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CASE REPORT

Posterior Reversible Encephalopathy Syndrome During Treatment with Aflibercept, 5-Fluorouracil, Leucovorin, and Irinotecan for Metastatic Colorectal Cancer

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Introduction

Posterior reversible encephalopathy syndrome (PRES) is an urgent neurologic condition that is associated with white and gray matter vasogenic edema primarily in parietal and occipital lobes [1]. Clinical features usually involve headache, altered mental status, seizures, and visual disturbances [1]. Although PRES is generally a rare reversible condition, it is increasingly reported in the literature, especially in the setting of cancer patients treated with chemotherapy and antiangiogenic drugs targeting the vascular endothelial growth factor (VEGF) pathway.

The combination of aflibercept with 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) has been approved for the treatment of patients with metastatic colorectal cancer (mCRC) after the failure of oxaliplatin-based chemotherapy to control the disease [2]. To the best of our knowledge, no cases of PRES related to aflibercept-FOLFIRI can be found in the published literature.

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Case

We present the case of a 64-year-old male patient with past medical history of arterial hypertension well managed with triple antihypertensive medication, who underwent left hemicolectomy at the age of 63 for a T3N1M0 (stage III) adenocarcinoma (mutated KRAS gene) of the sigmoid colon and subsequently started adjuvant chemotherapy with oxaliplatin and capecitabine (CAPEOX). As serum carcinoembryonic antigen was rising while on chemotherapy, imaging, including a positron emission tomography–computed tomography (PET-CT), was performed after the seventh cycle of CAPEOX and revealed relapse of his disease with bilateral perirectal and left posterior gluteal lesions. The relapse was considered resectable; therefore, the patient underwent a second operation for removal of these lesions 11 months after the left hemicolectomy. A postoperative computed tomography (CT) of the chest showed new bilateral pulmonary metastases. At that time, the patient's performance status was zero on the scale of the Eastern Cooperative Oncology Group.

As cancer had relapsed during oxaliplatin-based chemotherapy and the KRAS gene was mutated, the patient was started on aflibercept-FOLFIRI (aflibercept at the standard dose of 4 mg/kg and FOLFIRI with 20% dose reduction due to the poor tolerance of the prior chemotherapy regimen) every 2 weeks [2]. The first cycle of treatment was tolerated well without any side effects.

Two weeks after the second cycle of treatment, the patient was admitted to the hospital for worsening headache, confusion, deranged level of consciousness, and visual hallucinations. Physical examination revealed grade 4 arterial hypertension (200 mmHg systolic blood pressure and 120 mmHg diastolic). A CT scan of the brain could not shed any light, so a brain magnetic resonance imaging (MRI) was performed and revealed extended hyperintense signals in fluid attenuation

inversion recovery (FLAIR) sequences, representing white matter edema principally in the parietal and occipital lobes bilaterally, while the temporal lobes, the cerebellum, the pons, and the midbrain were also affected (Fig. 1). A magnetic resonance venography of the brain could not demonstrate any cerebral venous thrombosis.

Findings indicated PRES that was likely induced by aflibercept-FOLFIRI regimen in a hypertensive patient. Antihypertensive treatment and anticonvulsant prophylaxis with levetiracetam were offered. Symptoms subsided 6 days later, while resolution of the vasogenic edema was shown in a repeat brain MRI performed 3 weeks after the first one (Fig. 2).

Five weeks after the onset of PRES, the patient was feeling well, so restarting chemotherapy without aflibercept this time was decided. He underwent 7 cycles of FOLFIRI rechallenge without any signs indicating recurrence of PRES. Afterwards, chemotherapy was terminated because of disease progression in the lungs, new bone metastases, and pelvic recurrence.

Discussion

The origin of PRES can be found back in 1996, when Judy Hinchey and her colleagues described a reversible syndrome of posterior-dominant leukoencephalopathy occurring in 15 patients with bilateral principally posterior white matter vasogenic edema in brain imaging and symptoms such as headache, abnormal mental status, seizures, and vision disorders [3]. However, it is currently perceived that the syndrome may be neither always reversible nor exclusively posterior, as all cerebral lobes as well as both the cerebellum and the brain stem may be involved too

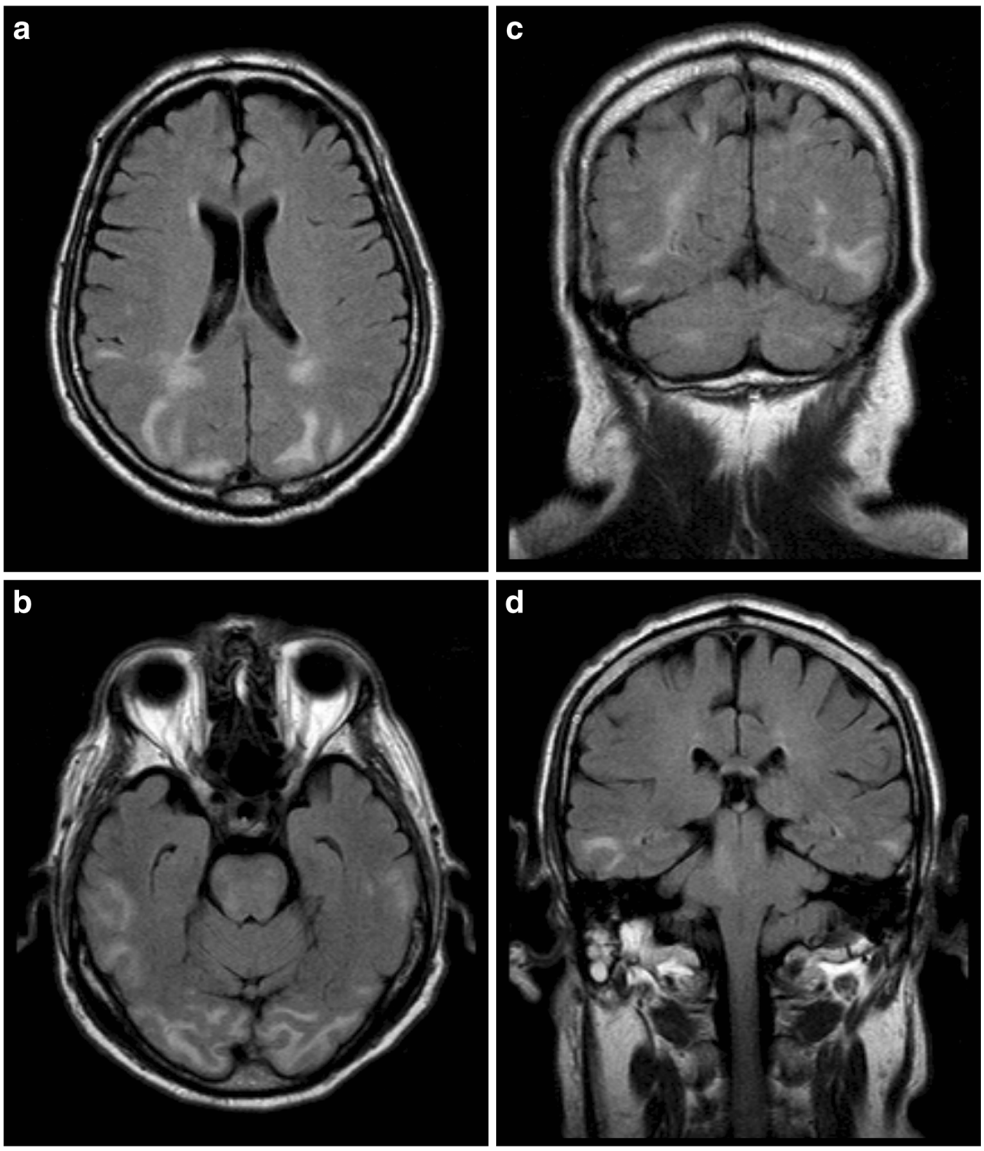

Fig. 1 Axial (**a**, **b**) and coronal (**c**, **d**) FLAIR slices of the brain MRI showing hyperintense signals in the white matter of parietal, occipital, and temporal lobes bilaterally, in both cerebellar hemispheres, in the pons, and in the midbrain

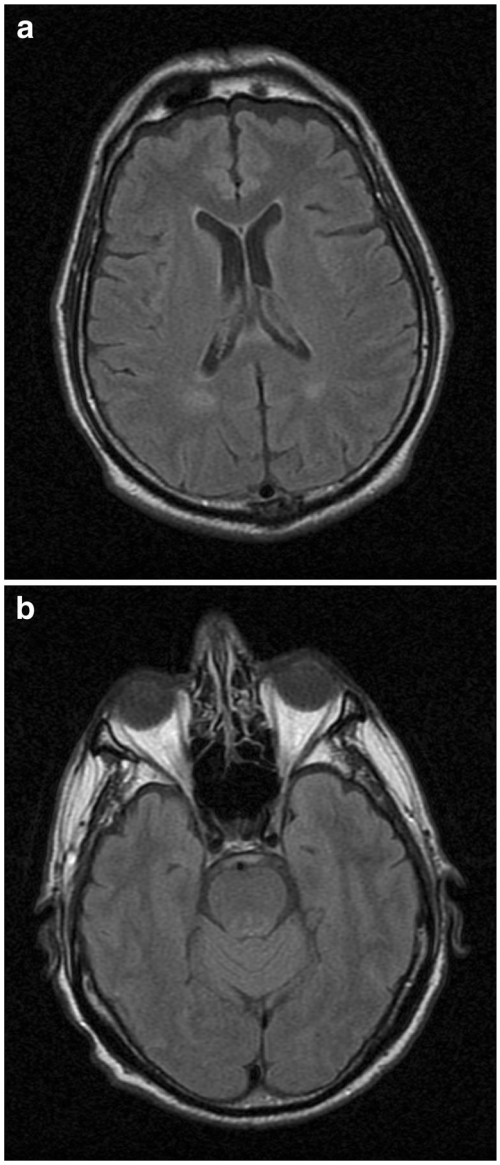

Fig. 2 Axial FLAIR slices of the repeat brain MRI showing resolution of prior findings

[1, 4, 5]. Arterial hypertension, preeclampsia/eclampsia, immunosuppressive and cytotoxic drugs, autoimmunities, renal failure, sepsis, and proteinuria induced by anti-VEGF agents have been associated with PRES [1, 6–8]. Although no guidelines exist so far, T2-weighted FLAIR sequences of the brain MRI are considered sensitive enough for the diagnosis of PRES, while treatment is non-specific aiming to manage underlying disorders and relieve symptoms [4, 9].

Two opposite theories have predominantly attempted to describe the pathogenesis of PRES [6, 7, 9]. First, vasogenic edema is caused by hyperperfusion due to the breakdown of the blood-brain barrier and the cerebral blood flow autoregulatory system. Alternatively, cerebral vasoconstriction results in hypoperfusion and subsequently in ischemia and edema. Other theories implicate impaired vascular endothelial permeability caused by either direct cytotoxic effects or immune-mediated mechanisms [6, 7, 9]. PRES in cancer patients treated with chemotherapeutic and antiangiogenic drugs has been increasingly reported lately [7, 8, 10–14]. In addition to arterial hypertension, disturbances in the vascular endothelium may play a role in the pathophysiologic process in these cases [8, 10].

To date, two retrospective studies have attempted to investigate the occurrence of PRES in cancer patients [5, 15]. The first one was carried out by Singer et al. in the Memorial Sloan Kettering Cancer Center (MSKCC) and included 31 cancer patients with PRES [15]. Among them, 55% had been treated with chemotherapy or targeted agents during the month prior to the development of the syndrome [15]. The second study was carried out by Kamiya-Matsuoka et al. in the MD Anderson Cancer Center [5]. Of the 69 cases of PRES involved, 70% had received chemotherapy during the 2 months preceding the appearance of PRES [5]. Both studies revealed that women seem to be more vulnerable, while hypertension was found in at least 75% of the cases [5, 15]. According to the second study, in addition to classic PRES lesions, atypical regions, such as the brain stem, the basal ganglia, the thalamus, and the corpus callosum, were likely to be affected, especially in thrombocytopenic patients, resulting in higher rates of intracranial hemorrhage and poorer prognosis [5]. After having reviewed the literature, the authors of that study concluded that oncology patients may be more prone to PRES-related death or remaining neurologic deficits than non-oncology patients [5]. Docetaxel was the most common chemotherapy drug involved in cases of PRES in MSKCC, whereas doxorubicin and vincristine were mostly administered in the second study [5, 15]. As regards targeted therapy, bevacizumab was most frequently used in patients all together. Interestingly, patients with malignant glioma were not shown to be susceptible to bevacizumab-related PRES [15]. Finally, authors of both studies noticed that postrecovery reintroduction of chemotherapy in cancer patients with PRES might sometimes be safe [5, 15]; however, whenever bevacizumab was suspected as the offending agent, rechallenge was not attempted [15].

Our patient was treated with aflibercept-FOLFIRI and developed PRES after the second cycle of the regimen. Aflibercept is an anti-VEGF agent made up of extracellular segments of VEGF receptors 1 and 2 fused to the fragment crystallizable (Fc) region of human immunoglobulin IgG1 [16, 17]. It targets VEGF-A, VEGF-B, and placental growth factor (PIGF); hence, it prevents their binding to their own receptors leading to inhibition of angiogenesis [16, 17]. Aflibercept has only been implicated in PRES when administered either as monotherapy or in combination with cisplatin and pemetrexed in lung cancer patients in clinical trials [18, 19]. Actually, the development of PRES in 3 out of 42 patients (7%) treated with aflibercept, cisplatin, and pemetrexed within a phase II clinical trial and the suspicion of the syndrome in another 2 patients resulted in the early termination of this study [18]. PRES was diagnosed after the first, second, or fifth cycle of treatment [18]. All three patients with

confirmed PRES were women and experienced arterial hypertension, while two of them developed renal failure [18]. As regards the chemotherapy drugs involved in our case, in the study of Singer et al., irinotecan was administered in 2 out of 17 patients (12%) with PRES treated with chemotherapy or targeted agents, while, less frequently, 5-fluorouracil has been part of regimens reported to trigger PRES, such as combinations with oxaliplatin or irinotecan [12–15].

The pivotal phase III VELOUR clinical trial revealed that the combination of aflibercept with FOLFIRI was superior to placebo plus FOLFIRI in patients with mCRC who experienced disease relapse or progression while on or after oxaliplatin-based treatment increasing median survival from 12.06 to 13.50 months [2]. According to the study, out of 612 patients who received aflibercept-FOLFIRI, no one was diagnosed with PRES [2]. To our knowledge, our report describes the first published case of PRES occurring in a patient with mCRC during treatment with this regimen. Interestingly, rechallenge of our patient with FOLFIRI alone without aflibercept was shown to be safe after recovery, as it did not cause recurrence of PRES.

Conclusion

PRES represents an oncologic-neurologic emergency in cancer patients treated with VEGF inhibitors and/or chemotherapy. Based on our case report, the syndrome should be part of differential diagnosis whenever cancer patients receiving such agents develop neurologic symptoms. Early identification of PRES in these cases can lead to successful evaluation of this urgent condition.

Compliance with Ethical Standards

Informed Consent Informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

Conflict of Interest The authors declare that they have no competing interests.

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