



Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Case report

Posterior reversible encephalopathy syndrome (PRES) with sub-arachnoid haemorrhage after bevacizumab and 5-FU

Jennifer Massey*

Department of Neurology, Royal North Shore Hospital, St Leonards, Sydney, NSW 2006, Australia

ARTICLE INFO

Article history:

Received 17 October 2016

Accepted 22 January 2017

Available online xxx

Keywords:

PRES

Hypertension

Bevacizumab

Seizures

ABSTRACT

PRES is a neurological syndrome characterised by reversible subcortical vasogenic brain oedema in patients with acute neurological signs and symptoms. It occurs in the context of fluctuations in blood pressure, renal failure, autoimmune disorders, eclamptic syndromes and with use of cytotoxic drugs. We present the case of a 60 year old female with advanced bowel cancer who was admitted with seizures and sub-arachnoid haemorrhage, with radiographic features of PRES, shortly after receiving bevacizumab (Avastin), a VEGF-inhibitor.

Crown Copyright © 2017 Published by Elsevier Ltd. All rights reserved.

1. Background

First described in 1996; [1] PRES is a neurologic syndrome qualified by well-defined clinical features and characteristic radiologic imaging. Clinical symptoms and signs in order of prevalence include encephalopathy, seizure, headache, visual disturbance, focal neurological deficit and status epilepticus [2]. Associations between PRES and bevacizumab, a recombinant humanized monoclonal anti-VEGF antibody have been reported since 2006 [3,4]. With increasing prevalence of the cytotoxic medication, numerous reports of bevacizumab associated PRES have emerged. There are approximately 40 cases currently reported in the literature, although reports of bevacizumab induced sub arachnoid haemorrhage in the context of PRES remain rare.

2. Case report

A 60 year old woman, diagnosed with metastatic bowel cancer, presented with generalised tonic clonic seizures and encephalopathy. This occurred 2 weeks subsequent to the patients 3th dose of bevacizumab and 5-FU as second line therapy for the malignancy. The neurologic examination was normal apart from altered mental status. The patient was normotensive through the majority admission with occasional readings of 140–150 mmHg systolic; however had been hypertensive above 180 mmHg systolic frequently in the fortnight prior to presentation, as recorded by her general practi-

tioner and treating oncologist. Laboratory investigations were within normal limits. Non-contrast CT scan revealed three areas of sulcal subarachnoid haemorrhage; and CT angiogram did not show any underlying vascular abnormality. MRI of the brain performed 48 h after admission showed patchy T2 hyperintense lesions in the subcortical white matter of the left posterior lobe (Fig. 1). The MRA revealed irregularities of the intimal aspect of the M1 segment bilaterally as well as changes consistent with vasospasm in the left posterior cerebral artery (Fig. 2).

The patient was diagnosed with PRES. Seizures settled with intra-muscular benzodiazepines. Oral levetiracetam was commenced for further seizure prophylaxis. Although the patient had received two chemotherapeutic agents in the month prior to presentation, based on frequency of bevacizumab induced PRES in the literature this was the presumed offending agent. Given the advanced stage of the patients disease, her ongoing difficulties with chronic pain and failure of first and second line cytotoxic agents (oxaliplatin intolerance in the context of peripheral sensory neuropathy); the patient elected to cease further chemotherapy and adopt a palliative approach to management.

3. Discussion

Whilst both bevacizumab and 5-FU have been associated with PRES, the anti-angiogenic effects of bevacizumab and its frequent association with hypertension make it the most likely offending agent inducing PRES in this case. Whilst the pathophysiology of PRES continues to be debated, a leading theory of the underlying mechanism relates to rapid development of hypertension that

* Fax: +61 2 94631734.

E-mail address: jennifer.massey@hotmail.com

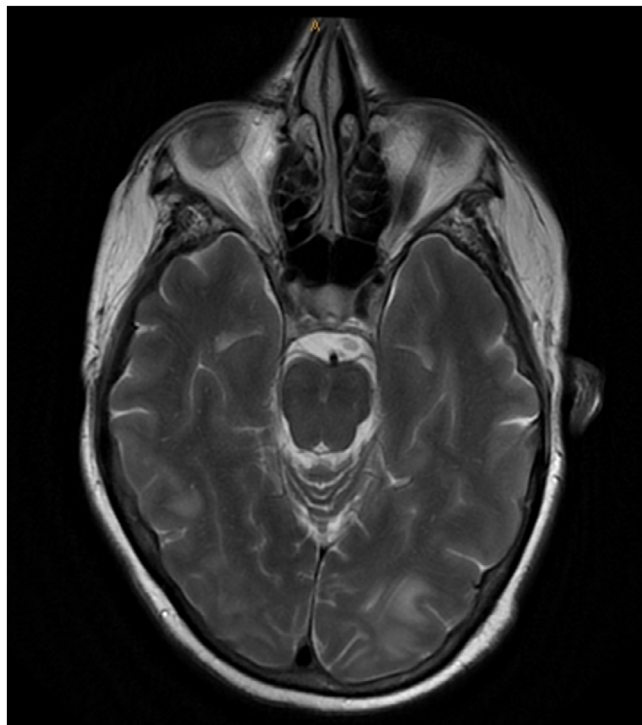


Fig. 1. T2 weighted sequence demonstrating hyperintense lesions in the subcortical white matter of the left posterior lobe.



Fig. 2. MR angiogram demonstrating irregularities of the intimal aspect of the M1 segment bilaterally and in the left posterior cerebral artery.

exceeds the limits of cerebral hyperperfusion. When the vascular autoregulatory response fails to accommodate to the patients systemic blood pressure rise, hyperperfusion occurs, damaging the blood brain barrier and allowing interstitial extravasation of plasma and macromolecules [2]. The other proposed mechanism for PRES, which may occur synergistically describes toxic substances including chemotherapeutics causing direct transient injury to the blood brain barrier by damaging the vascular endothelium, resulting in arterial microthrombosis, arterial occlusion and cerebral hypoxia/vasogenic oedema [5]. Classically PRES has been associated with the use of immunosuppressive, immunomodulatory and chemotherapeutic drugs, as well as intravenous contrast exposure, and illicit stimulant medication triggering hypertensive crises.

Intracranial haemorrhage is common, complicating 10–25% of cases [6–9]. Sulcal subarachnoid haemorrhage represents the second most common form of bleeding, and is reported as the isolated type of haemorrhage in 3–8% of cases [2]. Rates of over 80% of patients with PRES have imaging changes on CTA or MRA consistent with focal or diffuse vasoconstriction or pruning of distal intracranial arteries, particularly the posterior cerebral arteries. PRES has been seen in 17–38% of patients with a diagnosis of reversible cerebral vasoconstriction syndrome [10–12].

The mainstay of treatment is cessation of the offending cytotoxic agent and blood pressure control. Although there are no randomised trials of specific blood pressure agents in PRES, the goal is to reduce blood pressure by 25% in the first few hours, avoid large fluctuations in blood pressure and avoid excessive blood pressure reduction [2]. Anecdotal use supports the role of calcium channel blockers. Seizures are thought to occur both in response to areas of haemorrhage and secondary to the alterations in parenchymal macromolecules and regions of interstitial oedema. Generalized tonic clonic seizures occur in 60–75% of patients [13–15]. Treatment of seizures is with anti-epileptic drugs (AED), as would be used in any other condition, with no specific guidelines for certain AEDs. Encephalopathy is a defining feature of the syndrome, seen in majority of patients in varying severity from mild confusion to stupor and coma. Confounding factors include seizures, the post-ictal state and visual changes.

Since 2006 there have been increasing reports of bevacizumab associated PRES and hypertension is well reported to be the most common adverse reaction to bevacizumab treatment. Bevacizumab may cause hypertension either due to the rapid rises it causes in blood pressure resulting in dysregulation of cerebral vasculature, or via endothelial impairment as described above. In our case, significant hypertension had been recorded in the fortnight prior to presentation. The typical time to PRES onset post bevacizumab use is within its half life of 20 days [16,17] classically between 16 h and 11 days from last dose [5]. A higher burden of PRES has been reported with bevacizumab use in conjunction with other chemotherapeutics [17]. 5-FU has also been reported to cause leukoencephalopathy, however this is classically a multifocal, inflammatory variant occurring 6 weeks to 6 months post treatment [5]. No leukoencephalopathies have been reported with oxaliplatin to date.

Despite the reversibility of the syndrome, PRES is a potentially life threatening condition and its association with bevacizumab should be recognised by physicians prescribing the drug and managing patients presenting with the above complications. There have been reports of the syndrome in normotensive patients [18] and this should broaden physician's consideration of this diagnosis in the appropriate clinical setting. When promptly recognised the syndrome has a good prognosis. Most reports advise indefinite cessation of bevacizumab [19], post PRES, but the drug remains an important biologic agent in the use of many metastatic malignancy treatment protocols. Given the medication is currently only licensed in metastatic disease however, careful monitoring of hypertension and proteinuria should continue to be performed routinely due to the obvious risks in a palliative population. No predictive factors of PRES have been clearly identified to date [19]. Several studies report PRES following the use of other anti-angiogenics including sunitinib as well as other monoclonal antibodies including anti-tumour necrosis factor inhibitors such as infliximab [20,21].

In conclusion, this case highlights the association of bevacizumab with PRES and sub-arachnoid haemorrhage. Consideration of PRES as a differential diagnosis should be prevalent amongst physicians seeing patients with headache, confusion or visual disturbances during or shortly after bevacizumab treatment, particularly in patients with new onset hypertension. Prompt

withdrawal of the drug, treatment of blood pressure and management of associated complications increases chances of favourable outcomes.

References

- [1] Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med* 1996;334:494–500.
- [2] Fugate Jennifer E, Rabinstein Alejandro A. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. *Lancet Neurol* 2015;14:914–25.
- [3] Glusker P, Recht L, Lane B. Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med* 2006;354:980–2.
- [4] Ozcan C, Wong SJ, Hari P. Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med* 2006;354:980–2.
- [5] Wang W, Zhao LR, Lin XQ, et al. Reversible posterior leukoencephalopathy syndrome induced by bevacizumab plus chemotherapy in colorectal cancer. *World J Gastroenterol* 2014;20:6691–7.
- [6] Hefzy HM, Bartynski WS, Boardman JF, et al. Hemorrhage in posterior reversible encephalopathy syndrome: imaging and clinical features. *AJNR Am J Neuroradiol* 2009;30:1371–9.
- [7] Mueller-Mang C, Mang T, Pirker A, et al. Posterior reversible encephalopathy syndrome: do predisposing risk factors make a difference in MRI appearance? *Neuroradiology* 2009;51:373–83.
- [8] Li R, Mitchell P, Dowling R, et al. Is hypertension predictive of clinical recurrence in posterior reversible encephalopathy syndrome? *J Clin Neurosci* 2013;20:248–52.
- [9] Sharma A, Whitesell RT, Moran KJ. Imaging pattern of intracranial hemorrhage in the setting of posterior reversible encephalopathy syndrome. *Neuroradiology* 2010;52:855–63.
- [10] Fugate JE, Ameriso SF, Ortiz G, et al. Variable presentations of postpartum angiopathy. *Stroke* 2012;43:670–6.
- [11] Singhal AB, Hajj-Ali RA, Topcuoglu MA, et al. Reversible cerebral vasoconstriction syndromes: analysis of 139 cases. *Arch Neurol* 2011;68:1005–12.
- [12] Ducros A, Fiedler U, Porcher R, et al. Hemorrhagic manifestations of reversible cerebral vasoconstriction syndrome: frequency, features, and risk factors. *Stroke* 2010;2505–11.
- [13] Burnett MM, Hess CP, Roberts JP, et al. Presentation of reversible posterior leukoencephalopathy syndrome in patients on calcineurin inhibitors. *Clin Neurol Neurosurg* 2010;112:886–91.
- [14] Fugate JE, Claassen DO, Cloft HJ, et al. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. *Mayo Clin Proc* 2010;85:427–32.
- [15] Liman TG, Bohner G, Heuschmann PU, et al. The clinical and radiological spectrum of posterior reversible encephalopathy syndrome: the retrospective Berlin PRES study. *J Neurol* 2012;259:155–64.
- [16] Peter S, Hausmann N, Schuster A, et al. Reversible posterior leukoencephalopathy syndrome and intravenous bevacizumab. *Clin Exp Ophthalmol* 2008;36:94–6.
- [17] Koopman M, Muller EW, Punt CJ. Reversible posterior leukoencephalopathy syndrome caused by bevacizumab: report of a case. *Dis Colon Rectum* 2008;51:1425–6.
- [18] Abbas O, Shamseddin A, Temraz S. Posterior reversible encephalopathy syndrome after bevacizumab therapy in a normotensive patient. *BMJ Case Rep* 2013. <http://dx.doi.org/10.1136/bcr-2012-007995>.
- [19] Sciafani F, Giuseppe G, Mezynski J. Reversible posterior leukoencephalopathy syndrome and bevacizumab in breast cancer. *J Clin Oncol* 2012;30:257–9.
- [20] Cumurciuc R, Martinez-Almoyna L, Henry C, et al. Posterior reversible encephalopathy syndrome during sunitinib therapy. *Rev Neurol* 2008;164:605–7.
- [21] Zamvar V, Sugarman ID, Tawfik RF, et al. Posterior reversible encephalopathy syndrome following infliximab infusion. *J Pediatr Gastroenterol Nutr* 2009;48:102–5.