Case Reports & Case Series (CRP)

Diffuse, non-traumatic, non-aneurysmal subarachnoid haemorrhage during bevacizumab treatment of high grade glioma: case report and review of the literature

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Introduction

Bevacizumab is a recombinant monoclonal antibody against vascular endothelial growth factor (VEGF) approved by the United States Food and Drug Administration (FDA) for use against various cancers including high grade glioma (HGG) [1,2]. There are published case reports of subarachnoid haemorrhage (SAH), occasionally with diffuse vasospasm in patients undergoing bevacizumab therapy [1–4] though the causative role of the drug in these cases has been obscured by the presence of alternative aetiologies or incomplete investigation. Furthermore, there is no consensus regarding the risk of Central Nervous System (CNS) haemorrhage during bevacizumab treatment due to limited available study data. Case Description: A 53 year old female with recurrent gliosarcoma refractory to standard, temozolamide based chemo-radiotherapy presented to our facility in a post-ictal state 16 days after her second dose of intravenous bevacizumab. A Fisher grade III SAH was found on computerised tomography scanning with no causative vascular lesion found on two subsequent digital subtraction angiograms separated by a 10 day period and a Magnetic Resonance Imaging (MRI) scan 20 days post-bleed. Given the resolution of symptoms over an uncomplicated 13 day admission, she was discharged home with bevacizumab ceased prior to her scheduled third dose. Conclusion: We discuss here a case of diffuse, non-traumatic SAH during bevacizumab treatment of recurrent gliosarcoma in which alternative aetiologies of haemorrhage were excluded, to our knowledge the first such case in the English language literature. This adverse event is compatible with the known molecular mechanisms of bevacizumab and clinicians should be cognisant of the potential risk of CNS haemorrhage until larger studies are available to quantify this risk.

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Abbreviations: CNS, central nervous system; DSA, digital subtraction angioogram; FDA, Food and Drug Administration; HGG, high grade glioma; MRI, magnetic resonance image; SAH, subarachnoid haemorrhage; VEGF, vascular endothelial growth factor.

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intravenous bevacizumab of which she had received a second dose 16 days previously. A magnetic resonance imaging (MRI) scan was obtained before the initiation of bevacizumab and showed residual foci of tumour and chronic haemorrhage into the centre of the resection cavity as expected post-operatively with no signs of active bleeding [Fig. 1 A, B]. She was not on anticoagulant or antiplatelet medication. There was no history of hypertension, a bleeding diathesis or tobacco, alcohol or recreational drug use.

Initial physical examination was remarkable for a blood pressure of 150/110 mmHg. The Glasgow Coma Score was 13/15 with eye opening to speech and disorientation but improved to 15/15 following resolution of the post-ictal phase. There were no focal neurological deficits. Initial laboratory investigations revealed a mildly reduced platelet count of 132 × 10^9/L though this was unchanged over the preceding 3 months. All other cell counts and routine coagulation studies were within normal limits. A computerised tomography angiogram showed a Fisher grade III SAH positioned centrally, a reduction in the size of the more laterally located resection cavity with stable appearances of an overlying shallow chronic extra-axial collection [Fig. 1C, D, E, F]. There was no evidence of acute haemorrhage into or around the resection cavity compared to imaging performed 5 weeks previously [Fig. 1C, D, E, F]. On subsequent digital subtraction angiography (DSA) no causative intracranial vascular lesion was identified but an incidental finding of an irregular, mild left cervical segment internal carotid artery (ICA) stenosis was noted. [Fig. 2A, B] This was thought to most likely represent accelerated atherosclerosis though acute-on-chronic dissection could not be excluded.

The patient had an uncomplicated 13 day admission. A transient elevation in mean blood flow velocities by transcranial Doppler ultrasonography in the middle cerebral arteries was noted on daily monitoring, peaking at 160 cm/s bilaterally with corresponding Lindegaard Ratios of 4.1 and 3.3 for the left and right sides respectively though with no evidence of an ischaemic neurological deficit. Repeat DSA performed at day 10 was also unremarkable and demonstrated the stability of the focal left cervical ICA stenosis most likely to be an old non-flow limiting dissection [Fig. 2D, E, F]. The patient was subsequently discharged and in light of the inpatient admission, bevacizumab therapy was discontinued prior to the scheduled third dose by the treating neuro-oncology team. A repeat MRI obtained six days later showed complete resolution of SAH with no evidence of a causative vascular lesion and expected evolution of the resection cavity [Fig. 3A, B]. No further episodes of CNS haemorrhage occurred prior to the patient’s death approximately 2 months later due to tumour progression.

Discussion

In this patient with diffuse, non-traumatic SAH during bevacizumab therapy, haemorrhage could be reasonably linked to the use of bevacizumab due to the exclusion of all other potential causes. CNS haemorrhage due to glial series tumours is almost exclusively intra-parenchymal in nature, rarely presenting as an isolated diffuse SAH [7]. In the handful of cases in which a malignant glioma has presented in this manner, the tumour has been in close proximity to the

Fig. 1. (A) Axial T2-weighted magnetic resonance imaging (MRI) scan obtained before initiation of bevacizumab, 7 weeks prior to acute subarachnoid haemorrhage showing the resection cavity with evidence of chronic haemorrhage centrally (white arrow). (B) Coronal T1-weighted MRI with intravenous gadolinium contrast performed simultaneously with previous scan showing aforementioned findings and residual enhancing tumour medial to occipital horn of left lateral ventricle (black arrow) and anterolateral to the margin of the resection cavity (white arrow) with normal enhancement of the surrounding intracranial vasculature. (C) Coronal non-contrast computerised tomography (CT) scan obtained 5 weeks prior to acute subarachnoid haemorrhage showing a shallow extra-axial haematoma above the resection cavity (grey arrow) and minor surrounding vasogenic oedema with no evidence of acute haemorrhage into the resection cavity. (D) Axial CT with intravenous contrast showing Fisher Grade III subarachnoid haemorrhage with blood in the basal and suprasellar cisterns, interhemispheric and sylvian fissures extending to the sulci of the anterior left frontal lobe. (E) Para-sagittal view of same scan showing the chronic shallow extra-axial haematoma overlying the resection cavity (grey arrow) distant to acute subarachnoid haemorrhage visible in the stem of the left sylvian fissure surrounding the left middle cerebral artery (black arrow). (F) Coronal view of same scan showing the decreased size of resection cavity and overlying shallow extra-axial haematoma since previous imaging (grey arrow) with no evidence of regional contrast enhancement or haemorrhage into or around the resection cavity.
ventricles or the subarachnoid spaces with the largest blood burden [7]. In this case, as the haematoma was centrally located in the suprasellar and basal cisterns, distant to tumour foci in the left parieto-occipital lobe where there was also no acute haemorrhage seen on serial neuroimaging, intra-tumoural or peri-tumoural haemorrhage was thought to inadequately account for our patient’s condition. In the setting of diffuse, non-traumatic SAH, serial negative DSA separated by a 1 week period post-ictus as undertaken in this case is estimated to be 90%–93% accurate in the exclusion of a causative vascular lesion [8]. Factors which contribute to false negatives on serial DSA include persistent radiographic vasospasm and the delayed resorption of subarachnoid blood [8]. As we did not encounter such factors, the second negative angiogram was deemed sufficient to also exclude a structural vascular lesion. An angiographically occult vascular malformation, a rare but important cause of non-aneurysmal SAH could also be excluded due to its absence on the delayed post-bleed MRI scan. Given the absence of

![Fig. 2. (A) Digital subtraction angiography (DSA) following left common carotid artery injection, 90° right anterior oblique view on post-bleed day 1 showing an irregularly contoured left internal carotid artery (ICA) stenosis distal to the bulb (black arrow), no evidence of aneurysm, malformation or fistula and normal vessel calibre throughout. (B) 45° left anterior oblique view of the same. (C) Anteroposterior view of the same. (D) DSA following left ICA injection, lateral view on post-bleed day 10 showing the same non-flow limiting stenotic lesion (black arrow) with no aneurysm, fistula or malformation and normal vessel calibre throughout. (E) Anteroposterior view of the same. (F) DSA following right ICA injection, anteroposterior view on post-bleed day 10 showing normal appearances of the right-sided intracranial vasculature.](image1)

![Fig. 3. (A) Axial T2-weighted magnetic resonance imaging (MRI) scan obtained 20 days after acute subarachnoid haemorrhage showing expected evolution of the resection cavity (white arrow) with a reduction in size and no evidence of interval haemorrhage into or around the resection cavity since the previous MRI scan. (B) Coronal T1-weighted MRI with intravenous gadolinium contrast performed simultaneously showing the aforementioned findings (white arrow), interval reduction in the size of enhancing nodules of residual tumour, no new areas of parenchymal contrast enhancement and normal enhancement of the surrounding intracranial vasculature.](image2)
these and other causes of CNS haemorrhage in cancer including coagulopathy and antecedent trauma, SAH could be confidently attributed to bevacizumab therapy.

Between 1997 and 2009, 18 cases of SAH during bevacizumab treatment were recorded in the United States FDA MedWatch database; though the indication for therapy and the presence of alternative aetiologies of haemorrhage in these cases have not been detailed [2]. There are also two published reports of SAH in patients undergoing bevacizumab treatment of HGG but in each an alternative aetiology for haemorrhage is clearly described including trauma [1] and multiple aneurysms [3]. In another case, Baizabal-Carvallo et al. reported a non-traumatic, pre-truncal (perimesencephalic) SAH during bevacizumab treatment of colorectal cancer but only used a single magnetic resonance angiogram to exclude an aneurysmal cause [4] despite the established insensitivity of this imaging modality for this purpose [8]. Thus to our knowledge, this case represents the first report in the English language literature of diffuse, non-traumatic SAH during bevacizumab treatment of HGG in which all alternative causes were definitively excluded.

There are plausible molecular mechanisms accounting for VEGF blockade with bevacizumab causing diffuse, non-traumatic, non-aneurysmal SAH. In addition to stimulating angiogenesis, VEGF is also thought to be a physiological mediator of vascular integrity [6,9]. Putative protective actions include the up-regulation of pro-survival and anti-apoptotic intracellular signalling pathways within vascular endothelial cells together with stimulation of nitric oxide and prostacyclin production causing decreased atherosclerotic vessel wall injury [6,9]. VEGF blockade with bevacizumab may in turn promote the formation of defects in the vessel wall [9,10]. The reduced production of nitric oxide in the vascular endothelium due to bevacizumab is also known to promote arteriolar vasoconstriction with increased peripheral vascular resistance sufficient to cause systemic hypertension [9]. It is then conceivable that this combination of vessel wall defects and arterial hypertension may directly lead to haemorrhage from the small-calibre arteries of the cerebral vasculature with consequent diffuse SAH in the absence of trauma or structural vascular abnormalities. Drug induced vasoconstriction may also account for the bilateral elevation in mean middle cerebral artery blood flow velocities seen in this and other cases of SAH while on bevacizumab [4].

Notably, there is currently no consensus regarding an increased risk of CNS haemorrhage attributable to bevacizumab therapy [6]. A number of early studies including systematic reviews of phase II trials and a single-centre cohort study found a low rate of CNS haemorrhage among cancer patients treated with bevacizumab, similar to the rate in patients on standard treatment [5]. However, the estimated risk of haemorrhage from these studies was inherently limited by their retrospective non-randomised designs and the small and selected nature of study populations. The best available evidence is from a recent meta-analysis of cerebrovascular events in 16 phase II/III randomised controlled trials of bevacizumab [6]. Based on a subgroup analysis of 6163 patients enrolled across 7 included studies which reported the rate of CNS haemorrhage, the overall relative risk of CNS haemorrhage due to bevacizumab treatment was 3.09 (95% CI 1.36–6.99) [6]. Notably, over 50% of patients included in this subgroup analysis had newly diagnosed glioblastoma and were participants of a single phase III randomised placebo controlled trial in which the relative risk of CNS haemorrhage in the bevacizumab arm was 2.20 (95% CI 0.68–7.08) which approached but did not reach statistical significance [6]. Also, the meta-analysis did not include the other major trial of bevacizumab therapy for newly diagnosed glioblastoma RTOG 0825 where in contrast, there was no difference in the rates of ‘haemorrhage’ or ‘serious haemorrhage’ between arms, though the rate of CNS haemorrhage was not specified [10].

Conclusion

We report the first case of diffuse, non-traumatic subarachnoid haemorrhage in a patient undergoing bevacizumab treatment for HGG with no other cause evident despite rigorous investigation. Whilst there is currently no consensus regarding an increased risk of CNS haemorrhage attributable to the use of bevacizumab, an increasing number of studies together with the presence of plausible molecular mechanisms strongly suggest this to be the case. In our opinion, routine cerebrovascular investigation with digital subtraction angiography should be considered in the workup of all bevacizumab treated patients presenting with diffuse SAH though as illustrated in this case, such investigation may not yield a causative structural vascular lesion. Future phase III trials of bevacizumab together with further post-marketing surveillance are awaited to confirm and quantify the risk of this putative adverse event.

References