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Case Report A SCITECHNOL JOURNAL

Acute Hemorrhage Following Gamma Knife Radiosurgery to a Clival Meningioma

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Abstract

Background: Gamma Knife radiosurgery (GKS) is a primary treatment modality for small, surgically-challenging meningiomas of the skull base in carefully selected patients. Despite the overall low incidence of complications from this procedure, rare instances of hemorrhagic events following GKS have been reported. In fact, only a single, probable case of acute hemorrhage after GKS for a meningioma exists in the literature.

Case description: The authors present the case of a 59-year-old female treated with GKS to a clival meningioma who suffered an acute intra- and peritumoral hemorrhage within three hours after the procedure. The patient also had an ST-elevation myocardial infarction associated with the hemorrhage. At the time of her GKS she was taking aspirin and clopidogrel for treatment of coronary artery disease with multiple cardiac stents. Cerebral catheter angiography failed to reveal a source for the hemorrhage.

Conclusion: Acute hemorrhage following GKS to a meningioma is a rare, but potentially serious, complication and consideration should be given to counseling patients of this risk prior to treatment. We hypothesize that acute change to the structural integrity of the vascular endothelium after GKS may have precipitated cerebrovascular dysfunction resulting in hemorrhage. While the administration of anti-platelet therapy may have been a contributing factor to his event, it appears that the low incidence of acute tumoral bleeding after GKS does not justify routinely discontinuing anti-platelet and/or anti-coagulation in patients with severe associated medical co-morbidities.

Keywords

Intratumoral hemorrhage; Subarachnoid hemorrhage; Gamma knife; Radiosurgery; Meningioma

Introduction

Gamma Knife radiosurgery (GKS) is an effective therapy for small (<3 cm) meningiomas of the skull base in medically-complex patients for whom open surgery carries an unacceptable risk of morbidity and mortality [1]. While infrequent, hemorrhagic events after GKS do occur. To date, nine cases of intratumoral hemorrhage after GKS for meningiomas have been reported in the literature, with eight occurring in a delayed fashion [2-5]. and one manifesting acutely [6]. The risk of post-GKS hemorrhage in the setting of anti-platelet/anti-coagulant therapy is currently unknown, with a paucity of information/recommendations available in the literature. In this case report and literature review, the authors present a patient who suffered an intra- and peritumoral hemorrhage three hours following GKS. The patient was taking aspirin (81 mg PO daily) and clopidogrel (75 mg PO daily) for multiple coronary stents. Cerebral catheter angiography was negative for any evidence of aneurysm, vascular malformation, cortical thrombosis, or abnormal tumor vascularity. Here, we discuss the significance of our observation and propose potential mechanisms to explain this rare phenomenon.

Case Report

A 59-year-old, right-handed female with a history of hyperlipidemia and coronary artery disease status-post six prior coronary stenting procedures (on aspirin 81 mg PO daily and clopidogrel 75 mg PO daily) was referred to the neurosurgery clinic at Barnes-Jewish Hospital for evaluation of a clival-based mass. The lesion was discovered incidentally on neck computed tomography (CT) imaging for evaluation of a thyroid nodule. A non-contrast head CT was performed showing an isodense, extra-axial, skull-based mass ventral to the pons with mass effect on the brainstem (Figure 1A). The lesion avidly enhanced following contrast administration on CT images (Figure 1B). T1-weighted magnetic resonance imaging (MRI) sequences after gadolinium administration demonstrated a homogenously enhancing, dural-based, clival mass most consistent with a meningioma (Figures 2A-2C). Additional MR angiographic studies failed to reveal an aneurysm, a vascular malformation, or any evidence of tumor hypervascularity (Figure 2D).

The patient noted a several-year history of worsening hearing, horizontal diplopia (worse on lateral gaze), and gait instability. On physical examination, she was awake, alert, and fully oriented. Her speech was slow and dysarthric. Her cranial nerves were intact with the exception of decreased hearing bilaterally (left>right). Motor and sensory examinations were normal. No signs of myelopathy were present. Her gait was wide-based, but stable. The patient and family were counseled regarding the natural history of meningiomas and treatment options including conservative therapy (observation) or radiation therapy (fractionated versus GKS). Open surgery was not offered given her minimal symptoms, significant medical co-morbidities, and age. She wished to have the tumor treated and agreed with the recommendation for GKS.

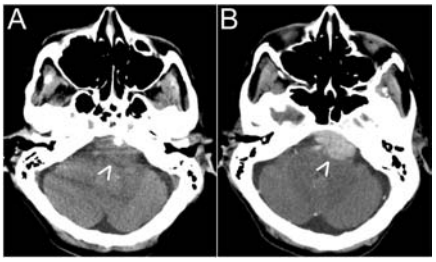

Figure 1: Axial section from a non-contrast head CT (A) demonstrates an isodense, extra-axial, clival-based mass centered in the left pre-pontine cistern with mass effect on the pons. Following contrast administration (B), the lesion shows avid, homogenous enhancement.

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MRI at the time of treatment demonstrated the 3.4×1.9 centimeter clival mass. The volume of the contoured tumor was 9.8 cubic centimeters. The target was treated with 14 Gy of radiation at the 50% prescription isodose line (Figure 3). The 50% prescription isodose line encompassed 98% of the target. Radiation to the brainstem was minimized with dynamic planning using the Gamma Knife software with the Perfexion Gamma Knife unit. The patient remained normotensive throughout her treatment and no intra-procedural complications were noted. Immediately after GKS and at her time of discharge, she was asymptomatic and at her neurological baseline.

Three hours after GKS, the patient experienced worsening confusion which rapidly progressed to obtundation. She was evaluated at a local institution where an electrocardiogram revealed an anteroseptal ST-elevation myocardial infarction. Initial troponin level was 4 ng/mL. Platelet count and coagulation profile were within normal limits. A non-contrast head CT showed intra- and peritumoral hemorrhage with a diffuse subarachnoid component within the basilar cisterns, left Sylvian fissure, and left temporal lobe sulci (Figure 4). Minimal hemorrhagic sediment was present in the fourth ventricle. She was intubated for airway protection and transported to our facility.

Upon arrival, the patient did not open her eyes to painful stimuli, regard the examiner, or follow commands. She demonstrated minimal pupillary reactivity on the left. Cough, gag, and oculocephalic reflexes were present. She localized briskly to painful stimuli with her left upper extremity and withdrew all other extremities to pain. High-dose dexamethasone therapy was initiated for cerebral edema. Her full-dose aspirin was continued; clopidogrel was held. A four-vessel cerebral catheter angiogram performed the following morning showed no evidence of aneurysm, vascular malformation, venous thrombosis, vasculitis, or abnormal tumor blush (Supplementary Figures 1A-1J).

With conservative therapy, she improved neurologically and was extubated 48 hours later. On subsequent neurological assessments, she was noted to have bilateral sixth nerve palsies and left peripheral seventh nerve palsy. She ultimately required a gastrostomy tube for nutrition. At discharge, she was fully awake, alert, and oriented. While her cranial nerve deficits persisted, her dysarthria resolved and she regained full motor strength. She was transferred to a rehabilitation facility on post-hemorrhage day eight.

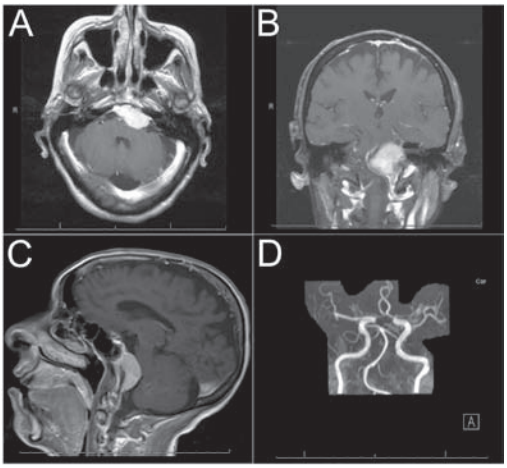

Figure 2: T1-weighted brain MRI imaging after gadolinium administration demonstrates a homogeneously-enhancing, dural-based, extra-axial mass in the region of the clivus. Axial (A), coronal (B), and sagittal (C) images are shown. The tumor fills the left pre-pontine cistern and exerts mass effect on the pons. MR angiography (D) shows no evidence of aneurysm, vascular malformation, or abnormal tumor vascularity.

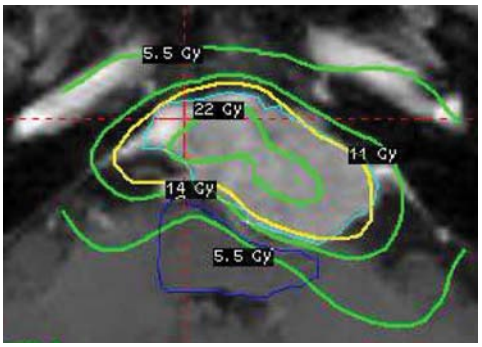

Figure 3: Brain MRI depicting GKS treatment plan. The clival mass measures 3.4×1.9 centimeters in maximal diameter. The tumor target was treated with 14 Gy at the 50% isodose line. The 50% prescription isodose line encompassed 98% of the contoured target (yellow line).

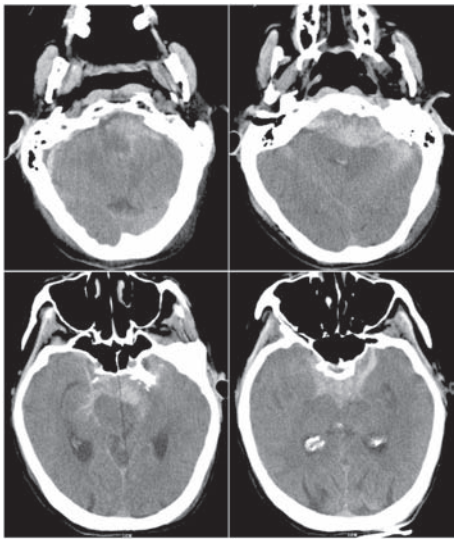

Figure 4: Axial sections from a non-contrast head CT taken three hours after GKS shows diffuse intra- and peritumoral hemorrhage with extratumoral extension into the subarachnoid space. Subarachnoid hemorrhage is present within the basilar cisterns, left Sylvian fissure, and left temporal lobe sulci. A small amount of blood is noted in the fourth ventricle as well, with a resultant mild increase in ventricular size.

The patient returned to clinic 6 months after her initial hemorrhage. She was now residing at home with 24-hour assistance. She exhibited modest neurological improvement. Mild residual cranial nerve deficits were again noted. The patient did not participate in any formal disability evaluation after her hemorrhage.

Discussion

Hemorrhagic complications following GKS for intracranial meningiomas are rare. It has been reported that the spontaneous peritumoral hemorrhage rate (e.g., number of cases of spontaneous hemorrhage per total follow-up time) in patients with untreated meningiomas occurs in ~1.3-2.7% of cases [7,8]. In their series of 173 patients with meningiomas treated by GKS, Kwon et al. [4] observed a rate of hemorrhage of 2.3%. Given that the spontaneous

rate of hemorrhage associated with meningiomas is similar to the rate of hemorrhage after GKS, the authors concluded that GKS does not significantly increase the incidence of hemorrhagic complications. This study did not examine the potential influence of anti-platelet therapy on the incidence of post-GKS hemorrhage.

To date, nine cases of hemorrhage following GKS for intracranial meningiomas have been documented in the literature. As mentioned above, Kwon et al. [4] reported four patients that suffered intratumoral hemorrhages in a delayed fashion after initial GKS (Table 1). Only one patient experienced a symptomatic hemorrhage (cranial nerve deficit), while the remaining cases were discovered incidentally on follow-up MR imaging. Mangubat et al. [5] contributed an additional case of symptomatic hemorrhage associated with a petroclival meningioma four years after GKS (Table 1). This patient had a previous open surgery one year prior to GKS that was aborted secondary to intraoperative bleeding and loss of somatosensory-evoked and brainstem auditory-evoked responses. Kim et al. [3] reported apoplectic symptomatic onset of intratumoral hemorrhage in a large, tentorial-based meningioma three years following GKS. This patient subsequently required an emergency craniotomy and tumor resection. In addition, Iwai et al. [2] described two patients with intratumoral hemorrhage following GKS to skull base meningiomas. In their series, the authors did not report precise tumor location, tumor volume, irradiation dose, or the temporal relationship between GKS treatment and symptom onset in those patients who experienced hemorrhage.

Su et al. [6] documented a single case of acute intratumoral bleeding in a recurrent anterior falcine meningioma three hours after GKS. To our knowledge, this is the only previous report of symptomatic hemorrhage in the immediate post-GKS period. While the previously reported case likely represents a true acute intratumoral hemorrhage, multiple points are worthy of discussion. First, the non-contrast head CT provided by the authors demonstrated a mildly hyperdense area within the tumor mass after GKS. However, there was no pre-treatment head CT available that could have excluded the possibility of a spontaneous bleed prior to GKS or calcification within the tumor bed. Similarly, a post-hemorrhage MRI scan was not obtained to better delineate the presence of blood. The authors speculated that GKS-induced occlusion of the superior sagittal sinus with subsequent venous infarction may have been responsible for the hemorrhage. Notably, no further imaging studies were performed to verify a venous sinus occlusion or infarct. As such, the precise mechanism of hemorrhage in this case remains enigmatic.

Several authorities have identified risk factors that may influence spontaneous intratumoral bleeding in meningiomas [9,10]. These risk factors include patient age (<30 or >70 years), tumor location (convexity and intraventricular), and histopathology (microcysts, necrosis, high proliferation rate). Other potential risk factors may also include hypertension, head injury, and the use of antiplatelet and/or anticoagulant therapy [9,11,12]. The use of antiplatelet medication is particularly relevant to our patient given that she was currently taking dual antiplatelet medication for multiple cardiac stents. Certainly, lack of a normal platelet plug secondary to aspirin/clopidogrel-mediated platelet dysfunction could have contributed to the hemorrhage. Given the available data on risk factors for hemorrhage following GKS for meningiomas (Table 1), one could speculate that location (petroclival and tentorial), WHO grade (II-III), and higher prescription dose are all potential factors promoting hemorrhage. However, the number of patients is too small to derive any meaningful conclusions. Furthermore, while the clival-based mass in our patient is likely to be a meningioma based upon its pattern of growth and radiographic features, we do not have histological confirmation of this suspicion.

The etiology of the intra- and peritumoral hemorrhage following GKS in our patient remains unknown. While GKS-induced cerebral aneurysm and pseudoaneurysm formation presenting as a delayed episode of subarachnoid hemorrhage has been reported [13-16], this explanation seems unlikely given the absence of vascular pathology on formal cerebral catheter angiography. By a similar logic, cortical venous thrombosis with subsequent intratumoral hemorrhage is not supported by our cerebral angiogram findings. It is also feasible

Table 1: Data from Patients with Intratumoral Hemorrhage Following *GKS for Meningiomas.

Data from Patients with Intratumoral Hemorrhage Following *GKS for Meningiomas									
No.	**Age in years (Sex)**	**Location**	**Volume (cm^3)**	**Dose (Gy)**	**†WHO grade**	**Time from initial/last GKS to hemorrhage**	**Symptoms**	**Notes**	**References**
1	36 (M)	Caverno-Petroclival	6.0; 16.0	17; 12	NR	8 yrs/1 yr	3rd and 6th cranial nerve palsies	GKS × 2 (tumor recurrence)	[4]
2	34 (F)	Tentorial	1.3	20	III	18 months	None	Hemorrhagic cyst	[4]
3	49 (F)	Tentorial	4.4	20	I	5 yrs	None	Hemorrhagic cyst	[4]
4	63 (M)	Temporal; Planum Sphenoidale	6.4; 1.8	18; 12	II	2 yrs/1 yr	None	GKS × 2 (once for each tumor)	[4]
5	62 (F)	Petroclival	NR	NR	II	4 yrs	Headache, V-XI cranial neuropathies	Initial surgery aborted due to bleeding	[5]
6	52 (F)	Tentorial	9.1	15	I	3 yrs	Apoplexy, headache	Worsening peritumoral edema on serial post-GKS MRI	[3]
7	NR	NR	NR	NR	NR	NR	NR	--	[2]
8	NR	NR	NR	NR	NR	NR	NR	--	[2]
9	39 (M)	Anterior falcine	12.3	15	I	3 hours	Seizure, Headache, Loss of consciousness	Likely due to venous sinus occlusion	[6]
10	59 (F)	Clival	9.8	14	NR	3 hours	Obtundation, hemiparesis	On full-dose aspirin and clopidogrel	This report

*GKS=Gamma Knife Radiosurgery
†WHO =World Health Organization
NR=Not Reported

that our patient experienced either a spontaneous intratumoral hemorrhage with subarachnoid extension or a perimesencephalic subarachnoid hemorrhage [17] caused by tearing of venous structures at the tentorial edge unrelated to GKS. However, the close temporal association of the bleeding event with GKS suggests a different underlying mechanism. Furthermore, both the severity of our patient's clinical presentation and the presence of hemorrhage within the tumor mass are inconsistent with a benign form of subarachnoid hemorrhage. Finally, a less likely explanation for our observation is that intra- and peri-tumoral hemorrhage occurred coincidentally following GKS.

It has been shown in murine models that vascular endothelium is exquisitely sensitive to ionizing radiation [18]. Within hours after radiation treatment, biochemical and mechanical changes occur within the cell leading to disruption of the basement membrane and progressive luminal obstruction [19]. In canine femoral arteries, endothelial injury was present <48 hours after high-dose irradiation with disruption of cell nuclei, deposition of intimal fibrin, and alteration of vascular architecture [20]. Radiation alters cerebrovascular physiology in rats by reducing cerebral blood flow and volume, increasing blood-brain barrier permeability [21], and impairing cerebral autoregulation [19]. While the mechanism of irradiation-induced damage to the vascular endothelium in humans is not well described, a possible explanation may be that acute changes in the structural integrity of the vascular endothelium may precipitate cerebrovascular dysfunction resulting in hemorrhage.

Conclusion

We present a case of acute hemorrhage following GKS for a clival meningioma. This case adds to the existing literature in which one possible [6] instance of acute post-GKS intratumoral hemorrhage has been described. While the mechanism underlying our patient's hemorrhage is unknown, we speculate that acute GKS-induced changes to the vascular endothelium may play a contributing role. Based on the rare reported association of acute peritumoral hemorrhage after GKS for meningiomas, we believe it is premature to routinely discontinue anti-platelet/anti-coagulation therapy in this patient population. In many patients with significant medical comorbidities, the risk of withholding anti-platelet/anti-coagulation therapy is likely greater than the risk of hemorrhagic complications after GKS. However, consideration may be given to withholding these agents if the medical risk is deemed acceptably low.

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