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LETTER TO THE EDITOR

Posterior Reversible Encephalopathy Syndrome Secondary to Regorafenib in Metastatic Colon Cancer

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Dear Editor,

Posterior revesible encephalopathy syndrome (PRES) is a very rare disorder and has been increasingly recognized. The pathogenesis is not fully known. Arterial hypertansion, renal dysfunction, collagen vasculer disorders, eclampsia and the usage of immunsuppressive agents and chemotherapy can be trigger PRES. Typical clinical findings are acute hypertension, headache, altered mental status, seizures and impaired vision. Typical magnetic resonance imaging findings such as symmetric posterior cerebral white matter edema, particularly parieto-occipital lobes.[1,2] Atypical PRES involvement has been reported to affect the frontal lobe, basal ganglia, brainstem and deep white matter.[3] In recent years, case series reporting the development of PRES following the use of anti-cancer drugs such as bevacizumab, sunitinib, sorafenib, pazopanib and regorafenib with antiangiogenic activity have increased. In patients receiving these therapies, PRES symptoms may resolve spontaneously or with discontinuation of treatment.[2] This case is important to draw attention to anticancer therapy associated PRES, which is a rare side effect and emphasize that it can be reversible.

A 66-year-old woman with operated metastatic colon carcinoma was admitted to the Emergency Room three tonic-clonic seizures in a day and elevated blood pressure of 200/90 mmHg. She had history of hypertension and was using regular medication. 1 months earlier, she received the fourth cycle of adjuvant chemotherapy of mFOLFOX4 (oxaliplatin 85 mg/m^2, levofolinic acid 200 mg/m^2, fluorouracil 400 mg/ m^2 bolus with 2400 mg/m^2/46 h infusor). She was being treated for a rectal adenocarcinoma for which she already received neo-adjuvant radiotherapy (25 fractions of 1.8 Gy) and 20 days ago Regorafenib (80 mg/d) had started. Laboratory data revealed normal. In post-seizure Brain T2 and Fluid-Attenuated-Inversion-Recovery (FLAIR) Magnetic Resonance Imaging (MRI), widespread density changes were observed in the cortical subcortical white matter in the frontal, parietal occipital and temporal regions on the right and left, in the bilateral thalamus, and more prominently in the pons and mesencephalon on the left (Fig. 1). No brain metastases or meningeal involvement were observed. The woman had confusion after the seizure, but other neurological examinations were normal. A diagnosis of regorafenib-related PRES was considered and this medication was discontinued. Anti-hypertansive (Hydralazine), anti-seizure (iv Levetirasetam) and anti-edema treatments (mannitol and dexomethasone) were started. After 1 day, the patient regained full consciousness and did not have another seizure.

Regorafenib is a novel oral vascular endothelial growth factor receptor (VEGFR) multikinase inhibitor recently approved for the treatment of patients with refractory metastatic colorectal cancer.[1] To date, 2 patients who developed PRES associated with regorafenib in 2014 and 2020 have been reported in the literature.[1,4] The time from starting a VEGF multi-kinase inhibitor to the onset of PRES symptoms ranges from 4 days (20 days, in our patient) to 9 months.[1] Permanent neurologic damage can be

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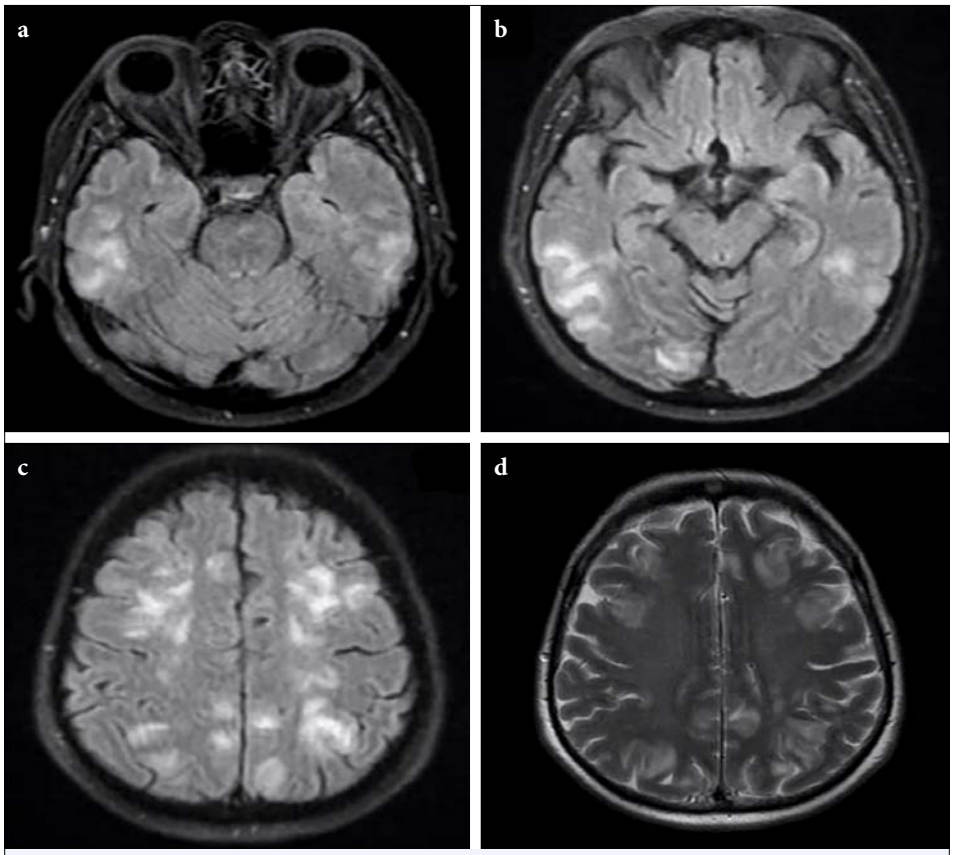

Fig. 1. (a-c) Axial Fluid-Attenuated-Inversion-Recovery (FLAIR) magnetic resonance imaging (MRI), widespread changes were observed in the cortical subcortical white matter in the frontal, parietal occipital and temporal regions on the right and left, in the bilateral thalamus, and more promimently in the pons and mesencephalon on the left. (d) Axial T2 MRI image shows cortical subcortical hyperintensity in similar areas.

prevented by rapid diagnosis, discontinuation of the drug and initiation of treatment. Complete or near complete recovery usually occurs within 2 weeks in 70% of patients with PRES and radiologic findings improve within 20 days in 88%.[1,5]

The increase in blood pressure with the use of VEGFR inhibitors is very small compared to hypertensive-associated PRES; This suggests that VEGFR inhibitor-associated PRES is not only due to increased blood pressure but may also have more to do with endothelial dysfunction and disruption of tumor vasculature.[2] PRES is extremely rare. Brain MRI should be performed after symptomatic treatment to differentiate it from stroke and metastasis.The primary treatment for patients with anti-VEGFR-related PRES is drug withdrawal. Subsequently, to reduce brain edema some medications such as mannitol, dexamethasone and antihypertensive drugs should be given immediately. In addition, blood pressure should be closely monitored and effective blood pressure control should be ensured. After discontinuation of anti-angiogenic drugs, the blood pressure of most patients will return to normal in a short time. In the majority of cases, the prognosis is good. Close monitoring of blood pressure in patients receiving VEGFR inhibitors will reduce the risk of developing drug-related PRES.[5]

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