Thrombosis and hemorrhage in the acute period following Gamma Knife surgery for arteriovenous malformation

Case report

JUANITA M. CELIX, M.D.,1 JAMES G. DOUGLAS, M.D.,1,2 DAVID HAYNOR, M.D.,3 AND ROBERT GOODKIN, M.D.1,2

Departments of 1Neurological Surgery, 2Radiation Oncology, and 3Radiology, University of Washington, Seattle, Washington

Bleeding of an arteriovenous malformation (AVM) following stereotactic radiosurgery (SRS) is a known risk during the latency interval, but hemorrhage in the 30-day period following radiosurgery rarely has been reported in the literature. The authors present the case of a 57-year-old man who underwent Gamma Knife surgery for a large AVM, and they provide radiographic documentation of a thrombus in the primary draining vein immediately preceding an AVM hemorrhage within 9 days after radiosurgery. They postulate that the pathophysiology of an AVM hemorrhage in the acute period following SRS is related to an association among tissue irradiation, acute inflammatory response, and vessel thrombosis.

The authors also review the literature on risk factors for hemorrhage due to untreated and radiosurgically treated AVMs. Recent evidence on the role of inflammation in the pathogenesis of AVMs and the pathophysiology of AVM rupture is presented. Inflammatory markers have been demonstrated in brain AVM tissue, and the association between inflammation and AVM hemorrhage has been established. There is an acute inflammatory response following tissue irradiation, resulting in structural and functional vascular changes that can lead to vessel thrombosis. Early hemorrhage following radiosurgical treatment of AVMs may be related to the acute inflammatory response and associated vascular changes that occur in irradiated tissue. In the first stage of a planned 2-stage Gamma Knife treatment for a large AVM in the featured case, the superior posteromedial portion of the primary draining vein was included in the treatment field. The authors present the planning images and subsequent CT scans demonstrating a new venous thrombus in the primary draining vein. An acute inflammatory response following radiosurgery with resultant acute venous thrombus formation and venous obstruction is proposed as one mechanism of an AVM hemorrhage in this patient. Radiographic evidence of the time course of thrombosis and hemorrhage supports the hypothesis that acute venous obstruction is a cause of intracranial hemorrhage. (DOI: 10.3171/2009.1.JNS08784)

**Key Words** • arteriovenous malformation • Gamma Knife • hemorrhage • stereotactic radiosurgery • thrombosis

**Abbreviations used in this paper:** AVM = arteriovenous malformation; GKS = Gamma Knife surgery; IL = interleukin; SRS = stereotactic radiosurgery; TNF = tumor necrosis factor.
There have been a few more documented cases of AVM hemorrhage within 4–30 days after SRS; with the exception of data in a case of AVM rupture 29 days post-SRS, the clinical and radiographic details of the remaining cases are not known.

We describe the clinical and radiographic details of a patient who underwent GKS for a large AVM and in whom a venous thrombus and an AVM hemorrhage developed within 9 days after SRS. We are the first authors to provide radiographic documentation of a venous thrombus immediately preceding intracranial hemorrhage, and we postulate that the pathophysiology of an AVM rupture in the acute period following SRS differs from that of a rupture occurring months later. A possible mechanism of AVM rupture in the acute period following SRS is also discussed.

**Case Report**

**History and Examination.** This 57-year-old right-handed man with a history of chronic alcohol use presented to the emergency department of another hospital following a witnessed seizure that was not characterized. Initial noncontrast CT studies revealed a poorly defined region of increased attenuation in the right posterior temporal lobe that was suspicious for an AVM, although there was no evidence of acute hemorrhage. The patient was referred to our institution for further evaluation and treatment. Both a CT angiogram and conventional 4-vessel cerebral angiogram demonstrated a large right temporoparietal AVM (Fig. 1).

**Treatment.** Options for treatment were reviewed with the multidisciplinary SRS team. Given the size and morphological features of the AVM, the case was considered to be high risk for resection. Planned treatment of this large racemose AVM consisted of 2 staged GKS treatments at 6-month intervals. At the first treatment, after 3D spoiled gradient recalled (SPGR) MR images, CT angiograms, and cerebral angiograms were acquired and transferred to the treatment-planning computer (GammaPlan, version 5.34, Elekta), the AVM volume was delineated. The total AVM volume was 29.1 cm³. The superior one-half of the AVM volume, ~ 16.9 cm³, was targeted. The first Gamma Knife treatment consisted of seven 18-mm and eight 8-mm coliminator isocenters with a prescription dose of 18 Gy to the 50% isodose line (Fig. 2). Ninety-five percent of the superior AVM volume, ~ 16.9 cm³, was targeted. The first Gamma Knife treatment consisted of seven 18-mm and eight 8-mm collimator isocenters with a prescription dose of 18 Gy to the 50% isodose line.

**Posttreatment Course.** The procedure was uncomplicated, and the patient was discharged to home the same day with a 5-day course of steroids.

Eight days after GKS the patient awoke in the early morning with a gustatory, olfactory, and auditory aura that waxed and waned throughout the morning. He presented to his primary care physician, who witnessed the patient...
confirmed. A noncontrast CT scan demonstrated an acute right temporoparietal hemorrhage at the AVM with intraventricular extension (Fig. 3). He was emergently taken to the operating suite where he underwent a right frontoparietal craniectomy and evacuation of the intraparenchymal hematoma. Despite aggressive postoperative care in the neurosurgical intensive care unit, the patient made no neurological recovery, and he died 16 days after the AVM hemorrhage.

Inflammation and AVM Hemorrhage

There is growing evidence that inflammation plays a role in the pathogenesis of AVMs and the pathophysiology of AVM rupture. Increased levels of the inflammatory markers matrix metalloproteinase–9 (MMP-9) and IL-6 have been demonstrated in brain AVM tissue. Interleukin-6 has a role in both physiological and pathological angiogenesis and may be a key factor in the abnormal angiogenesis that characterizes AVMs. Promoter polymorphisms in the gene for the inflammatory cytokine TNF-α have been shown to be associated with an increased risk of new hemorrhage in patients with AVMs, and those in the gene for IL-6 have been shown to be associated with a hemorrhagic presentation.

Discussion

Risk Factors for AVM Hemorrhage

Regarding cases of untreated AVMs, several studies have provided evidence of independent risk factors for AVM hemorrhage, including AVM size, venous drainage characteristics, arterial characteristics, Multiple aneurysms, perforating feeding vessels, and venous outflow compromise are additional factors that have been proposed to influence the risk of hemorrhage in untreated malformations. A history of AVM hemorrhage may also predispose to an increased risk of subsequent bleeding in cases of untreated AVMs.

Observational cohort studies on radiosurgically treated AVMs have provided valuable information on rates of AVM rupture and risk factors associated with AVM hemorrhage during the latency period. Authors have reported the risk of hemorrhage to be 1.2–6.5% per year prior to AVM obliteration. Several of the risk factors for hemorrhage following SRS are different from those associated with bleeding prior to treatment and include patient age, AVM size or volume, radiation dose and coverage, and AVM flow rate.

In the featured case, there were several AVM and radiosurgery characteristics that may have predisposed to lesion rupture. The malformation was large and diffuse, or racemose, and extended from the cortex to the lateral surface of the lateral ventricle, with a volume of 29.1 cm³. It had deep drainage to the internal cerebral veins, and the primary draining vein was ectatic. There were multiple venous aneurysms, the largest measuring 1.7 cm in diameter. The AVM was treated with multiple isocenters at a dose of 18 Gy to the 50% isodose line.

With so few published reports of AVM hemorrhage in the acute period following SRS, little is known about the risk factors for or the mechanisms of such bleeding at that time. To begin to understand potential differences between an AVM hemorrhage in the acute period following SRS and bleeding that occurs months to years after radiosurgery, it is important to comprehend the potential role of inflammation in the pathophysiology of AVMs, the immediate vascular effects of radiation, and how inflammation can result in hemodynamic alterations that influence AVM hemorrhage.

having a generalized seizure. The patient was transported to our institution. Imaging on admission included a noncontrast CT scan that demonstrated the known right temporoparietal AVM as well as findings consistent with a new intraluminal thrombus within the primary draining vein (Fig. 3). Routine medical evaluation for hypercoagulable risk factors failed to reveal any conditions predisposing to intravascular thrombus formation in this patient.

On post-SRS Day 9 the patient became acutely obtunded. A noncontrast CT scan demonstrated an acute right temporoparietal hemorrhage at the AVM with intraventricular extension (Fig. 3). He was emergently taken to the operating suite where he underwent a right frontoparietal craniectomy and evacuation of the intraparenchymal hematoma. Despite aggressive postoperative care in the neurosurgical intensive care unit, the patient made no neurological recovery, and he died 16 days after the AVM hemorrhage.
weeks after irradiation. Changes in vessel caliber and vascular permeability for the first few hours after irradiation and result in phasic dilation and endothelial permeability can occur within cytokine-mediated vascular changes resulting in vasodilation. Models of CNS irradiation have shown that vasculature cause a slowing of blood flow and perivascular changes following irradiation. Endothelial cells are highly radiosensitive, and even low doses of radiation can cause endothelial cell injury and death. Endothelial cell damage coupled with cytokine-mediated functional changes in the vasculature can cause hemodynamic alterations that lead to slowed blood flow and perivascular edema and predispose to stasis and thrombus formation. Independent of this pathway, inflammation and thrombosis are directly linked. Specific cytokines, such as TNF and IL-1, are important mediators of both the inflammatory and coagulation pathways, and there is evidence of the radiation-induced production of TNF-α and IL-1 by microglia and astrocytes. Models for the direct interactions between inflammation and thrombosis have been proposed to explain the association among endothelial injury, the inflammatory response, and thrombus formation. We postulate that one radiation-related factor contributing to AVM hemorrhage in the acute period after radiosurgery may be acute venous thrombus formation associated with the acute inflammatory response of irradiated tissue.

Hemodynamic Alterations and AVM Hemorrhage

Venous thrombosis is a proposed mechanism of intracranial hemorrhage, and there have been reports of venous malformation hemorrhages associated with thrombosis of the draining vein. In these reports, thrombus formation preceding hemorrhage is the hypothesized mechanism based on the presence of both thrombosis and hemorrhage on the same imaging study after hemorrhage; however, none of the reports have provided prehemorrhage imaging studies showing the temporal relationship of thrombosis and hemorrhage. Venous outflow impairment is believed to cause venous hypertension in a retrograde manner leading to elevated intranidal pressure and rupture of abnormal AVM vessels.

In the setting of AVMs, the risk of rupture due to venous stenosis or occlusion and the attendant venous drainage impairment have been debated. The concept of venous outflow restriction and consequent venous overload has been viewed by some as a critical determinant of nidal and perinidal hemodynamics that often precede AVM rupture. Biomechanical models based on electrical network analysis have been developed and used to theoretically evaluate the hemodynamics within an AVM nidus. In a study of the risk of AVM rupture due to venous outflow obstruction, the investigators have found that stenosis or occlusion of a high-flow draining vein is predictive of an AVM rupture. An acute alteration in cerebral hemodynamics following resection of an AVM is a known cause of postoperative hemorrhage. Occlusive hyperemia is one
mechanism of acute postoperative edema and/or hemorrhage due to obstruction of the primary venous drainage. In the setting of venous thrombosis, occlusive hyperemia has been proposed as a mechanism for neurological deterioration after radiosurgery for AVM. Pollock has provided radiographic evidence of acute draining-vein thrombosis after radiosurgery, and he has proposed that hemodynamic alterations not due to acute radiation injury occur in tissue surrounding the AVM and lead to venous outflow impairment and perinidal edema.

**Radiosurgery and Acute AVM Hemorrhage**

The acute inflammatory response following tissue irradiation provides a mechanism for both direct and indirect thrombus formation that could contribute to AVM rupture in the acute period following SRS. Stereotactic radiosurgery can induce an acute inflammatory reaction in the AVM vessels that causes cytokine-mediated vascular changes and endothelial cell injury leading to vessel thrombosis. Acute venous thrombus formation preceding intracranial hemorrhage is a physiologically sound etiological mechanism with support based on imaging of concurrent thrombus and hemorrhage. After a review of the English-language literature, we found no radiographic demonstration of acute venous thrombosis prior to intracranial hemorrhage; however, in the present case, we provide such radiographic evidence.

The radiographic determination of intravascular thrombus is based on density characteristics on CT and signal intensity characteristics on MR imaging. In the present case, calculations of the density of the draining vein, the large venous aneurysm, and the surrounding white matter immediately preceding intracranial hemorrhage were performed, and results were compared with the density values from the same regions prior to GKS (Fig. 3). Before Gamma Knife treatment, the density of the venous structures (draining vein and venous aneurysm) was normal, whereas immediately prior to intracranial hemorrhage the density of the draining vein was significantly increased, which is consistent with thrombus formation in the vein. Although spontaneous venous thrombosis occurs, in the setting of GKS the influence of radiation on the vasculature must be considered. As shown in Fig. 2, the superior postero medial aspect of the primary draining vein was included in the Gamma Knife treatment field. Intraluminal attenuation consistent with intravascular thrombus formation occurred at the superior postero medial aspect of the primary draining vein corresponding with the portion of the vein in the treatment field.

Complications are rare in the acute 30-day period following SRS for any lesion, and there is limited evidence of complications within this period. Reports of seizures and neurological deficits due to cerebral edema are more common than reports of intracranial hemorrhage. Venous thrombosis and outflow obstruction associated with a radiation-induced acute inflammatory reaction are very likely events, with clinical consequences ranging from none to edema and neurological deficits to rare devastating thrombosis and hemorrhage.

Clinically, the complications of increased endothelial permeability and altered vessel caliber that characterize the acute inflammatory reaction following SRS are most commonly manifest through the development of vasogenic cerebral edema rather than thrombus formation. Vasogenic edema begins within hours after irradiation, but symptomatic edema may not be evident for days or months, or the edema may never become symptomatic. At our institution, this acute complication of radiosurgery is, in most cases, treated prophylactically with glucocorticoid dexamethasone starting before SRS and continuing for 5 days after surgery. Although the short-term use of corticosteroids does not usually require tapering of the medication, a known complication of the abrupt discontinuation of steroids is rebound edema. There has been evidence from animal studies showing increased permeability of the cerebral endothelium after stopping glucocorticoid therapy. It is unknown in which patients an abrupt cessation of corticosteroids will cause rebound edema or with what frequency rebound edema occurs. The patient in the present case received a course of prophylactic glucocorticoids that is typical for those undergoing GKS at our institution. The venous thrombus and subsequent hemorrhage in the acute period following SRS occurred 4 days after ceasing the glucocorticoid therapy. It is possible that our patient experienced a rebound inflammatory response after the discontinuation of dexamethasone that manifested as altered blood flow and venous thrombosis.

Arteriovenous malformation rupture is an uncommon event. In the setting of radiosurgery there exists the real chance that thrombus formation and subsequent hemorrhage are unrelated to vessel irradiation. The cause of venous thrombus formation and AVM hemorrhage in our patient is not definitively known. We provided radiographic documentation of a venous thrombus in the primary draining vein immediately preceding AVM hemorrhage and proposed a mechanism for how it may have been related to recent radiosurgery. The temporal relationship among radiosurgery, venous thrombosis, and AVM hemorrhage prompted us to evaluate a possible connection. There is a paucity of histopathological AVM studies and essentially no studies on the early affects of radiation on human tissue, either normal or abnormal. This deficiency is certainly attributable to the general difficulty in obtaining human tissue for study. The proposed mechanism for thrombus formation in the patient in the featured case is based on current scientific evidence on the association among tissue irradiation, the acute inflammatory response, venous thrombus formation, and hemorrhage. Future studies of thrombosis in AVM veins, the response of normal and abnormal vasculature to irradiation, and the role of inflammation in the pathophysiology of AVM rupture will help to answer many of the questions raised here.

**Conclusions**

A risk of AVM hemorrhage following SRS persists during the latency interval. The pathophysiology of AVM rupture in the acute 30-day period after radiosurgery may be related to the acute inflammatory response of irradiated vessels, resulting in venous thrombus formation. This proposed mechanism of venous outflow obstruction...
leading to AVM hemorrhage after radiosurgery is supported by laboratory evidence and suggested by clinical evidence. We have provided radiographic documentation to support the hypothesis of venous thrombus formation and acute venous outflow obstruction immediately preceding intracranial hemorrhage, and we postulate that the origin of AVM hemorrhage in the acute period following SRS may be different from bleeding that occurs months to years after radiosurgery.

Disclosure

Robert Goodkin, M.D., is a consultant for Elekta.

References

36. Inoue HK, Ohye C: Hemorrhage risks and obliteration rates of


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100. Zipfel GJ, Bradshaw P, Bova FJ, Friedman MA: Do the morphological characteristics of arteriovenous malformations affect the results of radiosurgery? *J Neurosurg* 101:393–401, 2004


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Address correspondence to: Robert Goodkin, M.D., Department of Neurological Surgery, Harbovview Medical Center, University of Washington, 325 Ninth Avenue, Box 359924, Seattle, Washington 98104-2499, email: goodkin@u.washington.edu.