

Hypertensive-Nimodipine Therapy for Middle Cerebral Artery Vasospasm after Resection of Glioblastoma Multiforme: A Case Report and Literature Review

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Abstract

Delayed cerebral ischemia (DCI) due to post-brain tumor resection vasospasm is an often unrecognized yet debilitating complication. We present a patient with DCI after the resection of glioblastoma multiforme (GBM). To our knowledge, this is the first report on DCI after GBM resection. A 52-year-old female patient with headache for one month underwent subtotal resection of a left temporal GBM encasing the proximal middle cerebral artery (MCA). She was well during the immediate postoperative period but developed right upper limb dense monoparesis on postoperative day four with computed tomographic angiography confirming left MCA vasospasm. Symptoms were significantly alleviated with weeklong hypertensive therapy and nimodipine administration; however they recurred soon after cessation of treatment. A high index of clinical suspicion is needed for the diagnosis of post-tumor resection DCI. Any new postoperative neurological deficit that cannot be explained by hemorrhage, seizures or infection should be expeditiously investigated by angiography or transcranial Doppler sonography. Prompt initiation of hypertensive and nimodipine therapy can possibly reverse neurological deficit. Treatment should be guided by Doppler, angiographic or perfusion imaging studies and not by clinical improvement alone.

Keywords

Cerebral Vasospasm, Delayed Cerebral Ischemia, Glioblastoma Multiforme, Hypertensive Therapy, Nimodipine

1. Introduction

Vasospasm associated delayed cerebral ischemia (DCI) after brain tumor resection is a rare complication. While DCI is well documented in aneurysmal subarachnoid hemorrhage (SAH), occurring in 30% of patients, fewer than 50 cases have been reported following brain tumor resection [1] [2]. Resulting morbidity can be severe since the complication is often left unrecognized before timely treatment is initiated. It can be particularly distressful for patients, who often are preoperatively neurologically intact, and the neurosurgeon, responsible for an otherwise uneventful elective procedure [1]. Hemiparesis is the commonest manifestation and the time interval from tumor resection to symptom onset is comparable to aneurysmal SAH, peaking at seven days, although the complication can occur 30 days after the operation [1]. The pathogenesis of DCI in this setting is not clearly understood. Proposed causative factors include blood spillage in the subarachnoid space, operative manipulation of vessels and the release of vasoactive substances from the tumor [1] [4]. There is no widely accepted management strategy for post-tumor resection DCI and more than 70% of patients have either severe disability or death despite medical treatment, compared to 19% - 46% of SAH patients [1] [3]. We present a patient where neurological deficit due to DCI was partially reversed with hypertensive therapy and nimodipine administration, but recurred soon after discontinuation.

2. Case Report

A 52-year-old right-handed female with good past health had a headache of increasing severity for one month. The patient was fully conscious with right homonymous superior quadrantanopia. There was no other neurological deficit. Magnetic resonance imaging (MRI) revealed a left temporal intra-axial heterogeneously contrast-enhancing tumor with midline shift (**Figures 1(a)-(b)**). MR angiography showed that the tumor encased the middle cerebral artery (MCA) displacing it antero-superiorly (**Figure 1(c)**).

Craniotomy for subtotal excision of the tumor was performed with neuronavigation and intraoperative ultrasound assistance to localize the MCA. Subpial tumor resection was performed conducted using a cavitron ultrasonic aspirator. The proximal trunk and the bifurcating branches of the M1 segment were encountered and preserved using this technique. Microdissection was used to protect the lateral lenticulostriate arterial perforators that were traversing the lesion. No further dissection was performed when confronted with highly adherent tumor tissue (**Figures 2(a)-(b)**). The histological diagnosis was glioblastoma multiforme (GBM) demonstrating methylguanine methyltransferase promoter region (MGMT) methylation and wild-type isocitrate dehydrogenase-1 (IDH-1).

During the early postoperative period the patient was well with no discernible additional neurological deficit. On postoperative day four she experienced right upper limb dense monoparesis of Medical Research Council grade 2/5 and aphasia. The patient was afebrile and cerebrospinal fluid analysis did not indicate infection. Computed tomography (CT) revealed new hypodensities at the left frontal and insula cortex compatible with cerebral ischemia (**Figures 3(a)-(b)**). CT angiography depicted narrowing of the proximal left M1 segment of the

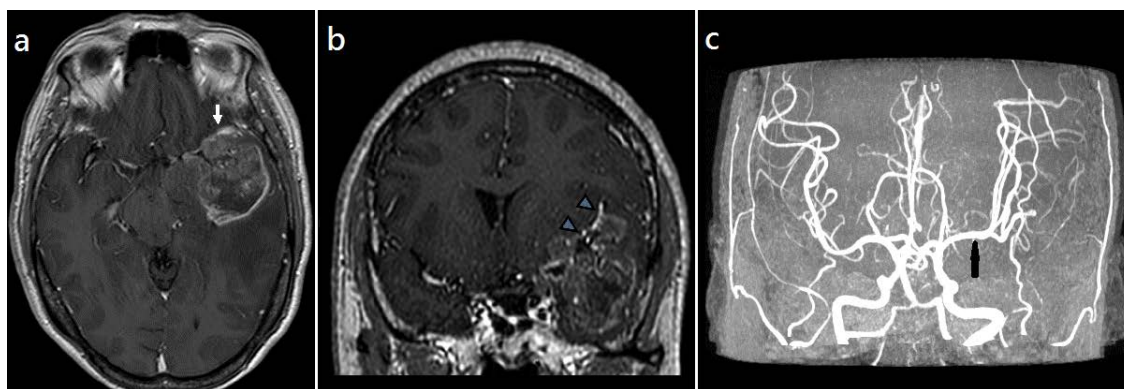


Figure 1. (a) Preoperative axial MRI showing a $3.7 \times 4.2 \times 4.5$ cm left temporal intra-axial tumor with heterogeneous enhancement. Note the anterior displacement of the MCA (arrow); (b) Coronal MRI shows similar findings (grey arrowheads); (c) MR angiography before the operation showed superior displacement of a normal caliber MCA (black arrow).

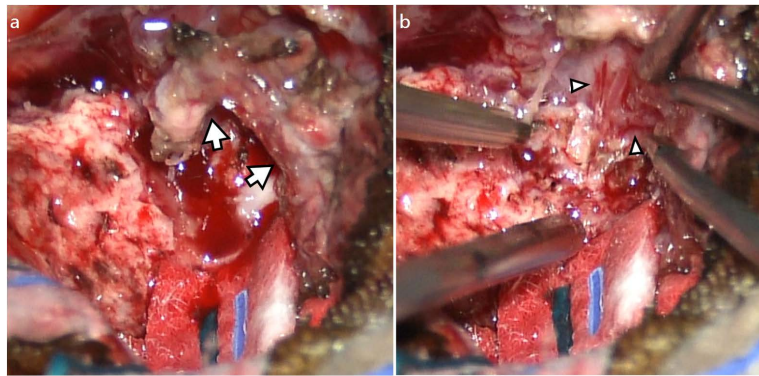


Figure 2. (a) The M1 segment of the MCA was completely dissected away from the encasing tumor (white arrows); (b) MCA branches and its perforators traversing the lesion were encountered and preserved (white arrowheads).

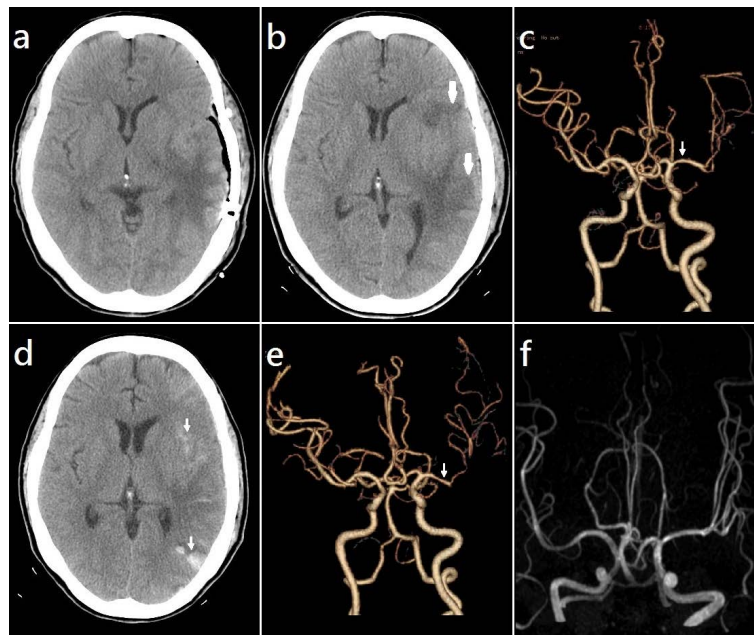


Figure 3. (a) CT on postoperative day 1; (b) CT on postoperative day 4 showing hypodensities over the left frontal and insular cortex (arrows); (c) CT angiography on day 4 demonstrating vasospasm (arrow) of the M1 segment of left MCA (arrow); (d) CT scan after cessation of hypertensive-nimodipine therapy showing luxury perfusion (arrows); (e) CT angiography demonstrating persistent MCA vasospasm (arrow) after hypertensive-nimodipine therapy; (f) 6-month MR angiography showing reconstitution of the left MCA.

MCA that was compatible with vasospasm (**Figure 3(c)**). Transcranial Doppler sonography (TCD) could not be performed due to a suboptimal bone window.

In view of DCI systemic nimodipine (60 mg orally every four hours) was started. In addition induced hypertension was administered by intravenous noradrenaline and dopamine to achieve a mean arterial pressure of greater than 110 mmHg and systolic blood pressure greater than 160 mmHg *i.e.* 20% above baseline. The patient responded to treatment over the course of five days with improved limb power to grade 4/5 and partial speech recovery to short sentences. After cessation of the weeklong therapy the patient developed a second episode of dense hemiparesis and aphasia. A CT scan revealed evidence of luxury perfusion that was managed expectantly (**Figure 3(d)**). A repeat CT angiogram showed persistent MCA vasospasm with progressive involvement of the temporal branch of the M2 segment (**Figure 3(e)**). This time the patient failed to improve after reintroduction of

hypertensive therapy and intensive rehabilitation. Upon discharge the patient's functional performance was a modified Rankin scale score of four and a Barthel Index of 62. In view of her severe disability the patient received palliative adjuvant radiotherapy without chemotherapy. A six-month follow-up MRA showed reconstitution of left MCA patency and reemergence of its temporal M2 segment branch (**Figure 3(f)**).

3. Discussion

Delayed cerebral ischemia as a consequence of arterial vasospasm is a rare but debilitating complication after tumor resection. A large clinical series of 470 patients with skull base tumors observed an incidence of 1.9% and current understanding is mainly limited to sporadic case reports [4]. The results of this complication are severe with almost half of patients experiencing permanent major neurological deficit [1]. When a malignancy with a poor long-term prognosis such as GBM is concerned, postoperative quality of life and functional performance are vital in determining the aim of adjuvant oncological therapy. In our case this unexpected complication led to the administration of palliative radiotherapy despite a favorable chemotherapy predictive biomarker profile. The commonest pathologies associated with vasospasm are pituitary adenomas and meningiomas [1]. For unknown reasons, DCI occurring after malignant brain tumor resection is rare with only four previously confirmed cases, involving medulloblastoma, esthesioneuroblastoma, primitive neuroectodermal tumor and metastatic adenocarcinoma [23] [26] [30] [32]. Despite GBM being the commonest primary malignant brain tumor in adults, to our knowledge this is the first report of postoperative vasospasm in the literature [5].

Risk factors predictive of post-tumor resection vasospasm can be broadly classified into patient, tumor and surgical factors. It is believed that the single most influential patient factor is age. A recent review of the literature observed that most patients with vasospasm were young with a mean age of 41 years (1 to 69) and is comparable to SAH patients where the mean age is 48 years [6]. This predilection for vasospasm occurring in younger patients may be related to increased vasoconstrictive reactivity in response to mechanical arterial stretching or subarachnoid blood metabolite irritation [6]-[8].

Several contributive tumor factors have been identified and lesion location is crucial. Most tumors were observed to be in the sellar, parasellar and middle cranial fosse regions in close proximity to the Circle of Willis [1] [9]. Similarly tumor arterial encasement and narrowing are also considered significant risk factors [1]. Increased tumor vascularity with subsequent blood spillage into the cisternal space has been a recognized tumor feature in over 40% of cases [1]. However, in our patient postoperative hemorrhage was minimal. It is also relevant to discuss the role of metabolic changes within the peritumoral microenvironment in relation to malignant gliomas. Potent vasoactive cytokine levels of endothelin-1, platelet-derived growth factor (PDGF) and interleukin-6 are known to be elevated [10]-[12]. These cytokines have been demonstrated to induce vasospasm in animal models and up-regulated PDGF receptors in the endothelium of tumor arterial feeders could predispose parent arterial vasoconstriction [13] [14]. Microdialysis studies during biopsy procedures on malignant glioma patients have also detected increased levels of glutamate in necrotic areas that can theoretically be released during resection [15]. Glutamate, a critical excitotoxin, has been shown to trigger a pathological rise in intracellular calcium concentrations and result in persistent contraction of vascular smooth muscle cells [16].

Intraoperative mechanical arterial manipulation causing either direct myogenic vasoconstriction or indirect stimulation of the vasa nervorum is perhaps one of the most important surgical factors. Since the 1970s animal studies have shown that direct impact or stretching of arterial vessels can cause immediate vasospasm and this was found to be a predictor for clinically significant DCI after skull base tumor surgery [4] [7] [17]. Despite compelling evidence that extent of GBM resection correlates with a stepwise improvement in overall survival, tumor encasement of the MCA limited aggressive excision in our case [18]. In retrospect, we suggest that exposed arteries be temporarily covered with cottonoids soaked with 3% papaverine solution when prolonged vessel manipulation is performed [19]. Papaverine, an effective phosphodiesterase inhibitor, has been demonstrated to relieve vasospasm and such practice is routinely conducted in our center after aneurysm clip ligation [20].

The management of post-tumor resection DCI presents unique challenges akin to trauma-related vasospasm. In SAH hypertensive and nimodipine therapy have been the mainstay of treatment after securing ruptured aneurysms [21]. In the post-tumor resection setting, as in severe traumatic brain injury, such treatment could aggravate cerebral edema or result in intracerebral hemorrhage. In the past 20 years (1994-2014), 21 cases of vasospasm following intracranial tumor resection treated by hypertensive therapy were identified. Approaching two-thirds of patients (61%) had good neurological outcomes after treatment and is evidence in support of possible clinical efficacy (**Table 1**) [4] [22]-[32]. From a recent review of the components of "triple-H" therapy (hyper-

Table 1. Outcomes of brain tumor patients with postoperative DCI.

Title	Age/ Sex	Pathology	Postoperative Day of Vasospasm Occurrence	Treatment	Outcome	Time of outcome assessment
Afshari 2014	9/F	Hypoglossal nerve Schwannoma	8	(1) IV milrinone and noradrenaline (2) Nimodipine	Full recovery	3 months
Rao 2013	10/F	Posterior fossa medulloblastoma	12	(1) Hypertension up to 165 mmHg (2) Nimodipine	Full recovery	Day 25
Jacob 2011	23/M	Posterior fossa ependymoma	12	(1) HHH (NS) (2) Balloon angioplasty (3) IA verapamil (4) Calcium-channel blocker (NS)	Full recovery	Day 24
Kasliwal 2008	34/F	Pituitary adenoma	13	(1) Hypervolemia (NS) (2) IA papaverine	Mortality	Day 14
Almubaslat 2007	41/F	Esthesioneuroblastoma	11	(1) HHH (NS) (2) Corticosteroid (3) Nimodipine	Homonymous hemianopia	Day 23
Ecker 2003	23/F	Sylvian dermoid cyst	2	(1) HHH (NS) (2) Balloon angioplasty	Mild hemiparesis	7 months
Nishioka 2001	41/M	Pituitary adenoma	12	(1) HHH (NS) (2) IA papaverine (3) Anticoagulation	Full recovery	NS
Bejjani 1999	48/F	Cavernous sinus meningioma	30	(1) HHH (NS) (2) Intraaortic balloon pump (3) Balloon angioplasty	Significant improvement	NS
Bejjani 1999	65/F	Foramen magnum meningioma	15	(1) HHH (NS) (2) Balloon angioplasty	Mortality	NS
Bejjani 1999	50/F	Cavernous sinus meningioma	4	(1) HHH (NS)	Significant improvement	NS
Bejjani 1999	57/M	Petroclival meningioma	1	(1) HHH (NS) (2) IA papaverine	Significant improvement	NS
Bejjani 1999	59/F	Cavernous sinus meningioma	2	(1) HHH (NS)	Significant improvement	NS
Bejjani 1999	50/F	Planum sphenoidale meningioma	1	(1) HHH (NS) (2) Balloon angioplasty	Significant improvement	NS
Chang 1999	45/M	Suprasellar pilocytic astrocytoma	5	(1) HHH (NS) (2) Nimodipine (3) IA papaverine	Aphasia, right hemiparesis	NS
Lee 1998	15 months /F	Posteriorfossa primitive neuroectodermal tumor	21	(1) IV dobutamine (2) IV albumin (3) Nimodipine (4) Anticoagulation	Mortality	5 weeks
Bejjani 1997	6/F	Oculomotor nerve Schwannoma	7	(1) HHH (US) (2) Balloon angioplasty	Full recovery	NS
Cervoni 1996	51/M	Pituitary adenoma	4	(1) Hypervolemia (NS) (2) Nimodipine	Full recovery	2 years
Cervoni 1996	48/F	Pituitary adenoma	5	(1) Hypervolemia (NS) (2) Nimodipine	Mortality	Day 12
Cervoni 1996	38/M	Craniopharyngioma	7	(1) Hypervolemia (NS) (2) Nimodipine	Significant improvement	1 year
Cervoni 1996	44/M	Frontal metastatic adenocarcinoma	5	(1) Hypervolemia (NS) (2) Nimodipine	Mortality	Day 15
Cervoni 1996	51/M	Petroclival meningioma	4	(1) Hypervolemia (NS) (2) Nimodipine	Mortality	Day 10

N.B. IV, intravenous; HHH = hypertension, hypervolemia, hemodilution; NS, not specified; IA, intrarterial.

tension, hypervolemia and hemodilution) on cerebral perfusion in SAH patients, hypertension seemed to be the most effective [33]. Although there is no consensus on how hypertensive therapy should be induced, our experience indicates that elevating mean arterial pressure and systolic blood pressure to at least 20% of preoperative values can attenuate symptoms of DCI. Nimodipine has been demonstrated to improve morbidity in aneurysmal SAH by exerting neuroprotection through unspecified mechanisms and corresponding supportive evidence has also been reported from a multicenter randomized-controlled trial for traumatic brain injury [34] [35]. Although a subsequent pooled analysis of several clinical trials, conducted for patients with traumatic SAH, concluded no difference in poor outcome, we decided to give the benefit of the doubt and administered nimodipine [36].

It was apparent from our case that neuroimaging or Doppler studies are required to guide treatment duration. Our experience suggests that the partial recovery of symptoms is insufficient to presume that vasospasm has resolved and may recur should therapy be stopped prematurely. We recommend that medical management should last for more than a week and discontinued when angiographic, sonographic or perfusion studies are supportive of vasospasm resolution. More aggressive management by pharmacologic or mechanical angioplasty could be an alternative treatment optional though there exists a risk of rupture, especially during balloon dilatation, of the arterial wall potentially weakened by tumor infiltration or previous radiotherapy [1] [4].

4. Conclusion

Delayed cerebral ischemia due to vasospasm after GBM resection is a rare complication. When such lesions are found to encase the MCA one should balance the risks and benefits of greater extent of resection versus excessive vessel manipulation. Any new postoperative neurological deficit that cannot be explained by hemorrhage, seizures or infection should be expeditiously investigated by angiography or transcranial Doppler sonography. Prompt initiation of hypertensive (aiming at least 20% above baseline blood pressures) and nimodipine therapy can partially reverse symptoms. Our case suggests that treatment duration should be guided by imaging studies and not by symptoms alleviation alone.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Abbreviations

CT: computed tomography
 DCI: delayed cerebral ischemia
 GBM: glioblastoma multiforme
 MCA: middle cerebral artery
 MRA: magnetic resonance angiography
 MRI: magnetic resonance imaging
 PDGF: platelet-derived growth factor
 SAH: subarachnoid hemorrhage
 TCD: transcranial Doppler sonography