

# Reversible Posterior Leukoencephalopathy Syndrome During Regorafenib Treatment: A Case Report and Literature Review of Reversible Posterior Leukoencephalopathy Syndrome Associated With Multikinase Inhibitors

Zaw W. Myint,<sup>1</sup> Jeremy M. Sen,<sup>2</sup> Nicole L. Watts,<sup>2</sup> Thomas J. Druzgal,<sup>3</sup> Barnett R. Nathan,<sup>4</sup> Melanie D. Ward,<sup>4</sup> James E. Boyer,<sup>1</sup> Paula M. Fracasso<sup>1</sup>

## Clinical Practice Points

- Reversible posterior leukoencephalopathy syndrome (RPLS) is a rare complication of angiogenesis inhibitors.
- Anti-vascular endothelial growth factor-directed therapies, including the novel vascular endothelial growth factor multikinase inhibitor regorafenib, are used in metastatic colorectal cancer.
- A 46-year-old man presented with seizures, agitation, altered mental status, and hypertension 4 days after starting regorafenib.
- Magnetic resonance imaging of the brain suggested RPLS.
- After discontinuation of regorafenib and the management of hypertension, no further seizure activity occurred and his mental status improved.
- Antineoplastic agents, including the new oral angiogenesis inhibitors, sunitinib, sorafenib, and pazopanib, have been linked to RPLS.
- The literature review indicates our case is the first published report of RPLS during regorafenib treatment.

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## Introduction

Reversible posterior leukoencephalopathy syndrome (RPLS), also known as posterior reversible encephalopathy syndrome, was first described in 1996.<sup>1</sup> It is characterized by a constellation of clinical features including headache, confusion, decreased level of consciousness, visual changes, and seizures and associated with characteristic neuroimaging findings of posterior cerebral white matter

edema and focal reversible vasogenic edema involving predominantly the parietal and occipital lobes.<sup>1,2</sup>

Angiogenesis inhibitors, including anti-vascular endothelial growth factor (VEGF) monoclonal antibodies,<sup>3</sup> VEGF multikinase inhibitors, mammalian target of rapamycin inhibitors (mTOR),<sup>4</sup> and thalidomide<sup>5</sup> have been associated with RPLS. Regorafenib is a novel oral VEGF multikinase inhibitor recently approved for the treatment of patients with refractory metastatic colorectal cancer. The US labeling states RPLS occurred in 1 out of 1200 patients in clinical trials.<sup>6</sup> To our knowledge, we report the first case of RPLS during regorafenib treatment in the published literature.

## Case

A 46-year-old Caucasian man with a history of hypertension was diagnosed with KRAS-mutated (Gly12Val), Stage IV (T3N1M1) adenocarcinoma with extensive disease in the peritoneal cavity and a dominant mass in the splenic flexure of the colon. He underwent hemicolectomy, small bowel resection, omentectomy, and resection

<sup>1</sup>Division of Hematology/Oncology, Department of Medicine and the UVA Cancer Center

<sup>2</sup>Department of Pharmacy Services

<sup>3</sup>Division of Neuroradiology, Department of Radiology and Medical Imaging

<sup>4</sup>Department of Neurology

University of Virginia Health System, Charlottesville, VA

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Address for correspondence: Zaw W. Myint, MD, University of Virginia Health System, Charlottesville, VA 22908  
Fax: 434-243-6086; e-mail contact: [zm3p@virginia.edu](mailto:zm3p@virginia.edu)

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of an umbilical lesion. He was initially treated with capecitabine, oxaliplatin, and bevacizumab. Restaging after 5 cycles demonstrated disease progression. Treatment was switched to capecitabine, irinotecan, and bevacizumab, but after approximately 9 months of this regimen, he was admitted to a local hospital with neutropenic fever, sepsis, hypotension, and acute renal failure. After recovery from his hospitalization, he was found to have progressive disease, and regorafenib, at a reduced dose (120 mg/d), was started. After 4 days of regorafenib treatment, the patient was admitted to a local hospital with several episodes of generalized tonic-clonic seizures (no prior history of seizures), agitation, and mental status changes. Physical exam revealed a blood pressure > 200/100 mm Hg, heart rate > 100 beats per minute, oxygen saturation 97% on 15 L face mask, and no other focal neurologic deficits. Laboratory data revealed normal electrolytes, renal, and liver function. Complete blood count was unremarkable except for leukocytosis of 19,000/ $\mu$ L white blood cell with a normal differential. Urinalysis revealed 100 mg/dL of protein with gross hematuria, which was likely secondary to traumatic Foley catheter insertion. Initial head computed tomography scan revealed low attenuation in the cerebellum and occipital poles. Regorafenib was discontinued, and he was given alprazolam, diazepam, hydromorphone, haloperidol, fosphenytoin, and piperacillin-tazobactam before transfer to our institution.

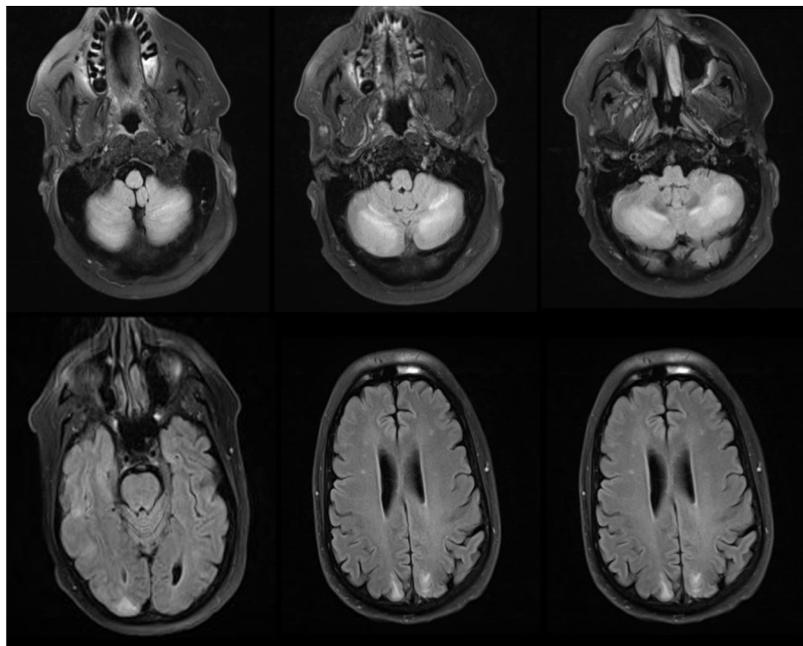
On admission to our hospital, the patient remained agitated and altered, with a blood pressure of 112/78 mm Hg. An electroencephalogram showed reactive diffuse slowing with frontal intermittent rhythmic delta activity, indicative of mild to moderate encephalopathy of nonspecific etiology. Lumbar puncture was unremarkable.

Magnetic resonance imaging (MRI) of the brain showed cortical and subcortical fluid attenuated inversion recovery signal abnormalities in the bilateral cerebellar hemispheres, posterior frontal, parietal, and occipital lobes suggestive of RPLS (Fig. 1). Hydralazine was used initially to improve blood pressure control, and his metoprolol tartrate dose was increased from 25 mg to 50 mg twice daily. Phenytoin was continued as seizure prophylaxis until reassessment with a follow-up MRI; however, the patient was given hospice care shortly after discharge, and the MRI was not performed. His neurologic exam throughout his hospitalization was notable for a nonfocal encephalopathy and when discharged, his neurologic status was near his baseline.

## Discussion

Reversible posterior leukoencephalopathy syndrome is a clinical radiographic syndrome of insidious onset of headache, confusion or decreased level of consciousness, visual changes, and seizures, which is associated with characteristic neuroimaging findings of posterior cerebral white matter edema.<sup>1</sup> RPLS is increasingly recognized and reported in the literature although the exact incidence is unknown. Patients in all age groups appear susceptible<sup>7</sup> and it is more common in women.<sup>1</sup> RPLS is reported to be associated with a wide variety of medical conditions such as hypertensive encephalopathy, acute or chronic renal diseases, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, eclampsia, vasculitis syndromes, porphyria, blood transfusion, exposure to contrast material, and various immunosuppressive, immunomodulatory, and chemotherapeutic agents.<sup>2</sup> RPLS has also been reported in patients treated with several

**Figure 1** Magnetic Resonance Imaging of the Brain Showing Cortical and Subcortical FLAIR Signal Abnormalities in the Bilateral Cerebellar Hemispheres, Posterior Frontal, Parietal, and Occipital Lobes Suggestive of RPLS



Abbreviations: FLAIR = fluid attenuated inversion recovery; RPLS = reversible posterior leukoencephalopathy syndrome.

agents active in the VEGF pathway.<sup>3-6</sup> Anti-VEGF agents might induce a number of vascular toxicities. Hypertension, the most common adverse effect,<sup>1,3</sup> can be well controlled using antihypertensive agents, and is rarely dose-limiting in routine practice.<sup>8</sup> Several different mechanisms such as failure of autoregulation of cerebral circulation,<sup>9</sup> cerebral ischemia,<sup>10</sup> or endothelial dysfunction<sup>11</sup> have been postulated. The primary involvement of the posterior brain regions is not well understood, and thought to be due to the regional heterogeneity of the sympathetic innervation of the intracranial arterioles.<sup>12</sup>

We conducted a MEDLINE search to evaluate reports of RPLS with US Food and Drug Administration-approved small molecule, VEGF multikinase inhibitors, using the phrase: (“Hypertensive Encephalopathy”[MeSH] OR leucoencephalopathy OR leukoencephalopathy OR encephalopathy) and drug name. The drugs included were axitinib, cabozantinib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib, and vandetanib. References from each article were examined to identify additional case reports. Articles

must have met the following criteria: English language, underlying malignant disease, and MRI findings consistent with RPLS.

Cases of RPLS associated with small molecule, VEGF multikinase inhibitors are summarized in Table 1.<sup>13-24</sup> Although sorafenib was the first VEGF multikinase inhibitor reported to induce RPLS, sunitinib was most often identified as the causative agent (8 of 13 case reports). Recently, 3 cases involving pazopanib were published. Most patients were being treated for metastatic renal cell carcinoma. The time interval from starting a VEGF multikinase inhibitor to onset of RPLS symptoms ranged from 4 days (in our case) to 9 months. Because of the long half-life of bevacizumab (estimated at 20 days with a range of 11 to 50 days), previous treatment with bevacizumab might have played a role in rapid onset of RPLS in our case even though the patient’s last dose of bevacizumab was more than 150 days before starting regorafenib. In our literature review, no other cases describe recent bevacizumab use as potentially associated with multikinase inhibitor-induced RPLS. After supportive measures, including the permanent discontinuation

**Table 1** Characteristics of Case Reports Describing RPLS in Association With Multikinase Inhibitors

Reference	Patient Sex/Age	Drug (Treatment Duration)	Underlying Disease <sup>a</sup>	Neurologic Symptoms	Maximum Blood Pressure (mm Hg)	Treatment <sup>b</sup>
Govindarajan et al, 2006 <sup>13</sup>	F/49	Sorafenib (4 months)	CC	Headache, vision loss, seizures, loss of consciousness	197/131	Antihypertensive agents
Medioni et al, 2007 <sup>14</sup>	F/81	Sunitinib (22 weeks)	RCC	Dizziness, loss of consciousness, confusion	155/85	Not described
Martin et al, 2007 <sup>15</sup>	F/70	Sunitinib (2 weeks)	RCC	Seizures, headache, changes in vision	170/100	Anticonvulsant, antihypertensive agents
Kapiteijn et al, 2007 <sup>16</sup>	F/54	Sunitinib (34 weeks)	GIST	Vision loss, seizures	210/110	Antihypertensive agents, phenytoin
Cumurciuc et al, 2008 <sup>17</sup>	F/39	Sunitinib (1 week)	RCC	Asthenia, vomiting, headache, abdominal pain, seizures, confusion	160/102	Clonazepam, fosphenytoin, antihypertensive agents
Chen and Agarwal, 2009 <sup>18</sup>	F/48	Sunitinib (1 week)	RCC	Headache, gait unsteadiness, seizures, upper extremity weakness, deep tendon hyperreflexia	190/130	Antihypertensive agents
Padhy et al, 2011 <sup>19</sup>	M/65	Sunitinib (8 days)	RCC	Headache, dizziness, upper extremity weakness, vision loss, seizures, deep tendon hyperreflexia	160/100	Antihypertensive agents
Hadj et al, 2012 <sup>20</sup>	M/61	Sunitinib (15 weeks)	RCC	Seizures	202/101	Midazolam, phenytoin, sodium valproate, antihypertensive agents
Khan et al, 2012 <sup>21</sup>	F/48	Sunitinib (9 weeks)	RCC	Nausea, vomiting, headache, vision changes, dysdiadokinesia, finger past-pointing, seizures	178/117	Phenytoin, dexamethasone, antihypertensive agents
Chelis et al, 2012 <sup>22</sup>	F/40	Pazopanib (3 weeks)	RCC	Seizures, vision loss, headache	165/105	Phenytoin, mannitol, antihypertensive agents
Asaithambi et al, 2012 <sup>23</sup>	M/76	Pazopanib (1 month)	RCC	Vision loss, headache, vomiting, disorientation	219/55	Antihypertensive agents
Foerster et al, 2013 <sup>24</sup>	F/62	Pazopanib (8 weeks)	RCC	Headaches, seizures, left arm paresis, gait instability, nausea, vomiting	>300 (systolic)	Diazepam, levetiracetam, antihypertensive agents
Our case, 2013	M/46	Regorafenib (4 days)	CRC	Seizures, agitation, altered mental status	200s/100s	Diazepam, fosphenytoin, phenytoin, antihypertensive agents

Abbreviations: CC = metastatic cholangiocarcinoma; CRC = metastatic colorectal cancer; F = female; GIST = gastrointestinal stromal tumor; M = male; RCC = metastatic renal cell carcinoma; RPLS = reversible posterior leukoencephalopathy syndrome.

<sup>a</sup>No brain metastases in any case.

<sup>b</sup>Resolution of clinical symptoms occurred in all patients after discontinuation of the offending agent.

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of the offending agent, all patients reviewed experienced resolution of their symptoms, which included seizures (11 patients [85%]), headache (9 patients [62%]), changes in vision (7 patients [54%]), and vomiting (4 patients [31%]).

Prompt recognition and treatment can make the difference between reversal of the condition and permanent neurological deficits. Patients with RPLS usually recover within 2 weeks.<sup>3</sup> Radiological signs of RPLS normally improve with a median of 20 days in 88% of patients, with complete or near complete resolution in 70% of patients.<sup>1</sup> When MRI shows resolution of abnormalities, discontinuation of anticonvulsant treatment can be considered.<sup>25</sup>

### Conclusion

To our knowledge, this is the first published case of RPLS during regorafenib treatment. Our case is unique because the duration of onset of RPLS is short and questions were raised as to whether previous exposure to bevacizumab might play a role in this rapid development of RPLS. Although it is usually reversible, if untreated, RPLS is a serious and potentially life-threatening adverse effect. In this era of agents targeting the VEGF pathway for the treatment of various malignancies, an increase in RPLS incidence in cancer patients is anticipated, and all clinicians should be aware of this serious but treatable syndrome.

### Disclosure

The authors have stated that they have no conflicts of interest.

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