

Case Report

Posterior Reversible Encephalopathy Syndrome Associated with Oxaliplatin Use for Pancreatic Adenocarcinoma

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Keywords

Encephalopathy · Syndrome · Oxaliplatin · Pancreas · Posterior reversible encephalopathy syndrome

Abstract

The posterior reversible encephalopathy syndrome (PRES) was first described by Hinchey's group in 1996 as a reversible vasogenic brain edema on magnetic resonance imaging (MRI). Hypertension represents the most frequent manifestation associated with PRES. In the present report, we present a patient diagnosed with locally advanced pancreatic adenocarcinoma who received 3 cycles of a 5-fluorouracil plus oxaliplatin-based chemotherapy regimen and developed PRES after the third cycle. Several days after receiving the second cycle of FOLFOX chemotherapy, the patient started having episodes of hypertensive crisis (systolic pressure = 180, diastolic pressure = 100), that was controlled with amlodipine, irbesartan, and hydrochlorothiazide. After the administration of the third cycle, this time with the FOLFIRINOX regimen, he appeared lethargic and disoriented in place and time. MRI revealed bilateral areas of signal hyperintensity in the thalamus, hypothalamus, fibers of reticular formation, anterior section of cerebral vermis and a mild edema of left parahippocampal gyrus, with no signs of brain metastases. Ultimately, the patient was diagnosed with PRES syndrome, and he was treated with glucose, 5% saline, thiamine supplementation, levetiracetam (Keppra®), and i.v. dexamethasone. Three weeks later, he gradually became conscious, with cognitive function recovery, and capable of executing movements.

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Introduction

The posterior reversible encephalopathy syndrome (PRES), was first described by Hinchey et al. [1] in 1996, as a reversible vasogenic brain edema on magnetic resonance imaging (MRI). Hypertension represents the most frequent manifestation associated with PRES [2]. Other risk factors include eclampsia/pre-eclampsia, sepsis, renal failure, certain antineoplastic agents, and systemic lupus erythematosus [3]. PRES is characterized by an altered level of consciousness, seizures, nausea, headache, visual loss, including cortical blindness, and hypertension [4]. The mechanism(s) underlining this syndrome remain poorly defined, but it is believed that rapidly developing hypertension leads to a failed cerebral auto-regulation, typically in posterior region and the caused hyperperfusion results in the development of vasogenic edema [5, 6]. In the present report, we present a patient diagnosed with locally advanced pancreatic adenocarcinoma who received 3 cycles of a 5-fluoruracil (5-FU) plus oxaliplatin-based chemotherapy regimen and developed PRES after the third cycle. Moreover, we review some other cases from the existing literature connecting PRES not solely with anti-vascular endothelial growth factor (VEGF) agents but also with oxaliplatin [7]. The clinical manifestations in the presented case in association with the imaging findings in T2A MRI and FLAIR images led us to the conclusion that our patient developed PRES [8].

Case Report

A 75-year-old male patient presenting with painless obstructive jaundice was diagnosed with pancreatic adenocarcinoma after an endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) cytology on January 2020, and was admitted to our hospital for initiation of antineoplastic chemotherapy. In view of a raising direct bilirubin: 10 mg/dL (171 μ mol/L) and obstructive jaundice, a percutaneous biliary tract stent was placed, and bilirubin levels normalized within 1 week.

At baseline computed tomography (CT) of the abdomen, a 2.9 \times 2.5 cm lesion was apparent in the uncinate process of pancreas causing dilatation of the pancreatic and biliary ducts. The lesion was surrounding the superior mesenteric artery by more than 270° and was initially deemed unresectable.

The patient was treated with two cycles of a mFOLFOX regimen consisting of oxaliplatin, leucovorin calcium and infusional 5-FU over 2 days, followed by one cycle of FOLFIRINOX consisting of oxaliplatin, irinotecan, leucovorin calcium, and infusional 5-FU.

Several days after receiving the second cycle of FOLFOX chemotherapy, the patient started having episodes of hypertensive crisis (systolic pressure = 180, diastolic pressure = 100), that controlled with amlodipine, irbesartan, and hydrochlorothiazide. After the administration of the third cycle, this time with the FOLFIRINOX regimen, he appeared lethargic and disoriented in place and time. His vital signs were as follows: (1) blood pressure 180/100 mm Hg, (2) heart rate 110 bpm, and (3) temperature 38°C. A laboratory investigation revealed a normal white blood cell count 4,100/ μ L, an elevated C-reactive protein (90 mg/L), and mild hyponatremia 129 mEq/L. Moreover, intermittent left upper and lower extremity shaking was observed, without further mental status decline, compatible with focal/partial epileptic seizures. A cerebrospinal fluid sample obtained by lumbar puncture yielded a negative cytology for metastatic cells (meningeal carcinomatosis), tests and cultures for Gram-positive/-negative bacteria, and virological tests for HSV, herpes zoster/VZV, EBV, CMV, JC, BK, adenoviruses, influenza viruses, etc., fungal causes such as coccidiomycosis, *Aspergillus* spp., *Candida* spp., tuberculosis/atypical mycobacteria, listeria, borellia, etc., and respective cultures were all negative. The patient was treated empirically with meropenem and vanco-

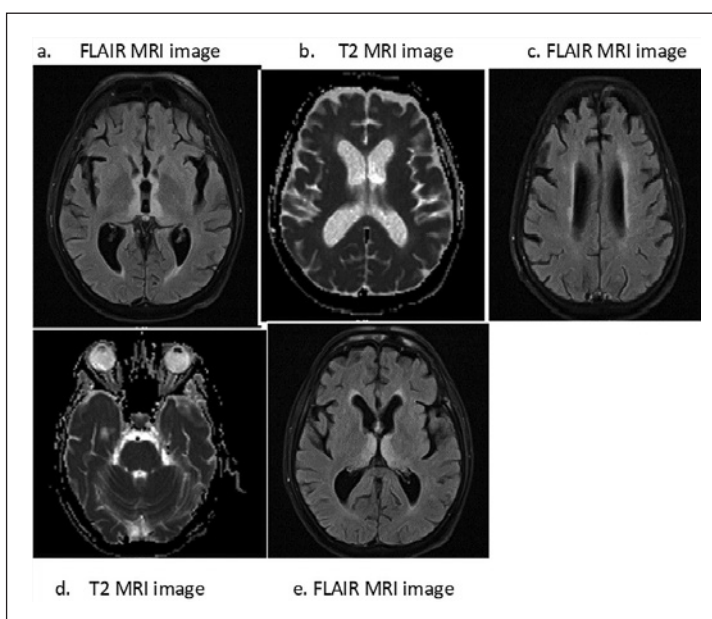


Fig. 1. T2 and FLAIR images of bilateral areas of signal hyperintensity in the thalamus, hypothalamus, fibers of reticular formation, anterior section of cerebral vermis, and a mild edema of left para-hippocampal gyrus, with no signs of brain metastases.

mycin, acyclovir, and anidulafungin. The following day, he was clinically deteriorating. He had horizontal and vertical nystagmus and no reaction to painful stimuli.

MRI revealed bilateral areas of signal hyperintensity in the thalamus, hypothalamus, fibers of reticular formation, anterior section of cerebral vermis, and a mild edema of left para-hippocampal gyrus, with no signs of brain metastases (Fig. 1).

Ultimately, the patient was diagnosed with PRES syndrome, and he was treated with glucose 5% saline, thiamine supplementation, levetiracetam (Keppra®), and i.v. dexamethasone. Three weeks later, he gradually became conscious, with cognitive function recovery, and capable of executing movements.

Discussion

PRES syndrome in MRI is characterized by reversible vasogenic edema with symmetrical FLAIR hyperintensities. Edema is thought to be due to fluid extravasation, and for that reason, MRI rather than CT is preferred [9]. As it was initially highlighted, there are various clinical conditions predisposing to the development of PRES, such as eclampsia/pre-eclampsia of pregnancy, sepsis, renal failure, systemic lupus erythematosus, and antineoplastic agents. In the present case report, the most likely causal factor for PRES was oxaliplatin. Sudden onset of severe hypertension can lead to endothelial injury and a failed autoregulation of local circulation with defective vasoconstriction, leading to ischemia and edema, that are the most important consequences [10–12]. It is also believed that high blood pressure leads to the breakdown of the blood-brain barrier and a situation of hyperperfusion. The latter represents the vasogenic theory. Additionally, there is the cytotoxic theory, where severe hypertension provokes cytotoxic edema which causes cerebral vasoconstriction resulting in hypoperfusion and cerebral ischemia [13, 14]. Posterior cerebral circulation has reduced adrenergic innervation; therefore, the blood vessels are more sensitive to endothelial damage due to blood pressure changes [15]. Early detection of the syndrome, gradual blood pressure normalization, and withdrawal of any offensive agent are the only way to manage cases with

Table 1. Comparison of cancer type, treatment, and outcome in patients diagnosed with PRES syndrome

| Authors | Age, sex | Cancer type | Treatment | Outcome |
|---------------------------------|----------|---|--|---|
| Colorectal carcinoma | | | | |
| Ozcan et al. | 52, F | Rectal adenocarcinoma | FOLFOX+bevacizumab | Complete recovery |
| Formica et al. | 45, F | Colon cancer | Capecitabine+oxaliplatin | Change of treatment agents |
| Skelton et al. | 19, F | Rectal adenocarcinoma | 5-FU, oxaliplatin | Recovered from PRES, but she died later |
| Pinedo et al. | 62, F | Rectal adenocarcinoma | Oxaliplatin, bevacizumab, capecitabine | Complete recovery, treatment changed |
| Peter et al. | 62, F | Metastatic colon cancer | FOLFOX | Complete recovery |
| Lau and Paunipagar | 63, F | Rectosigmoid carcinoma | FOLFOX+bevacizumab | Complete recovery |
| Negata et al. | 35, F | Sigmoid adenocarcinoma | Oxaliplatin, capecitabine | Complete recovery |
| Femia et al. | 56, M | Colon adenocarcinoma | Oxaliplatin, capecitabine | Deterioration of symptoms, he died later |
| Truman and Nethercott | 73, F | Caecal adenocarcinoma | Oxaliplatin, 5-FU | Complete recovery |
| Porcello et al. | 27, F | Colorectal adenocarcinoma | FOLFOX | Complete recovery, but she died later due to cancer complications |
| Rahal et al. | 50, M | Mixed adenoneuroendocrine carcinoma of appendix | FOLFOX | Complete recovery and change of treatment regimens |
| Tang | 81, M | Colorectal adenocarcinoma | Oxaliplatin, capecitabine | Complete recovery |
| Eiichi katada et al. | 44, F | Metastatic colon cancer | FOLFOX+bevacizumab | Improvement of MRI findings, she died later due to cancer deterioration |
| Edouard Chanal et al. | 53, M | Colon cancer | FOLFOX | Complete response, he died later due to cancer complications |
| Non colorectal carcinoma | | | | |
| Levy et al. | 6, M | Hepatoblastoma | GEMOX + bevacizumab | Complete recovery |
| Kim et al. | 42, F | Metastatic gastric cancer | FOLFOX | Complete recovery |
| Moris et al. | 42, M | Urothelial bladder cancer | GEMOX | Complete recovery, but he died later due to pneumonia |
| Chue et al. | 47, F | Cervical carcinoma | Cisplatin, 5-FU | Complete recovery |
| Ki et al. | 44, M | GIST | Doxorubicin, mitomycin-C, 5-FU | Ongoing disability |
| Chang et al. | | Intrahepatic cholangiocarcinoma | GEMOX + bevacizumab | |

PRES. Despite the fact that PRES is reversible, there are secondary complications, like status epilepticus, intracranial hemorrhage, and ischemic infraction, that on top of the major neoplastic disease, may significantly worsen the whole patient situation and lead to performance status deterioration that may preclude further cytotoxic chemotherapy administration [16]. There are many cytotoxic/antineoplastic agents that have been implicated in the development of the syndrome, with the first category being agents targeting angiogenesis, such as the anti-VEGF agents, bevacizumab, as well as agents targeting the VEGF receptor

tyrosine kinase (VEGFR-TKI), such as sunitinib, sorafenib, pazopanib, etc. Since initial descriptions of the syndrome associated with anti-neoplastic chemotherapy, either bevacizumab [17] or cytotoxic chemotherapy for hematologic malignancies, physicians became familiar with early recognition of PRES, and therefore many case reports or case series have been reported with various chemotherapeutic and/or biological therapy agents strongly associated with this syndrome, as reviewed by How et al. [18].

As a result, a number of agents after a review of the Medline/PubMed database, have been implicated in the development of PRES. Certain combination regimens that have been associated with the development of PRES, relevant to the current case, are the combination of capecitabine and oxaliplatin (XELOX), and the FOLFOX regimen (5-FU/leucovorin and oxaliplatin) with or without bevacizumab. Overall, 18 cases with colorectal carcinoma that received oxaliplatin-based combinations, XELOX or FOLFOX, have been reported; 10 cases with and 8 without bevacizumab (Table 1). Moreover, 4 cases with non-colorectal tumors have been reported so far; 2 cases: 1 gastric (FOLFOX) and 1 urothelial/bladder (GEMOX) carcinoma without bevacizumab; and 2 cases: 1 hepatoblastoma and 1 intrahepatic cholangiocarcinoma (both treated with GEMOX) with bevacizumab (Table 1). Notwithstanding, in the present report, our case represents the first non-colorectal cancer patient who received FOLFIRINOX, a non-bevacizumab-based regimen, and developed a clinically typical and radiologically very suggestive PRES that resolved with supportive measures after approximately 3–4 weeks.

It should be emphasized that anti-VEGF agents were the first believed to be related to the development of PRES. It is rather important to stress-out that there are case reports in the literature, where patients diagnosed with PRES were given other antiangiogenic agents, that is VEGFR-TKIs, like sunitinib, pazopanib, and sorafenib [19–21]. In our case, it appears that oxaliplatin was the main cytotoxic agent which could lead to PRES. There are many cases which link the development of PRES with oxaliplatin, even if the mechanism is not so clear. Encephalopathy is the characteristic constellation of symptoms through changes in mental status, development of generalized or focal seizures, visual hallucinations, headache, impaired cognitive function, and vomiting [22]. In the differential diagnosis are brain metastases, episodes of hypoglycemia, brain hemorrhage and stroke. Neurological examination may show extremity weakness, myopathy, or positive Babinski sign [23]. When the occipital lobes are involved, cortical blindness may be observed, whereas on the other hand, coma is observed when more widespread cortical edema or thalamic involvement is present. In our case, the change in mental status in addition to hypertension, nystagmus, and partial seizures led us to suggest the development of PRES. Then, the MRI findings which revealed bilateral regions of signal hyperintensity in the thalamus, hypothalamus, fibers of reticular formation, anterior section of cerebral vermis, and mild edema of left para-hippocampal gyrus, with no signs of brain or leptomeningeal metastases, made this diagnosis more likely. The administration of dexamethasone, seizure control with antiepileptics, and normalization of hypertension gradually improved patient's mental status, leading to clinical improvement and resolution of PRES.

Conclusion

Posterior encephalopathy syndrome is a significant situation in patients who underwent chemotherapy, so we must be careful to establish the diagnosis early in order to initiate appropriate management.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

There is no conflict of interest in none category, financial, political or any other.

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Author Contributions

David G. Symeonidis: Resident Medical Oncologist, author, Metaxa Memorial Cancer Institute, Piraeus, Greece, Author of main submission, responsible for the organization of the submission. *Alexandros Liatsos*: Resident of Internal Medicine, co-author, Metaxa Memorial Cancer Institute, Piraeus Greece, co-authorship of discussion section. *Evriliki K. Mazlimoglou*: Resident of Internal Medicine, co-author, Metaxa Memorial Cancer Institute Piraeus Greece, contributor to the discussion section, as she was the main doctor who made the PRES diagnosis. *Eleni C. Geraki*: Resident of Internal Medicine, co-author, Metaxa Memorial Cancer Institute Piraeus Greece, contributor to the discussion section, as she helped with the PRES diagnosis. *Christos Kosmas*: Head of Oncology Department, co-author, Metaxa Memorial Cancer Institute Piraeus Greece, introduction section, he made any corrections needed for the submission.

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