

Reversible Posterior Leukoencephalopathy Syndrome After Bevacizumab/FOLFIRI Regimen for Metastatic Colon Cancer

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Objective: To describe a patient with reversible posterior leukoencephalopathy syndrome following the administration of bevacizumab (Avastin), a monoclonal antibody against vascular endothelial growth factor.

Design: Case report/literature review.

Setting: University hospital.

Patient: A 52-year-old man receiving chemotherapy for stage IV rectal carcinoma.

Results: Clinical and radiographic evidence consistent

with reversible posterior leukoencephalopathy syndrome was found following the administration of irinotecan hydrochloride, leucovorin calcium, and fluorouracil (FOLFIRI) regimen chemotherapy and bevacizumab.

Conclusions: Reversible posterior leukoencephalopathy syndrome following treatment with angiogenesis modulators can occur. In addition to raising clinical suspicion in appropriate patients, this report may yield clues to the pathophysiologic underpinnings of reversible posterior leukoencephalopathy syndrome.

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REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME (RPLS) is a clinicoradiologic syndrome characterized by headache, confusion, visual disturbance, and seizures accompanied by subcortical edema, predominantly involving the parietal and occipital lobes.¹ Imaging abnormalities often demonstrate marked improvement after the initiation of appropriate therapy. Causes of RPLS include hypertensive encephalopathy, renal failure, eclampsia, and immunosuppressive and cytotoxic medications. Potential pathogenic mechanisms of RPLS have been proposed, but a unifying mechanism connecting the causes remains elusive.

We describe a patient with RPLS who presented 2 weeks after the infusion of irinotecan hydrochloride, leucovorin calcium, and fluorouracil (FOLFIRI)/bevacizumab (Avastin) regimen chemotherapy, suggesting a link between RPLS and bevacizumab, a compound that specifically blocks the actions of vascular endothelial growth factor (VEGF).

REPORT OF A CASE

A 52-year-old man with stage IV rectal carcinoma with neuroendocrine differentia-

tion on liver biopsy recently completed an 8-cycle course of cisplatin, 60 mg/m², and etoposide phosphate, 120 mg/m², over a 6-month period. Five weeks after cisplatin and etoposide therapy, cycle 1 of the FOLFIRI regimen and bevacizumab was initiated. Dosing consisted of irinotecan, 180 mg/m²; leucovorin, 400 mg/m²; fluorouracil, 400 mg/m² (intravenous push); fluorouracil, 2400 mg/m² (infused); and bevacizumab, 5 mg/kg. On day 11 after the FOLFIRI/bevacizumab infusion, the patient was hospitalized for neutropenic fever, thrombocytopenia, anemia, and diarrhea. On day 15, the patient awoke with a headache and bilateral cortical blindness. Magnetic resonance imaging revealed patchy areas of increased fluid-attenuated inversion recovery signal intensity in the occipital and posterior parietal lobes, consistent with RPLS (**Figure 1**). The patient's blood pressure during hospitalization was mildly elevated (systolic blood pressure range, 140-150 mm Hg), which was aggressively treated subsequent to the vision loss. A qualitative urine assessment revealed proteinuria, which was not present before the initiation of FOLFIRI/bevacizumab chemotherapy. Other laboratory values included hematocrit, 28.3% (pre-FOLFIRI/bevacizumab therapy level, 28.6%), which

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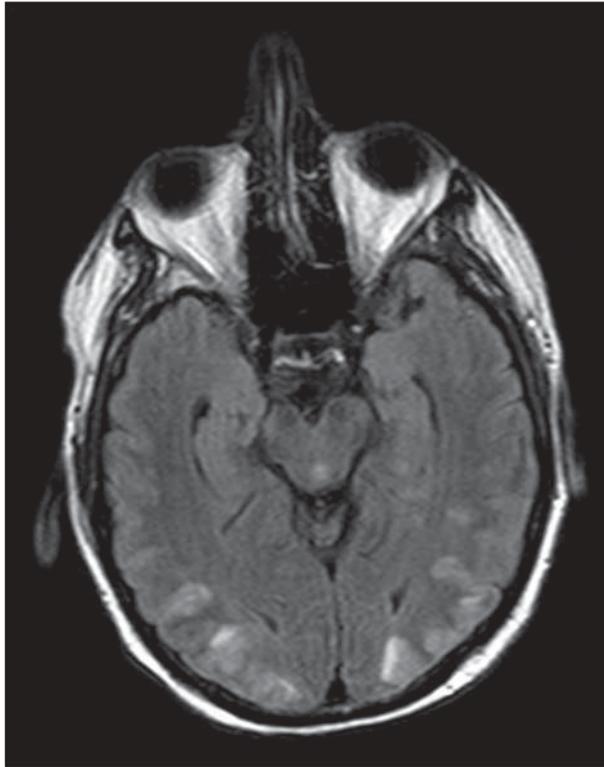


Figure 1. Fluid-attenuated inversion recovery magnetic resonance image taken the day of neurologic symptom development shows a bilateral occipital and posterior parietal abnormality.

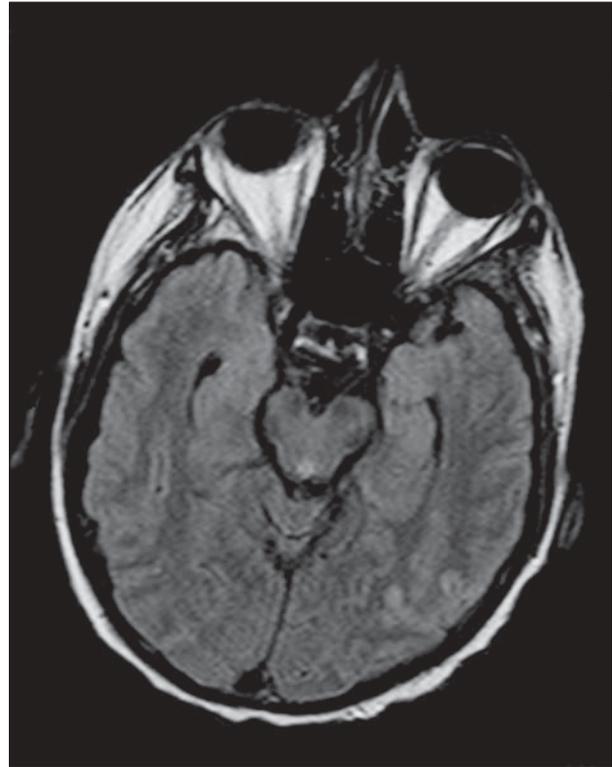


Figure 2. Fluid-attenuated inversion recovery magnetic resonance image taken 1 week after neurologic symptom development. There was interval improvement of occipital and parietal hyperintensities.

was normal; serum urea nitrogen and creatinine levels were also measured, liver function testing was performed, and a peripheral blood smear was obtained. On day 17, the patient developed transcortical global aphasia with intermittent spells of confusion and agitation. By day 18, his speech and visual disturbance began to improve. On day 19, he experienced a generalized tonic-clonic seizure. A diagnostic lumbar puncture showed a normal opening pressure and normal cerebrospinal microscopic and biochemistry results. Subsequent magnetic resonance imaging on day 19 showed interval improvement in fluid-attenuated inversion recovery hyperintensities (**Figure 2**). By day 25, the patient's neurologic deficits had completely resolved.

Over the next 6 weeks, the patient developed new bony lesions involving the thoracic and lumbar vertebrae, with cord compression. Treatment was initiated with corticosteroids and palliative radiation. No further chemotherapy cycles were given, and no further neurologic spells occurred.

COMMENT

The onset and resolution of cortical blindness and seizure activity observed in our patient correlated with the radiographic abnormalities and were consistent with the natural history of RPLS. The focal nature and immediate onset of our patient's visual disturbance might suggest that an ischemic event had occurred. However, imaging studies pointed to vasogenic edema as the chief cause, rather than infarction. Furthermore, the patient's

clinical improvement correlated with radiographic occipital lobe edema resolution. Although not entirely understood, the mechanism of RPLS is considered to be secondary to failed autoregulation of cerebral blood flow leading to cerebral vasogenic edema.¹⁻⁴ Failed cerebral vascular autoregulation results in hyperperfusion and dilation of cerebral arterioles, disruption of the endothelium, immediate breakdown of the blood-brain barrier, and, finally, transudation of plasma and red blood cells into the interstitium. A relative paucity of sympathetic adrenergic innervation to the vertebral-basilar system is suggested to account for the tendency for this syndrome to involve structures supplied by the posterior circulation.^{5,6} Hypointense T1 lesions and hyperintense T2 lesions are often seen bilaterally in occipital and parietal lobe white matter. Predisposing factors consistent with this proposed mechanism of vascular dysregulation have been described by Tam and colleagues,² who regard patients with significant fluid overload (>10% of the baseline weight), a mean blood pressure higher than 25% of baseline, and a creatinine level greater than 1.8 mg/dL (>160 μmol/L) to be high risk for RPLS.

Toxic damage to the vascular endothelium or blood-brain barrier caused by immunosuppressant and cytotoxic medications is further postulated to contribute to the pathophysiological features of RPLS.^{1,2,7} Direct causal relationships between chemotherapy agents and RPLS have been difficult to establish, and the correlation is more common with cyclosporine and tacrolimus. Other associated agents include methotrexate; the alpha

interferons; cisplatin; cytarabine; cyclophosphamide, doxorubicin hydrochloride (Adriamycin), vincristine sulfate (Oncovin), and prednisone; or combinations involving doxorubicin, ifosfamide, and etoposide. While we cannot be certain of the causal relationship between bevacizumab and the RPLS in our patient, it seems most likely by the following process of elimination: the chemotherapeutic regimen in our patient also consisted of FOLFIRI. The cerebral toxicity of fluorouracil, although rare, is well described as a multifocal inflammatory leukoencephalopathy.^{8,9} Multifocal inflammatory leukoencephalopathy typically develops 6 weeks to 5 months after the initiation of combination chemotherapy with levamisole hydrochloride and fluorouracil. Multifocal inflammatory leukoencephalopathy is a clinically and radiographically distinct syndrome from RPLS, making it unlikely that fluorouracil caused our patient's syndrome. To our knowledge, no reports in the literature associate irinotecan, a type I topoisomerase inhibitor, with the development of RPLS or other encephalopathy syndromes. Leucovorin, a derivative of folic acid, would not be expected to contribute to the development of RPLS. During the review of this report, several other investigators¹⁰ observed an association between RPLS and bevacizumab administration.

Bevacizumab, a monoclonal antibody against VEGF, has recently been approved as a first-line treatment for patients with metastatic colorectal cancer when administered in combination with FOLFIRI.¹¹ Vascular endothelial growth factor is a naturally occurring, endothelial, cell-specific glycoprotein that stimulates blood vessel formation and has been implicated in tumor growth and spread. Nitric oxide and prostacyclin production are enhanced by VEGF, thus promoting vasodilation.¹² The effects of VEGF inhibition on the systemic endothelium have been described.¹³ Soluble fms-like tyrosine kinase 1 is a naturally occurring VEGF antagonist expressed by the placenta and is thought to produce an antiangiogenic state by binding VEGF and placental growth factor. Vascular endothelial growth factor and placental growth factor bound to soluble fms-like tyrosine kinase 1 render them biologically inactive, thus inducing endothelial cell dysfunction.^{13,14} Animal studies by Sugimoto and colleagues¹⁵ demonstrated that administration of anti-VEGF antibodies and soluble fms-like tyrosine kinase 1 resulted in glomerular endothelial cell detachment and hypertrophy. The resulting glomerular endotheliosis has been suggested to be responsible for the hypertension and proteinuria commonly seen in preeclamptic patients.^{13,15} Furthermore, alterations in angiogenic factors have been postulated to disrupt normal systemic endothelial cell function and increase the cerebral vascular permeability of the blood-brain barrier, thus contributing to RPLS in preeclamptic patients.¹⁶ The precise role of the antiangiogenic and angiogenic factors, soluble fms-like tyrosine kinase 1, VEGF, and placental growth factor, remains under investigation.

Bevacizumab is a potent inhibitor of VEGF function, disrupting angiogenesis and depriving tumors of their blood supply.^{17,18} Angiogenesis inhibitors are thought to be beneficial in cancer treatment by normalizing patho-

logic tumor vasculature and restoring proangiogenic and antiangiogenic factors and, thereby, allowing for more efficient delivery of chemotherapeutic agents to tumors.^{19,20} Hypertension and proteinuria are commonly reported adverse effects of bevacizumab.²¹ We suggest that the development of RPLS in our patient may have been secondary to bevacizumab. Several mechanisms may be contributory. First, bevacizumab may have contributed to the patient's hypertensive state in an otherwise non-hypertensive patient, because hypertensive crises are known adverse effects of this medication. Although our patient had a mean blood pressure higher than 25% of baseline, he was not otherwise at high risk for the development of RPLS. He was not hypervolemic, and his serum creatinine level was normal. Second, a global endothelial cell dysfunction induced by bevacizumab may have led to RPLS. Although microangiopathic hemolytic anemia was not suggested by our patient's blood smear result, hypertension and proteinuria were present. We speculate that inhibition of VEGF induced systemic endothelial cell dysfunction and, in particular, that of the cerebral vasculature, which, when exposed to moderately elevated perfusion, was unable to appropriately accommodate. The induction of RPLS in our patient and possibly in preeclamptic patients may be secondary to this mechanism.

We postulate that the RPLS in our patient resulted from systemic endothelial cell dysfunction induced by bevacizumab. A more detailed understanding of the mechanism of VEGF modulators on the cerebral vasculature is needed. Regardless, high clinical suspicion is encouraged toward patients presenting with symptoms characteristic of RPLS while receiving bevacizumab, particularly when in combination with FOLFIRI therapy. Prompt recognition of this syndrome will allow initiation of immediate treatment and appropriate alterations in chemotherapy regimens.

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Announcement

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