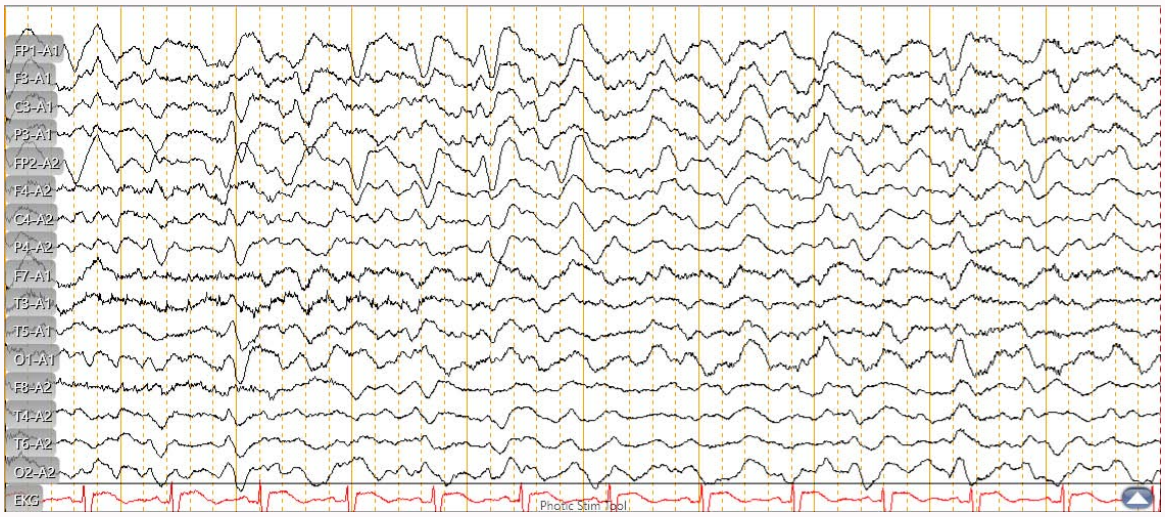

Figure 3: EEG showed background slowing and paroxysmal intermittent generalized high voltage 1.5 Hz to 2 Hz spike-slow wave complexes.

after chemotherapy and presented with evidence of PRES on brain MRI. The only common denominator in these cases was the treatment of colorectal cancer with oxaliplatin combined with other drugs.

PRES is a neurotoxic state characterized by seizures, headache, vision change, paresis, nausea and altered mental status. In its mild form, this disorder might cause only one clinical symptom (headache or seizure) and cerebral imaging might show few areas of vasogenic edema or even normal brain imaging in some rare cases. In its severe form, PRES might cause substantial morbidity and even mortality. In most cases, PRES resolves spontaneously and patients show both clinical and radiological improvements [17]. MRI is more sensitive than CT to PRES, displaying hyperintense lesions in T2-weighted or Fluid-Attenuated Inversion Recovery (FLAIR) sequences. MRI lesions depicting vasogenic oedema usually follow a parieto-occipital pattern. Although usually bihemispheric, lesions may be distributed asymmetrically [6]. However, atypical imaging features, such as involvement of the anterior cerebral regions, deep white matter regions, and the brainstem are also frequently seen [18,19]. EEG in PRES cases showed diffuse theta or delta slowing, rhythmic delta activity, sharp-slow wave activity, periodic lateralizing epileptiform discharges, and diffuse or focal symmetric slowing of background activities [6]. This patient showed severe symptoms of status epilepticus, but her brain MRI was normal. Her EEG showed background slowing and intermittent generalized epileptiform discharges. Thus, in this case, we could not say that she had a milder form of PRES. She had severe symptoms with normal brain imaging.

Case reports in the literature have observed that oxaliplatin-induced PRES occurs between 10 days and 3 months after administration of this drug [12]. Status epilepticus in this patient occurred only 2 days after oxaliplatin administration. This further sets this case apart from other cases of oxaliplatin-induced seizures, where PRES was surmised to be the cause. Additionally, in this patient, her blood pressure remained normal throughout the episode. In other case reports, hypertension was present before the seizures occurred. Different conditions have been associated with PRES, and it is frequently reported in toxemia of pregnancy, solid organ or bone marrow transplantation, immunosuppressive treatment, cancer chemotherapy, autoimmune diseases, renal failure,

and hypertension. The prognosis is usually benign with complete reversal of clinical symptoms within several days, when adequate treatment is immediately initiated [18]. The exact pathophysiology of PRES is still unknown but the two most accepted theories are the vasogenic and cytotoxic theories. The vasogenic theory states that, when blood pressure rises above the autoregulatory capacity of the cerebral vasculature (i.e., mean arterial pressure above 150 mmHg to 160 mmHg), focal transudation of fluid and petechial hemorrhages will occur due to a disruption of the endothelial junctions of the blood-brain barrier, usually in the white matter. The cytotoxic theory states that a sudden, severe elevation of blood pressure can cause vasospasm which leads to ischemia of brain tissue, cytotoxic edema and secondary extracellular oedema. However, neither theory can explain everything, since there have been reports of cases with normal or low blood pressure [6]. Another plausible theory suggests that cytotoxic drugs have direct toxic effects on vascular endothelial cells, disrupting the blood brain barrier. This disruption overwhelms cerebral autoregulation resulting in breakthrough hyperemia, which produces direct cytotoxic effects causing PRES [7].

There was only one other reported case of oxaliplatin-induced seizures in the absence of PRES. The first case was reported by Rahal et al. [4]. The patient was a 50-year-old male with colorectal cancer. He was treated with folinic acid, fluorouracil, and oxaliplatin. He had seizures after the third cycle of chemotherapy, and was seizure free after the regimen was changed to exclude oxaliplatin. This patient had normal brain MRI [4]. Our patient was a 74-year-old female who developed status epilepticus after only one cycle of therapy with folinic acid, fluorouracil, and oxaliplatin. In our case brain MRI was also normal. These cases challenge the hypothesis that PRES caused the seizures induced by chemotherapy-related toxicity of oxaliplatin. Not all oxaliplatin-induced seizures were caused by PRES. We have to look for other mechanisms for the seizures.

Conclusion

This case highlights the increasing number of patients who developed seizures after oxaliplatin therapy. The risk of seizures induced by oxaliplatin is very low. However, physicians need to be aware of this risk and inform their patients accordingly. Although quite rare, oxaliplatin can induce seizures and its occurrence warrants a more thorough investigation. Seizures can be caused by PRES or other still unknown mechanisms.

References

1. Culy CR, Clemett D, Wiseman LR. Oxaliplatin. A review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. Drugs. 2000;60(4):895-924.
2. Van Pelt Q, Stragier E, Roelandt P, Van Cutsem E. Posterior reversible encephalopathy syndrome secondary to oxaliplatin-based chemotherapy and regorafenib in metastastic colorectal cancer: Case reports and literature review. Acta Gastroenterol Belg. 2020;83(1):47-50.
3. Tsukamoto JS, Oliveira MB de, Peixoto RD. Tonic-clonic seizure following cytoreductive surgery with intraperitoneal oxaliplatin: A case report and review of the literature. Case Rep Oncol. 2016;9(1):89-94.
4. Rahal AK, Truong PV, Kallail KJ. Oxaliplatin-induced tonic-clonic seizures. Case Rep Oncol Med. 2015;2015:e879217.
5. Femia G, Hardy TA, Spies JM, Horvath LG. Posterior reversible encephalopathy syndrome following chemotherapy with oxaliplatin and a fluoropyrimidine: A case report and literature review. Asia Pac J Clin Oncol. 2012;8(2):115-22.
6. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. J Neurol. 2017;264(8):1608-16.
7. Janjua TK, Hassan M, Afridi HK, Zahid NA. Oxaliplatin-induced Posterior Reversible Encephalopathy Syndrome (PRES). BMJ Case Rep. 2017;2017.
8. Skelton MR, Goldberg RM, O'Neil BH. A case of oxaliplatin-related posterior reversible encephalopathy syndrome. Clin Colorectal Cancer. 2007;6(5):386-8.
9. Sharief U, Perry DJ. Delayed reversible posterior encephalopathy syndrome following chemotherapy with oxaliplatin. Clin Colorectal Cancer. 2009;8(3):163-5.
10. Truman N, Nethercott D. Posterior Reversible Encephalopathy Syndrome (PRES) after treatment with oxaliplatin and 5-fluorouracil. Clin Colorectal Cancer. 2013;12(1):70-2.
11. Porcello Marrone LC, Marrone BF, Pascoal TA, Schilling LP, Soder RB, Ferreira SS, et al. Posterior reversible encephalopathy syndrome associated with FOLFOX chemotherapy. Case Rep Oncol Med. 2013;2013:306983.
12. Kim CH, Kim CH, Chung CK, Jahng TA. Unexpected seizure attack in a patient with spinal metastasis diagnosed as posterior reversible encephalopathy syndrome. J Korean Neurosurg Soc. 2011;50(1):60-3.
13. Pinedo DM, Shah-Khan F, Shah PC. Reversible posterior leukoencephalopathy syndrome associated with oxaliplatin. J Clin Oncol. 2007;25(33):5320-1.
14. Nagata Y, Omuro Y, Shimoyama T, Sasaki E, Okamoto R, Maeda Y, et al. [A case of colon cancer with reversible posterior leukoencephalopathy syndrome following 5-FU and oxaliplatin (FOLFOX regime)]. Gan To Kagaku Ryoho. 2009;36(7):1163-6.
15. Tang KH. Oxaliplatin-induced posterior reversible encephalopathy syndrome with isolated involvement of pons. J Cancer Res Ther. 2015;11(4):1022.
16. Chang Y, Mbeo G, Littman SJ. Reversible posterior leukoencephalopathy syndrome associated with concurrent bevacizumab, gemcitabine, and oxaliplatin for cholangiocarcinoma. J Gastrointest Cancer. 2012;43(3):505-7.
17. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: Clinical and radiological manifestations, pathophysiology, and outstanding questions. Lancet Neurol. 2015;14(9):914-25.
18. Staykov D, Schwab S. Posterior reversible encephalopathy syndrome. J Intensive Care Med. 2012;27(1):11-24.
19. Kastrup O, Schlamann M, Moenninghoff C, Forsting M, Goericke S. Posterior reversible encephalopathy syndrome: The spectrum of MR imaging patterns. Clin Neuroradiol. 2015;25(2):161-71.