Posterior Reversible Encephalopathy Syndrome Associated with Bevacizumab

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Abstract
Posterior Reversible Encephalopathy Syndrome (PRES) is characterized by neurologic symptoms with hyper-intense lesions on magnetic resonance imaging and it presents signs including a sudden onset headache, hypertension, and fever. The pathophysiology underlying PRES have been postulated to be severe hypertension leading to failed cerebral vascular auto-regulation and endothelial injury/vasogenic edema, vasoconstriction leading to brain ischemic and subsequent vasogenic edema. PRES may be associated with recent chemotherapy agents, in particular, bevacizumab which is a recombinant, humanized, monoclonal IgG1 antibody that binds and inhibits vascular endothelial growth factor. We experienced the case of PRES associated with Reversible Cerebral Vasoconstriction Syndrome (RCVS) 15 months later after a variety of combined chemotherapies containing bevacizumab for metastatic colon cancer. PRES and RCVS are frequently associated like this case and have overlapping or similar pathophysiological mechanism. We speculated that bevacizumab may have induced vasospasm coupled with hypertension and/or endothelial dysfunction due to bevacizumab 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, and which led to PRES.

Keywords: Posterior reversible encephalopathy syndrome; Bevacizumab; Vasospasm; Reversible cerebral vasoconstriction syndrome

Introduction
Posterior Reversible Encephalopathy Syndrome (PRES) is characterized by neurologic symptoms with hyper-intense lesions on Magnetic Resonance Imaging (MRI) and it presents signs including a sudden onset headache, hypertension, and fever [1]. The neurologic symptoms, signs and radiological lesions of PRES are mostly reversible. However, the syndrome is not always reversible. The pathophysiology underlying PRES have been postulated to be severe hypertension leading to failed auto-regulation and endothelial injury/vasogenic edema, vasoconstriction leading to brain ischemic and subsequent vasogenic edema [2]. The risk factors for this syndrome include malignant hypertension, eclampsia, renal failure and treatment with chemotherapy agents.

As molecularly targeted therapy becomes more prevalent in oncology, newer agents may become important contributors to these conditions. A number of chemotherapy agents have been associated with PRES [3]. Recently, bevacizumab which is a recombinant, humanized, monoclonal IgG1 antibody that binds and inhibits Vascular Endothelial Growth Factor (VEGF) has been associated with PRES [4-15] [Table 1].

The combined chemotherapies containing bevacizumab are related to a risk of highly graded hypertension in up to 16 percent of patients, possibly secondary to vasospasm [16]. Severe hypertensive encephalopathy leads to PRES and vasogenic edema of the posterior cerebral white matter, induced by endothelial dysfunction and a disrupted blood-brain barrier.

We speculated that bevacizumab may have induced vasospasm coupled with hypertension and/or endothelial dysfunction due to bevacizumab 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, and which led to PRES [4].

Clinical context of the study
We experienced the case of PRES, who was 44-year-old woman and presented with the acute onset of a headache, drowsiness and seizure with a fever and hypertension fifteen months later after a variety of combined chemotherapies containing bevacizumab for metastatic colon cancer [4]. In this case, follow-up brain MRI revealed radiographic resolution of parieto-occipital lobe edema, which correlated with clinical improvement, however, Magnetic Resonance Angiography (MRA) performed at the same time indicated that spasm of the bilateral cerebral arteries had progressed compared to the situation prior to treatment. Furthermore, instead of continuing treatment of PRES, when the patient developed cerebral infarction presenting as moderate right hemiparesis, brain MRI revealed new lesions in the left front-parietal area, but MRA indicated an improvement in the spasms of bilateral cerebral arteries [4].

Highlight on the potential effects and adverse effects of bevacizumab to elicit PRES
Bevacizumab, which is the anti-VEGF monoclonal antibody decreases tumor perfusion, vascular density, and interstitial fluid pressure and improves the rate of tumor regression and survival in patients with...
colorectal carcinoma [14,15]. In the view of its adverse effects, it has been a frequent occurrence that bevacizumab-based combination chemotherapy induces a risk of grade-3 hypertension in up to 16% of patients, possibly secondary to vasospasm [16]. On the other side, it has been suggested that bevacizumab could elicit vasospasm leading to PRES, induced by endothelial dysfunction and a disrupted blood-brain barrier without causing significant hypertension. It is rare for severe hypertensive encephalopathy to lead to PRES and vasogenic edema of the posterior cerebral white matter. It is important to differentiate PRES from acute cerebral ischemia, which is also associated with bevacizumab.

Pathophysiology underlying PRES

The pathophysiology underlying PRES is not completely clarified; however, two main hypotheses have been put forward. They are the break through theory and the vasospasm theory (Figure 1). The break through theory indicates that elevated blood pressure exceeds the auto-regulatory capacity of the cerebral vasculature leading to a breakdown of the endothelial junctions that form the blood-brain barrier. The cerebral vascular auto-regulation is playing a role of maintaining cerebral blood flow regardless of changes in the mean arterial pressure. In excess of mean arterial pressure of the upper limit of the cerebral vascular auto-regulation, the auto-regulation falls, leading to vasodilation and endothelial dysfunction [17]. The vasodilation and

<table>
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<tr>
<th>Author</th>
<th>Patients (age, sex)</th>
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<th>Treatment</th>
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<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Katada et al. [4]</td>
<td>44F Colon cancer</td>
<td>XELOX, FOLFIRI mFOLFOX6, Bevacizumab</td>
<td>headache, drowsiness and seizure</td>
<td>PRES recovery, Cerebral infarction</td>
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<tr>
<td>Hamid et al. [5]</td>
<td>44F Colon cancer</td>
<td>XELOX, FOLFIRI mFOLFOX6, Bevacizumab</td>
<td>headache, drowsiness and seizure</td>
<td>PRES recovery, Cerebral infarction</td>
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<td>Frantzen et al. [6]</td>
<td>70F Colon cancer</td>
<td>Oxaliplatin, 5 fluorouracil Folic acid, Bevacizumab</td>
<td>coma</td>
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<td>Wang et al. [7]</td>
<td>56F Rectal cancer</td>
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<td>Abbas et al. [9]</td>
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<td>Cross et al. [10]</td>
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<td>Carboplatin, Gemcitabine Bevacizumab</td>
<td>headache, nausea, vomiting photophobia, blurred vision</td>
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<tr>
<td>Lau et al. [11]</td>
<td>63F Rectosigmoid carcinoma</td>
<td>Oxaliplatin, Folic acid 5-fluorouracil, Bevacizumab</td>
<td>headache, drowsiness, visual disturbance, headache</td>
<td>PRES full recovery</td>
<td></td>
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<tr>
<td>Bürki  F et al. [12]</td>
<td>33F Breast cancer</td>
<td>Bevacizumab, Liposomal doxorubicin</td>
<td>headache, gastralgia, nausea, vomiting</td>
<td>PRES full recovery</td>
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<tr>
<td>Allen et al. [13]</td>
<td>52M Rectal carcinoma</td>
<td>FOLFIRI, Bevacizumab</td>
<td>headache, seizure</td>
<td>PRES recovery</td>
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<tr>
<td>Ozcan et al. [14]</td>
<td>52F Rectal adenocarcinoma</td>
<td>Fluorouracil, Leucovorin Oxaliplatin, Bevacizumab</td>
<td>loss of vision, headache, confusion</td>
<td>PRES full recovery</td>
<td></td>
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<tr>
<td>Glusker et al. [15]</td>
<td>59F Renal cancer</td>
<td>Bevacizumab</td>
<td>lethargy</td>
<td>PRES recovery, Cerebral hemorrhage</td>
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Table 1: Published cases of posterior reversible encephalopathy syndrome involving bevacizumab

Figure 1: Pathophysiology of posterior reversible encephalopathy syndrome
endothelial dysfunction results in the development of vasogenic edema that preferentially occurs in the white matter. As it is supported that hypertension is the cause of PRES, some reports described a number of cases occurring in the cortex of normal blood pressure or blood pressure that does not exceed the upper limit of cerebral vascular auto-regulation. The vasospasm theory suggests that the parenchymal changes are due to cytotoxic edema induced by a sudden increase in blood pressure. The sudden rise in blood pressure causes cerebral vasoconstriction resulting in hypoperfusion and cerebral ischemia [18]. The white matter changes are particularly detected in watershed areas between vascular territories where changes in perfusion are causing a lot of damage. Supporting this theory comes from cerebral angiography [19,20] and MRA [4] performed on patients with clinical and radiological evidence of PRES. PRES shares clinicoradiographic characteristic with RCVS, suggesting the existence of common pathophysiological mechanisms among them. Moreover, PRES is associated with endothelial cell dysfunction due to bevacizumab and was initially thought to be caused by severe hypertension such as the frequent adverse effects of bevacizumab, leading to altered cerebral auto-regulation with hypoperfusion and vasogenic edema [21]. However, a quarter of patients of 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, such as bevacizumab has been shown 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]. Tajima demonstrated narrowing of the posterior cerebral artery induced by vasoconstriction and hypoperfusion in the posterior white matter [20]. This theory may state changes seen outside the posterior region in watershed areas such as the paramedial regions of the frontal lobes and the superior cerebellar hemispheres. Despite the support for this theory, changes causing cytotoxic edema secondary to vasoconstriction and cerebral ischemia are irreversible and therefore this theory cannot explain the reversibility of radiological changes associated with most PRES cases. Ischemia and cytotoxic edema formation leads to irreversible brain defects or gliosis, and ultimately leads to permanent hyper-intense signal alterations on MRI. Both vasogenic and cytotoxic edema are relevant to the development of PRES.

Comment

It is important to come to mind PRES early in the clinical course when the patient treated with bevacizumab shows the sign and symptoms resembling cerebrovascular disease. Considering PRES, immediately discontinuing bevacizumab is the first, and control of blood pressure strictly during and after the bevacizumab infusion is necessary.

References