

[ CASE REPORT ]

## Posterior Reversible Encephalopathy Syndrome after a Variety of Combined Chemotherapies Containing Bevacizumab for Metastatic Colon Cancer

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### Abstract:

A 44-year-old woman with advanced metastatic colon cancer received chemotherapies comprising oxaliplatin and capecitabine (XELOX), irinotecan hydrochloride, leucovorin calcium and fluorouracil irinotecan (FOLFIRI)/panitumumab and mFOLFOX6/bevacizumab. Fifteen months later, she presented with the acute onset of a headache, drowsiness and seizure with a fever and hypertension. Brain magnetic resonance imaging (MRI) indicated bilateral regions of signal hyperintensity in the white matter with spasms of bilateral cerebral arteries apparent on magnetic resonance angiography. Posterior reversible encephalopathy syndrome (PRES) was diagnosed, and treatments resulted in improvement of the MRI findings, but the patient experienced cerebral infarction and ultimately died of deterioration of cancer on day 26 after the onset of PRES.

**Key words:** posterior reversible encephalopathy syndrome, colon cancer, bevacizumab, XELOX, FOLFIRI, mFOLFOX 6

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### Introduction

Posterior reversible encephalopathy syndrome (PRES) is a neuro-radiological syndrome characterized by cortical blindness, an altered level of consciousness and seizures. PRES is associated with hyper-intense lesions on magnetic resonance imaging (MRI), typically in the posterior region (1). In most cases, the symptoms and radiological lesions of PRES are reversible. However, the term PRES is not precisely suitable, as the syndrome is not always reversible (2) and is often not confined to either the white matter or posterior regions of the brain (3).

The mechanisms underlying PRES have been postulated to be severe hypertension leading to failed auto-regulation and endothelial injury/vasogenic edema, or vasoconstriction leading to brain ischemic and subsequent vasogenic edema (4). The risk factors for this syndrome include malignant hypertension, eclampsia, renal failure and treatment with anti-neoplastic agents.

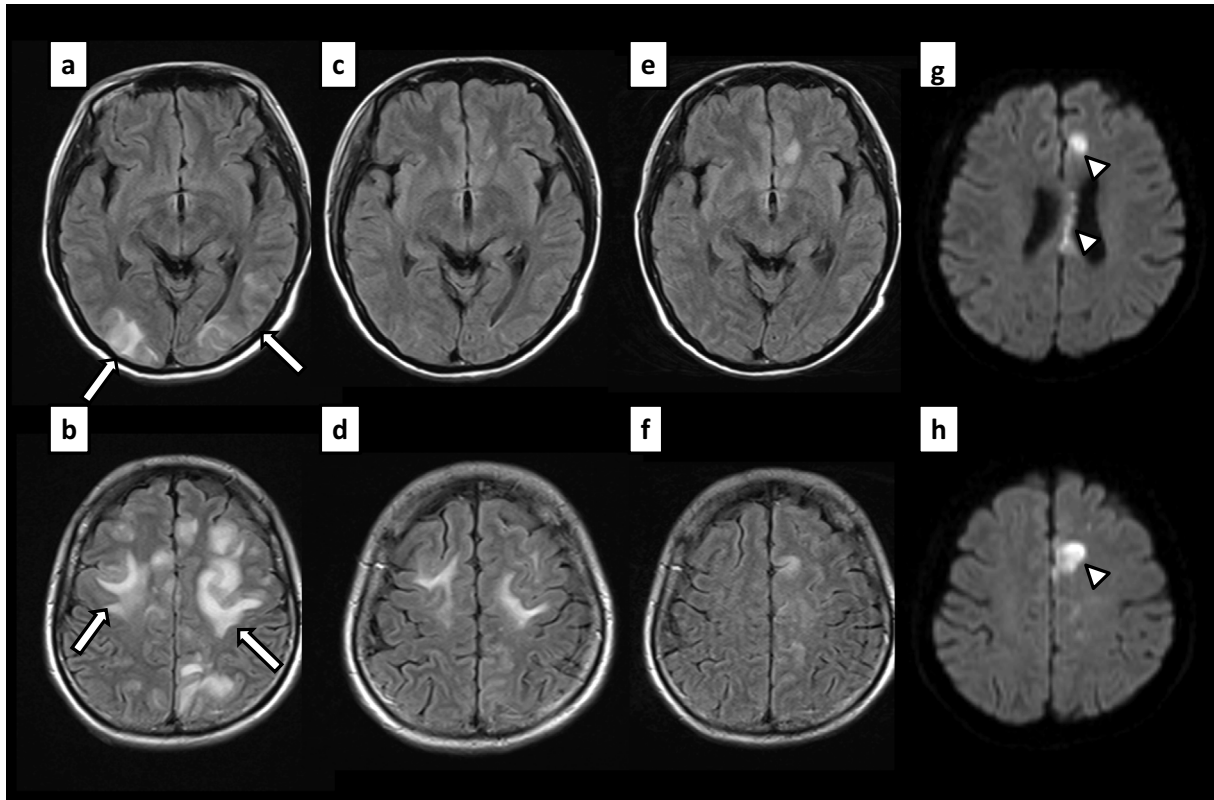
Certain combination regimens have been associated with PRES, including a XELOX regimen comprising oxaliplatin, capecitabine and folinic acid; a panitumumab plus FOLFIRI regimen comprising irinotecan hydrochloride, leucovorin calcium and fluorouracil; and a bevacizumab plus mFOLFOX6 regimen comprising oxaliplatin, 5-fluorouracil and L-leucovorin (2, 5-14).

We herein report the case of a patient with advanced metastatic colon cancer who received chemotherapies of a XELOX regimen, a FOLFIRI regimen plus panitumumab and a mFOLFOX 6 regimen plus bevacizumab. The diagnosis of PRES was supported by the findings on MRI and MR angiography (MRA), and the patient died of deterioration of cancer. A link between PRES and bevacizumab, which was ultimately administered with mFOLFOX6 after the XELOX and panitumumab/FOLFIRI regimens, was therefore suggested.

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**Figure 1.** Axial-section fluid-attenuation inversion recovery (FLAIR) magnetic resonance imaging (MRI) (1.5 T; TR, 9,000 ms; TE, 105ms) performed on the day of the onset of PRES (a, b), on day 11 after the onset (c, d) and on day 19 after the onset, when the patient developed moderate right hemiparesis (e, f), and diffusion-weighted imaging (DWI) (1.5 T; TR, 3,000 ms; TE, 88 ms) performed on the day that moderate right hemiparesis developed (g, h). FLAIR images indicate bilateral increases in the signal intensity in the occipital, parietal and periventricular white matter (arrows) (a, b), partial improvement of the brain MRI findings 11 days later (c, d), new lesions in the left fronto-parietal area (e, f) and new hyperintense lesions in the left fronto-parietal area on DWI (arrowheads) (g, h).

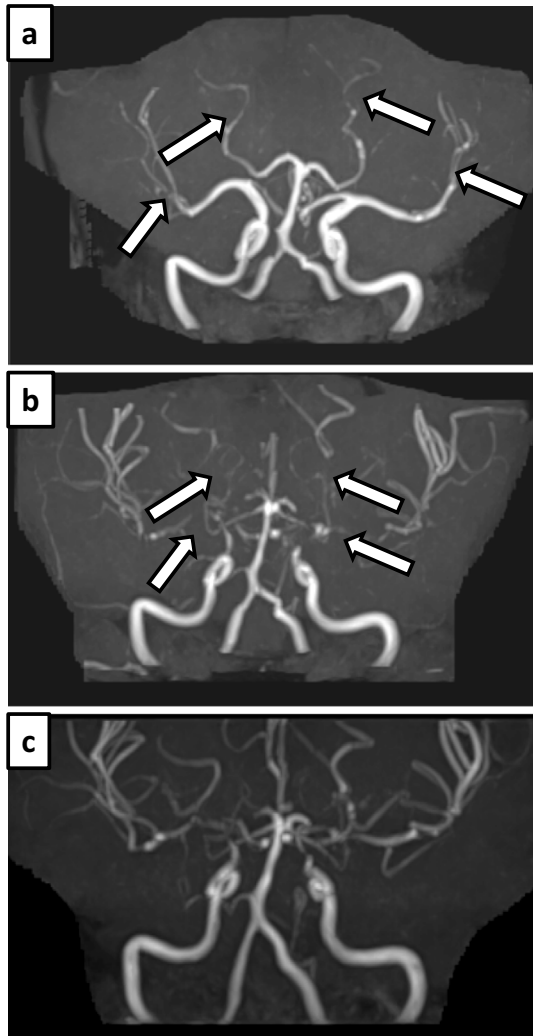
## Case Report

A 44-year-old woman underwent rectosigmoid colectomy and left mesorectal resection for rectosigmoid carcinoma in April 2015 with stage IIIb NSCLS (tumor-node-metastasis staging score, T3N2M0). A histopathological examination revealed poorly differentiated adenocarcinoma that had infiltrated the subserosa and regional metastases to the left supraclavicular lymph nodes. The patient was started on a XELOX regimen comprising oxaliplatin, capecitabine and folinic acid in May 2015. Thereafter, additional metastases to the para-aortic lymph node at the level of the left renal artery were detected on abdominal computed tomography. After radiation therapy to the lesion, a 7-cycle course of panitumumab plus FOLFIRI regimen consisting of irinotecan hydrochloride, leucovorin calcium and fluorouracil was administered from January 2016, followed by an 8-cycle course of bevacizumab plus the mFOLFOX6 regimen, comprising oxaliplatin, 5-fluorouracil and L-leucovorin, from June 2016.

Treatment was uneventful until September 2016, when she presented with the acute onset of a headache, drowsi-

ness and seizure. Vital signs indicated a fever and hypertension (188/112 mmHg) with no history of hypertension. A neurological examination indicated a limited attention span, disorientation, generalized hyperreflexia, bilateral Babinski sign and no focal neurological signs in the limbs. A laboratory investigation revealed an elevated white blood cell count (15,540/ $\mu$ L; normal range, 3,800-8,500/ $\mu$ L), mildly elevated C-reactive protein (1.5 mg/dL; normal range, 0.0-0.3 mg/dL), a normal ammonia level, a normal renal function, mild hyponatremia (128 mmol/L; normal range, 138-146 mmol/L) and a mildly elevated glucose level (122 mg/dL; normal range, 70-109 mg/dL). Brain MRI was performed on the day of the onset of neurological symptoms. Fluid-attenuated inversion recovery (FLAIR) imaging revealed bilateral regions of signal hyperintensity in the occipital, parietal and periventricular white matter (Fig. 1a and b), but T1-weighted imaging indicated regions of signal isointensity in the same areas. MRA indicated spasms of the bilateral anterior, middle and posterior cerebral arteries (Fig. 2a). The patient was ultimately diagnosed with PRES associated with reversible cerebral vasoconstriction syndrome (RCVS).

Her blood pressure was controlled within a normal range



**Figure 2.** Magnetic resonance angiography (MRA) performed on the day of the onset of PRES (a), on day 11 after the onset (b) and on day 19 after the onset, when the patient developed moderate right hemiparesis (c). MRA reveals spasms of the bilateral anterior, middle and posterior cerebral arteries (arrows) (a); progression of the spasms of the bilateral anterior, middle and posterior cerebral arteries (b); and a tendency toward improvement of the spasms of the bilateral anterior, middle and posterior cerebral arteries (c).

through the administration of nimodipine given intravenously to control her hypertension and the spasms of cerebral arteries, followed by the administration of anticonvulsants, anti-platelet drugs and anti-coagulants. To reduce the cerebral edema, edaravone, glycerol and steroid were administered. She recovered gradually from the symptoms and regained full consciousness, with a partial improvement of her findings on brain MRI 11 days later (Fig. 1c and d). In addition, she showed progression of spasms in the bilateral anterior, middle and posterior cerebral arteries (Fig. 2b). Treatment with the above drugs continued, but she developed cerebral infarction presenting as moderate right hemiparesis. Brain MRI revealed new lesions in the left fronto-parietal area (Fig. 1e-h), and a tendency toward the improvement of spasms in the bilateral anterior, middle and posterior cere-

bral arteries (Fig. 2c). The patient ultimately died of deterioration of cancer on day 26 after the onset of PRES.

## Discussion

PRES is a rare neurological syndrome with presenting symptoms ranging from headache, altered mental status, seizures and visual loss to loss of consciousness. The term describes a potentially reversible imaging appearance and symptomatology with a variety of causes (1). The term PRES is not necessarily accurate, as brain edema is often not isolated to the posterior region (3), and the syndrome is not uniformly reversible. As discussed previously, cerebral hemorrhaging and infarction are the most common reasons for incomplete recovery, and PRES can prove fatal in severe cases (2).

PRES is primarily associated with hypertension, eclampsia, renal impairment, cytotoxic drugs, immunosuppressants and molecular-targeted agents. Chemotherapy-induced complications show a wide spectrum of clinical manifestations, including PRES. Certain combination regimens have also been associated with PRES, including the combination of capecitabine and oxaliplatin (XELOX), the combination of irinotecan hydrochloride, leucovorin calcium and fluorouracil (FOLFIRI)/panitumumab, and oxaliplatin, 5-fluorouracil and L-leucovorin (mFOLFOX6)/ bevacizumab (2, 5-14). The development of PRES associated with RCVS in our patient may therefore have been secondary to bevacizumab, given her clinical course.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), was recently approved as a first-line treatment for patients with metastatic colorectal cancer when administered in combination with FOLFIRI (13). Bevacizumab may have contributed to a hypertensive state in an otherwise non-hypertensive patient, as hypertension is a known adverse effect of this medication. Global endothelial cell dysfunction induced by bevacizumab may then have led to PRES.

The mechanisms underlying PRES are not entirely understood. The syndrome has been postulated to represent either severe hypertension leading to failed auto-regulation and endothelial injury/vasogenic edema, or vasoconstriction leading to brain ischemia and subsequent vasogenic edema. Sudden elevations in the systemic blood pressure disrupt the blood-brain barrier, causing a local exchange of fluids. The cerebral white matter is composed of myelinated fiber tracts in an extracellular matrix of glial cells, arterioles and capillaries and is susceptible to vasogenic edema (15). The hypothesis that pronounced hypertension can lead to the breakdown of the blood-brain barrier, hyperperfusion and increased interstitial edema in PRES was initially proposed (16). However, many recent radiological perfusion studies have suggested an opposing hypothesis, in which hypoperfusion is central to the pathophysiological changes and brain imaging findings associated with PRES, and vaso-spasm may precipitate vasogenic edema, leading to cyto-



toxic edema if left untreated (1, 17).

PRES and RCVS share many clinicoradiographic features, suggesting overlapping or similar pathophysiological mechanisms. PRES and RCVS are frequently associated, and reversible brain edema occurs in 8-38% of all cases of RCVS (18, 19). Multifocal cerebral vasoconstriction has been noted in more than 85% of patients with PRES, and this vasoconstriction was shown to be reversible on follow-up MRA (20). PRES is associated with endothelial cell dysfunction and was initially thought to be caused by severe hypertension, leading to altered cerebral autoregulation with hyperperfusion and vasogenic edema (21). However, a quarter of patients with PRES are normotensive, and these patients have more extensive edema than do hypertensive patients, suggesting that hypertension may be a protective reaction (21). Recently, endothelial dysfunction of any cause has been shown able to affect the regulation of the cerebral arterial tone and trigger vasoconstriction with subsequent hypoperfusion, breakdown of the blood-brain barrier, and vasogenic edema (22).

In the present case, follow-up MRI of the brain revealed radiographic resolution of parieto-occipital lobe edema, which correlated with clinical improvement. However, brain MRA performed at the same time indicated that spasms of the bilateral cerebral arteries had progressed compared to the situation prior to treatment. Furthermore, instead of continuing treatment for PRES, when the patient developed cerebral infarction presenting as moderate right hemiparesis, brain MRI revealed new lesions in the left fronto-parietal area, but MRA indicated an improvement in the spasms of bilateral cerebral arteries. Cerebral infarctions induced by PRES occur mainly in the arterial watershed regions of the cerebral hemispheres, often between the posterior circulation and carotid territories (18, 23). Edema resulting from PRES is often seen on MRI with symmetrical FLAIR hyperintensities, usually showing total reversal within one month after the clinical onset, which is much earlier than the reversal of vasoconstriction (17). The maximum vasoconstriction of the branches of the middle cerebral arteries is reportedly reached a mean of 16 days after the clinical onset (23). The MRA findings in the present case might support this report.

We suspect that PRES in our patient resulted from systemic endothelial cell dysfunction induced by bevacizumab. Clinical suspicion toward patients presenting with symptoms characteristic of PRES while receiving bevacizumab is encouraged, particularly when administered in combination with the FOLFIRI or mFOLFOX6 regimens. In conclusion, we should consider PRES when cancer patients are treated with new molecular-targeted agents, as PRES is an oncological emergency.

**The authors state that they have no Conflict of Interest (COI).**

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