

Bevacizumab-Mediated Interference With VEGF Signaling Is Sufficient to Induce a Preeclampsia-Like Syndrome in Nonpregnant Women

Sarah N. Cross, MD,¹ Elena Ratner, MD,¹ Thomas J. Rutherford, MD, PhD,¹ Peter E. Schwartz, MD,¹ Errol R. Norwitz, MD, PhD²

¹Department of Obstetrics, Gynecology & Reproductive Sciences, Yale University School of Medicine, New Haven, CT; ²Department of Obstetrics and Gynecology, Tufts University School of Medicine, Boston, MA

Preeclampsia (gestational proteinuric hypertension) complicates 5% to 8% of all pregnancies, and is a major cause of maternal and perinatal morbidity and mortality. It is a multisystem disorder specific to human pregnancy and the puerperium. Although the etiology is unknown, increasing evidence from both animal and human studies suggests that an imbalance in circulating pro- (vascular endothelial growth factor [VEGF], placental growth factor) and anti-angiogenic factors (soluble fms-like tyrosine kinase 1, soluble endoglin) may be important. Bevacizumab (Avastin[®]; Genentech, South San Francisco, CA), a humanized recombinant monoclonal IgG antibody that binds VEGF, has been shown to inhibit endothelial cell proliferation, suppress angiogenesis, and shrink a variety of solid tumors. We present two cases of bevacizumab toxicity that mimic preeclampsia with a reversible syndrome characterized by acute-onset severe hypertension, proteinuria, central nervous system irritability (headache, photophobia, blurred vision, seizures), abnormal laboratory tests (elevated liver function tests, thrombocytopenia), and evidence of reversible posterior leukoencephalopathy on neuroimaging. In both cases, the clinical and laboratory manifestations returned to normal with discontinuation of bevacizumab therapy and supportive care. Bevacizumab toxicity can mimic preeclampsia in nonpregnant women. These data suggest that interference with VEGF signaling is sufficient to induce a preeclampsia-like syndrome in nonpregnant patients. VEGF signaling therefore appears to play a central role—perhaps *the* central role—in the pathogenesis of preeclampsia, and provides a potential biomarker for the prediction, prevention, and treatment of this dangerous disorder.

[Rev Obstet Gynecol. 2012;5(1):2-8 doi: 10.3909/riog0179]

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KEY WORDS

Bevacizumab • Hypertension • Preeclampsia • Eclampsia • Vascular endothelial growth factor • Reversible posterior leukoencephalopathy syndrome

Preeclampsia (gestational proteinuric hypertension) complicates 5% to 8% of all pregnancies. It is the second most common cause of pregnancy-related maternal death in the United States (after thromboembolism), accounting for 15% of all maternal deaths and an estimated 50,000 maternal deaths per year worldwide.^{1,2} It is estimated that a woman dies every 6 minutes somewhere in the world from complications of preeclampsia. Preeclampsia is a clinical diagnosis that requires two elements: new-onset hypertension (defined as a sustained sitting blood pressure [BP] $\geq 140/90$ mm Hg in a previously normotensive woman) and proteinuria (defined as > 300 mg/24 h or $\geq 1+$ on a clean-catch urine specimen in the absence of a urinary tract infection).³ Preeclampsia cannot be accurately predicted or prevented. The only effective treatment is delivery. As such, pregnancy outcome depends primarily on early diagnosis, the type of preeclampsia present (mild or severe), prevention of complications (such as seizures), and timely delivery. Perinatal outcome is dependent largely on gestational age at birth.

Preeclampsia is a multisystem disorder specific to human pregnancy and the puerperium; it does

its development is laid down early in pregnancy. The pathologic hallmark appears to be a complete or partial failure of the second wave of trophoblast invasion from 16 to 20 weeks of gestation, which is responsible in normal pregnancies for destruction of the muscularis layer of the spiral arterioles and remodeling of the placental vasculature.³⁻⁶ As pregnancy progresses, the metabolic demands of the fetoplacental unit increase. However, because of the abnormally shallow invasion of the placenta, the spiral arterioles in pregnancies destined to develop preeclampsia are unable to dilate sufficiently to accommodate the required increase in blood flow. This results in placental dysfunction and the release of a toxemia factor from the ischemic placenta that leads to generalized vasospasm and endothelial injury, which are the clinical hallmarks of preeclampsia.³ The identity of the toxemia factor remains elusive, although increasing evidence from both animal⁷ and human⁸ sources suggests that an imbalance in pro-(vascular endothelial growth factor [VEGF], placental growth factor [PlGF]), and anti-angiogenic factors (soluble fms-like tyrosine kinase 1 [sFlt1], soluble endoglin [sEng]) in the maternal circulation,⁸⁻²⁵ fetal circulation,²⁶⁻²⁸ placenta,^{7, 24, 29-37} and

that pregnancy may be unmasking some underlying predisposition to vascular reactivity in such women. However, which of these factors is most important and whether the imbalance is a cause or a consequence of preeclampsia is not known.

Bevacizumab (Avastin®; Genentech, South San Francisco, CA) is a monoclonal humanized recombinant IgG1 antibody that binds and inhibits VEGF activity.⁴⁰ Because VEGF induces vasodilatation by enhancing endothelial-type nitric oxide production,⁴¹ the anti-VEGF activity of bevacizumab has been demonstrated to reduce perfusion of malignant tumors by inhibiting endothelial cell proliferation and angiogenesis.⁴² In 2004, bevacizumab received approval from the US Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancer. Since that time, it has received FDA approval for the treatment of other solid tumors including metastatic renal cell carcinoma, metastatic non-small cell lung cancer, and progressive glioblastoma. Clinical trials are underway to evaluate its use in other tumors, including pancreatic cancer and advanced ovarian cancer.^{43,44} We present two cases of bevacizumab toxicity in nonpregnant subjects that mimic preeclampsia.

Preeclampsia is a multisystem disorder specific to human pregnancy and the puerperium; it does not occur naturally in other animal species.

not occur naturally in other animal species. Although the pathophysiology of preeclampsia is poorly understood, it is clear that the blueprint for

amniotic fluid³⁸ may be important. Moreover, alterations in these factors have been shown to persist beyond pregnancy,³⁹ suggesting

Case 1

A 69-year-old white woman with recurrent stage IIIA papillary serous ovarian cancer was being treated with carboplatin, gemcitabine, and bevacizumab. Her

past medical history was remarkable for a remote history of borderline hypertension well controlled without medication for several years. Eight days after her fifth dose of bevacizumab (at a standard dose of 15 mg/kg), the patient presented with elevated BP to 170/98 mm Hg and was started on an angiotensin-converting enzyme (ACE) inhibitor. The next day, she was noted to have worsening BP to 204/126 mm Hg and was complaining of a headache, nausea and vomiting, photophobia, and blurred vision. She was noted to be somnolent and disoriented and had a tonic-clonic seizure. Noncontrast computed tomography (CT) of the head was unremarkable. A subsequent brain MRI demonstrated T2 prolongation in the occipital lobes as well as in the parietal and posterior temporal lobes and cerebellar hemispheres bilaterally (Figure 1). There was no evidence of hemorrhage or stroke. Laboratory studies revealed new-onset 3+ proteinuria and transaminitis to nine times normal (alanine transaminase [ALT] 240 [normal < 40] and aspartate transaminase [AST] 324 [normal < 56] IU/L) and

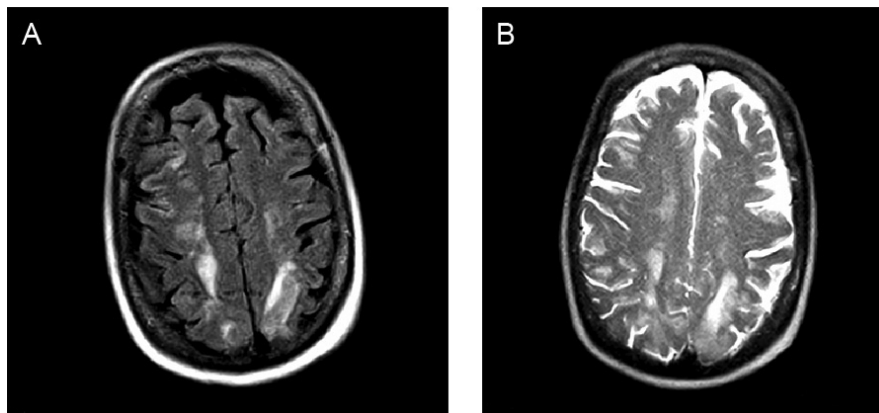
thrombocytopenia ($17 \times 10^3/\mu\text{L}$). A lumbar puncture was unrevealing. In the medical intensive care unit (MICU), a labetalol infusion was started for BP control as well as the initiation of antiseizure medications. Her clinical condition continued to improve, and she was discharged to a rehabilitation center on hospital day 9 on two oral antihypertensive agents only. A 6-week follow-up revealed her to be normotensive with normal baseline mental status, and her antihypertensive medications were discontinued. Her chemotherapy regimen was changed from bevacizumab to doxorubicin.

Case 2

A 52-year-old white woman with recurrent stage IIC poorly differentiated ovarian carcinoma was undergoing treatment with carboplatinum, gemcitabine, and bevacizumab. The patient's fourth cycle was postponed due to thrombocytopenia and hypertension (BP 162/114 mm Hg), and an ACE inhibitor was started. A CT of the head, performed because of complaints of dizziness, showed

mild cerebral atrophy and chronic small vessel ischemic disease, but no evidence of infarction or hemorrhage. Six days after her fifth cycle of bevacizumab (at a standard dose of 15 mg/kg), the patient presented with worsening hypertension (179/116 mm Hg) and complaints of dizziness, blurred vision, and headache. A repeat CT of the head was unchanged. A subsequent brain magnetic resonance imaging (MRI) scan showed multiple foci of increased T2/fluid attenuated inversion recovery (FLAIR) white matter signal (Figure 2A). Laboratory studies revealed new-onset 2+ proteinuria, a transaminitis to 3.5 times normal (AST 123, ALT 70), and thrombocytopenia ($19 \times 10^3/\mu\text{L}$). At the time of discharge, her symptoms had resolved and her BP was controlled on three antihypertensive medications. The decision was made to decrease her bevacizumab dose from 15 to 10 mg/kg. Eight weeks after her next bevacizumab treatment, she presented with severe hypertension (170/110 mm Hg), mental status changes, and abdominal pain suspicious for a bowel perforation. A repeat brain MRI demonstrated T2 prolongation in the periventricular and subcortical white matter, cerebellar hemispheres, brainstem, and thalami as well as a 5-mm acute hemorrhage in the left paracentral lobule with adjacent vasogenic edema, all consistent with reversible posterior leukoencephalopathy syndrome (RPLS) (Figure 2B). Laboratory studies showed continued 2+ proteinuria and thrombocytopenia, but with resolution of the transaminitis. The patient expired due to complications of bowel perforation during the same hospitalization.

Figure 1. Brain magnetic resonance imaging (MRI) scan on admission suggestive of posterior reversible leukoencephalopathy syndrome. Imaging shows T2 prolongation in the bilateral cerebellar hemispheres, bilateral occipital, and parietal and posterior temporal lobes, as well as in the watershed areas in the bilateral frontal white matter. Abnormal signal is seen predominantly in the white matter with involvement of the cortex in bilateral occipital lobes, right greater than left. (A) T2-weighted MRI. (B) Fluid attenuated inversion recovery MRI.



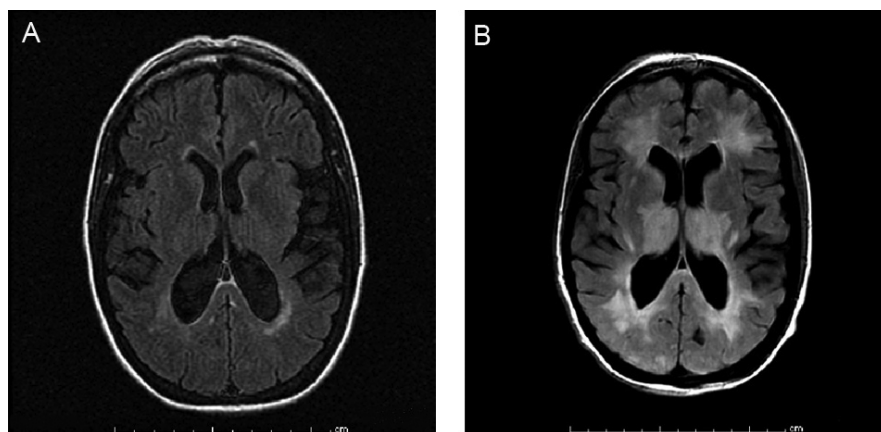


Figure 2. Brain fluid attenuated inversion recovery magnetic resonance imaging (FLAIR MRI) scan. (A) Initial brain FLAIR MRI showing multiple foci of increased FLAIR white matter signal. (B) Brain FLAIR MRI consistent with posterior reversible leukoencephalopathy syndrome. T2 prolongation in periventricular, subcortical white matter, cerebellar hemispheres, brainstem, and thalami is seen. There is also evidence of a 5-mm acute hemorrhage in the left paracentral lobule with adjacent vasogenic edema.

Comments

The pathophysiology of preeclampsia is incompletely understood, but there is mounting evidence that dysregulation of VEGF has a central role to play. In this report,

has been reported in up to 67% of patients.⁴³ It is seen more commonly at high (10–15 mg/kg) rather than lower doses (≤ 7.5 mg/kg).^{43,44} Importantly, in addition to new-onset hypertension, bevacizumab

and capillary diameter leading to increased peripheral vascular resistance, although the rapidity with which the hypertension develops and resolves makes this unlikely.^{43,46}

Proteinuria is another common side effect of bevacizumab therapy, and is thought to result from drug-induced thrombotic microangiopathy.⁴³ However, not all patients are at equal risk. Bevacizumab-induced proteinuria is more common in black patients and in patients on high- versus low-dose bevacizumab (63% vs 41%, respectively).⁴³ Importantly, the renal damage associated with bevacizumab therapy appears to be irreversible.⁴³

Transaminitis and thrombocytopenia are also well described side effects of treatment with VEGF-targeted inhibitors,⁵¹ although not specifically with bevacizumab.⁴⁶ It is unclear whether the transaminase elevations are due to a direct toxic effect of the drug on hepatocytes or to an effect on the endothelial cells of the small blood vessels within the liver.⁴⁶

RPLS is a clinical syndrome characterized by headache, nausea and vomiting, visual disturbances (including cortical blindness), altered mental status (agitation, confusion, coma), and seizures. Radiologically, RPLS is characterized by white matter lesions in the posterior parieto-temporal-occipital region of the cerebral hemispheres bilaterally without evidence of infarction or hemorrhage. Lesions are often symmetric, but some degree of asymmetry is common.⁵² On MRI, lesions are hyperintense on T2-weighted images and demonstrate increased FLAIR signal consistent with edema.^{53,54} RPLS most often affects the posterior cerebral hemispheres, although reports of isolated brainstem⁵⁵ and frontal lobe abnormalities^{56,57} have also been described.

In this report, we demonstrate that the toxicity profile of the anti-VEGF antibody, bevacizumab, mimics preeclampsia in nonpregnant women with a reversible syndrome characterized by severe hypertension, proteinuria, transaminitis, thrombocytopenia, seizures, and neuroimaging suggestive of RPLS.

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Bevacizumab has been used for the treatment of several malignancies, including ovarian cancer.^{43,44} A number of side effects have been described in both animal and human studies, including hypertension, proteinuria, and arterial (but not venous) thromboembolism.⁴³ The most common side effect is hypertension, which

can also worsen preexisting hypertension.^{43,45–47} The hypertension is usually easily managed with such medications as ACE inhibitors and calcium channel blockers,^{43,46,48} but can be dose limiting in up to 18% of patients^{43,46} (Table 1). The mechanism of bevacizumab-induced hypertension is thought to be a combination of direct vasospasm⁴⁹ and generalized endothelial injury with upregulation of pro-inflammatory cytokines⁵⁰ and a decrease in nitric oxide production leading to vasoconstriction and decreased sodium excretion.⁴³ An alternative hypothesis is that of vascular rarefaction, which refers to a functional decrease in arteriole

TABLE 1**National Cancer Institute Common Toxicity Criteria for Hypertension⁶³**

0	1	2	3	4
None	Asymptomatic, transient increase by > 20 mm Hg (diastolic) or to > 150/100 mm Hg if previously WNL; not requiring treatment	Recurrent or persistent or symptomatic increase by > 20 mm Hg (diastolic) or to > 150/100 mm Hg if previously WNL; not requiring treatment	Requiring therapy or more intensive therapy than previously	Hypertensive crisis

WNL, within normal limits

The pathophysiology of RPLS, first described by Hinchey in 1996,⁵² appears to be cerebral edema without infarction due to disruption of the integrity of the cerebral vascular endothelium leading to generalized capillary leakage. The inciting event is often a sudden and severe elevation in systemic BP (mean arterial BP > 120 mm Hg) that exceeds the autoregulatory capability of the cerebral vasculature, resulting in a breakdown in the blood-brain barrier with arteriolar vasodilatation, endothelial dysfunction, and capillary leakage. The end result is transudation of fluid out of the cerebral vasculature into the surrounding tissues, leading to vasogenic cerebral edema.^{53,54} The posterior (vertebrobasilar) circulation has less sympathetic innervation than the anterior (carotid) circulation, which explains why it is that RPLS predominantly affects the posterior part of the brain.^{58,59} In addition to severe hypertension, immune-mediated mechanisms may contribute to the pathophysiology of RPLS by disrupting the vascular endothelium of the blood-brain barrier either indirectly or by a direct cytotoxic effect.^{52,53}

The mechanism responsible for bevacizumab-induced RPLS has yet to be elucidated, but is likely due to both the indirect effects of hypertension and vasospasm as well as to a direct cytotoxic effect of the drug on the cerebral endothelium.⁴⁶ Because the half-life of bevacizumab is 20 days, the observation that bevacizumab-related RPLS resolves rapidly with aggressive BP control suggests that the effect of hypertension may be more important in this regard than the direct cytotoxic effect of the medication on the vascular endothelium.

The management of RPLS involves aggressive BP control, the introduction of anticonvulsant medications, and elimination or dose reduction of the offending cytotoxic medication.⁵³ BP reduction should follow the same guidelines as those in hypertensive encephalopathy (ie, a reduction by 20% to 25% within the first 1 to 2 hours to achieve a diastolic BP reduction to < 100 mm Hg). Anticonvulsant medications are usually no longer required once there is radiographic evidence of resolution of RPLS.⁵³ In general, RPLS is a reversible syndrome without long-term sequelae.

Indeed, repeat neuroimaging within 1 week of presentation is typically associated with near or complete resolution.⁵² However, a failure to recognize the syndrome in a timely fashion and to institute immediate and aggressive BP control may increase the risk of long-term injury, including intracranial hemorrhage^{57,60} and even death.^{53,61,62}

The clinical profile of anti-VEGF inhibitor toxicity suggests that interference with VEGF signaling is necessary and sufficient to induce a preeclampsia-like syndrome in humans. VEGF signaling therefore appears to play a central role—perhaps *the* central role—in the pathogenesis of preeclampsia, and provides a potential biomarker for the prediction, prevention, and treatment of this dangerous disorder. ■

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MAIN POINTS

- Preeclampsia (gestational proteinuric hypertension) complicates 5% to 8% of all pregnancies, and is a major cause of maternal and perinatal morbidity and mortality. It is a multisystem disorder specific to human pregnancy and the puerperium. Although the etiology is unknown, increasing evidence from both animal and human studies suggests that an imbalance in circulating pro- (vascular endothelial growth factor [VEGF], placental growth factor) and anti-angiogenic factors (soluble fms-like tyrosine kinase 1, soluble endoglin) may be important.
- Bevacizumab (Avastin®; Genentech, South San Francisco, CA), a humanized recombinant monoclonal IgG antibody that binds VEGF, has been shown to inhibit endothelial cell proliferation, suppress angiogenesis, and shrink a variety of solid tumors.
- Bevacizumab toxicity can mimic preeclampsia in nonpregnant women. VEGF signaling therefore appears to play a central role—perhaps the central role—in the pathogenesis of preeclampsia, and provides a potential biomarker for the prediction, prevention, and treatment of this dangerous disorder.

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