International Journal of Neurorehabilitation
ISSN: 2376-0281

Katada, Int J Neurorehabilitation Eng 2018, 5:4
DOI: 10.4172/2376-0281.1000325

Mini Review Open Access

Posterior Reversible Encephalopathy Syndrome Associated with Bevacizumab

Eiichi Katada*

Department of Neurology, Nagoya City West Medical Center, Japan

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. 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 the cerebrovasucular disease.

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 spasms 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]. On the basis of radiographic resolution on these MRI and MRA findings, the patient was ultimately diagnosed with PRES associated with reversible cerebral vasoconstriction syndrome (RCVS). PRES and RCVS are frequently associated like this case and have overlapping or similar pathophysiological mechanism.

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

***Corresponding author:** Eiichi Katada, MD, Department of Neurology, Nagoya City West Medical Centre Hirate-cho 1-1-1, Kita-ku, Nagoya, 462-8508, Japan; E-mail: katada-ngi@umin.ac.jp

Received June 23, 2018; **Accepted** July 17, 2018; **Published** July 24, 2018

Citation: Katada E (2018) Posterior Reversible Encephalopathy Syndrome Associated with Bevacizumab. Int J Neurorehabilitation 5: 325. doi: 10.4172/2376-0281.1000325

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

Author	Patients (age, sex)	Primary/metastasis	Treatment	Symptoms and onset	Outcome
Katada et al. [4]	44F	Colon cancer	XELOX, FOLFIRI mFOLFOX6, Bevacizumab	headache, drowsiness and seizure	PRES recovery, Cerebral infarction
Hamid et al. [5]	44F	Colon cancer	XELOX, FOLFIRI mFOLFOX6, Bevacizumab	headache, drowsiness and seizure	PRES recovery, Cerebral infarction
Frantzen et al. [6]	70F	Colon cancer	Oxaliplatine, 5 fluorouracil Folinic acid, Bevacizumab	coma	PRES full recovery
Wang et al. [7]	56F	Rectal cancer	FOLFIRI, Bevacizumab	coma, convulsion	PRES recovery
	58F	Colon cancer	mFOLFOX6, Bevacizumab	headache, diziness	PRES recovery
Miyamoto et al. [8]	67F	Colon cancer	mFOLFOX6, Bevacizumab	headache, convulsion, unconsciousness	PRES full recovery
Abbas et al. [9]	31F	Ovarian adenocarcinoma	Bevacizumab, Paclitaxel	seizure	PRES full recovery
Cross et al. [10]	69F	Ovarian cancer	Carboplatin, Gemcitabine Bevacizumab	headache, nausea, vomiting photophobia, blurred vision	PRES recovery
	52F	Ovarian cancer	Carboplatin, Gemcitabine Bevacizumab	dizziness, blurred vision, headache	PRES recovery
Lau et al. [11]	63F	Rectosigmoid carcinoma	Oxaliplatin, Folinic acid 5-fluorouracil, Bevacizumab	headache, drowsiness, visual disturbance	PRES full recovery
Bürki F et al. [12]	33F	Breast cancer	Bevacizumab, Liposomal doxorubicin	headache, gastralgia, nausea, vomiting	PRES full recovery
Allen et al. [13]	52M	Rectal carcinoma	FOLFIRI, Bevacizumab	headache, seizure	PRES recovery
Ozcan et al. [14]	52F	Rectal adenocarcinoma	Fluorouracil, Leucovorin Oxaliplatin, Bevacizumab	loss of vision, headache, confusion	PRES full recovery
Glusker et al. [15]	59F	Renal cancer	Bevacizumab	lethargy	PRES recovery Cerebral hemorrhage

Table 1: Published cases of posterior reversible encephalopathy syndrome involving bevacizumab

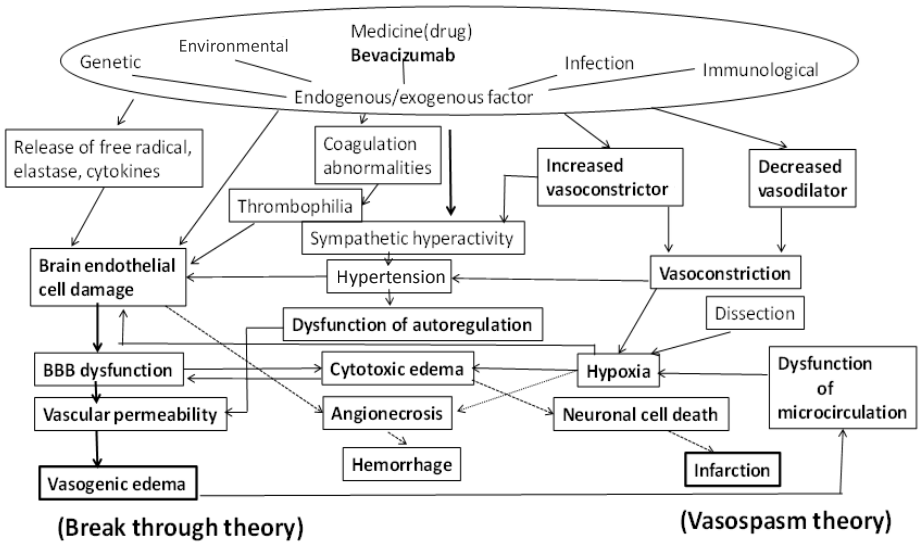

Figure 1: Pathophysiology of posterior reversible encephalopathy syndrome

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 hyperperfusion 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 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]. 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 cerebrovasucular disease. Considering PRES, immediately discontinuing bevacizumab is the first, and control of blood pressure strictly during and after the bevacizumab infusion is necessary.

References

1. Fugate JE, Rabinstein AA (2015) Posterior reversible encephalopathy syndrome: Clinical and radiological manifestations, pathophysiology and outstanding questions. Lancet Neurol 14: 914-925.
2. Sugimoto S, Yamamoto YL, Nagahiro S, Diksic M (1995) Permeability change and brain tissue damage after intracarotid administration of cisplatin studied by double-tracer autoradiography in rats. J Neurooncol 24: 229-240.
3. Han CH, Findlay MP (2010) Chemotherapy induced posterior reversible encephalopathy syndrome. Intern Med J 40: 153-159.
4. Katada E, Mitsui A, Sasaki S, Uematsu N, Anan C (2018) Posterior reversible encephalopathy syndrome after a variety of combined chemotherapies containing bevacizumab for metastatic colon cancer. Intern Med.
5. Hamid M, Ghani A, Micaily I, Sarwar U, Lashari B, et al (2018) Posterior reversible encephalopathy syndrome (PRES) after bevacizumab therapy for metastatic colorectal cancer. J Community Hosp Intern Med Perspect 8:130-133.
6. Frantzen L, Rondeau-Lutz M, Mosquera F, Martinez C, Labani A, et al (2016) Reversible posterior encephalopathy syndrome and cardiomyopathy after bevacizumab therapy. Rev Med Interne 37: 50-52.
7. Wang W, Zhao LR, Lin XQ, Feng F (2014) Reversible posterior leukoencephalopathy syndrome induced by bevacizumab plus chemotherapy in colorectal cancer. World J Gastroenterol 7: 6691-6697.
8. Miyamoto S (2014) Bevacizumab-induced reversible posterior leukoencephalopathysyndrome in a patient with metastatic colorectal cancer. Nihon Shokakibyo Gakkai Zasshi 111: 743-747.
9. Abbas O, Shamseddin A, Temraz S, Haydar A (2013) Posterior reversible encephalopathy syndrome after bevacizumab therapy in a normotensive patient. BMJ Case Rep.
10. Cross SN, Ratner E, Rutherford TJ, Schwartz PE, Norwitz ER (2012) Bevacizumab-mediated interference with VEGF signaling is sufficient to induce a preeclampsia-like syndrome in nonpregnant women. Rev Obstet Gynecol 5: 2-8.
11. Lau PC, Paunipagar B (2011) Posterior reversible encephalopathy syndrome with bevacizumab. Hong Kong Med J 17: 80-81.
12. Bürki F, Badie K, Bartoli P, Montastruc JL, Bagheri H (2008) Reversible posterior leukoencephalopathy syndrome associated with bevacizumab/doxorubicin regimen. Br J Clin Pharmacol 65: 793-794.
13. Allen JA, Adlakha A, Bergethon PR (2006) Reversible posterior leukoencephalopathy syndrome after bevacizumab/FOLFIRI regimen for metastatic colon cancer. Arch Neurol 63: 1475-1478.
14. Ozcan C, Wong SJ, Hari P (2006) Reversible posterior leukoencephalopathy syndrome and bevacizumab. N Engl J Med 354: 980-982.
15. Glusker P, Recht L, Lane B (2006) Reversible posterior leukoencephalopathy syndrome and bevacizumab. N Engl J Med 354: 980-982.
16. Kabbinavar FF, Schulz J, McCleod M, Patel T, Hamm JT, et al (2005) Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: Results of a randomized phageα trial. J Clin Oncol 23: 3697-3705.
17. Dinsdale HB, Robertson DM, Haas RA (1974) Cerebral blood flow in acute hypertension. Arch Neurol 31: 80-87.
18. Stott VL, Hurrell MA, Anderson TJ (2005) Reversible posterior leukoencephalopathy syndrome: A misnomer reviewed. Intern Med J 35: 83-90.
19. Ito Y, Niwa H, Iida T, Nagamatsu M, Yasuda T, et al (1997) Post-transfusion reversible posterior leukoencephalopathy syndrome with cerebral vasoconstriction. Neulogy 49: 1174-1175.
20. Tajima Y, Isonishi K, Kashiwaba T, Tashiro K (1999) Two similar cases of encephalopathy, possibly a reversible posterior leukoencephalopathy syndrome: Serial findings of magnetic resonance imaging, SPECT and angiography. Intern Med 38: 54-58.
21. Bartynski WS (2008) Posterior reversible encephalopathy syndrome, part 2: Controversies surrounding pathophysiology of vasogenic edema. AJNR Am J Neuroradiol 29: 1043-1049.
22. Staykov D, Schwab S (2012) Posterior reversible encephalopathy syndrome. J Intensive Care Med 27: 11-24.