The Laryngoscope

Clinically Significant Intratumoral Hemorrhage in Patients With Vestibular Schwannoma

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Objectives: The frequency of intratumoral hemorrhage (ITH) in vestibular schwannoma (VS) remains undefined.

Methods: Retrospective case series of all patients diagnosed with hemorrhagic VS between 2003 and 2015 at a single tertiary academic skull base center.

Results: Five patients with ITH were evaluated, representing 0.4% of all newly diagnosed VS evaluated at the authors' center during this time. The median age at time of diagnosis was 66 years (range 39–83), four of five cases occurred in men, and all had sporadic unilateral tumors. The frequency of ITH among patients receiving anticoagulation was 5.6% (2 of 36), compared to only 0.2% (3 of 1356) in non-anticoagulated patients ($P = 0.006$), representing a 25-fold increase.
At time of hemorrhage, all patients had acute onset of headache, disequilibrium, and progression of hearing loss; three reported trigeminal symptoms, and two exhibited acute moderate facial paresis. The median tumor size at diagnosis of hemorrhage was 3.1 cm (range 2.4–4.2 cm), and three patients had radiological evidence of hydrocephalus. All patients underwent microsurgical resection. There were no perioperative deaths. At a median follow-up of 25 months (3–70 months), no patient has experienced tumor recurrence.

Conclusion: Tumor-associated hemorrhage in VS occurs in 0.4% of cases and commonly presents with acute neurological change. The risk of clinically significant hemorrhage is greater in patients receiving anticoagulation compared to the general VS population. Prompt microsurgical resection should be pursued when possible since tumor removal may improve neurological symptoms, relieve brainstem compression, and reduce the risk of repeat hemorrhage.

Key Words: Vestibular schwannoma, acoustic neuroma, microsurgery, skull base surgery, anticoagulation, warfarin, hemorrhage, intratumoral hemorrhage, subarachnoid hemorrhage.

Level of Evidence: 4.

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INTRODUCTION

Vestibular schwannoma (VS) represent 8% of all primary intracranial neoplasms and greater than 80% of tumors involving the cerebellopontine angle (CPA) and internal auditory canal (IAC).[1] The majority of VSs present with insidious onset unilateral hearing loss, tinnitus, and imbalance, prompting intracranial imaging. Natural history studies demonstrate that more than half of all VSs do not grow over extended periods of follow-up, whereas the growth rate for tumors exhibiting radiological progression is typically 1 to 2 mm per year.[2,3] Although most VSs exhibit an indolent clinical course, a subset of patients experience acute neurological deterioration associated with rapid solid or cystic tumor growth, or much less commonly, acute intratumoral hemorrhage (ITH).[4–7]

The development of intracranial hemorrhage in primary and metastatic brain tumors is a well-described phenomenon; however, the incidence and clinical course of ITH in VS remains understudied.[7–11] Additionally, the literature demonstrates that the rate of spontaneous and anticoagulation-associated hemorrhage varies significantly by tumor type.[12–14] Understanding the risk and consequences of ITH with systemic anticoagulation is valuable toward patient counseling. Furthermore, such knowledge may help optimally balance the risk–benefit ratio of systemic anticoagulation against other treatment alternatives. Herein, the authors investigate the frequency of clinically significant ITH in a large cohort of patients with previously untreated VS at a single institution. Details regarding the clinical course of five index patients are outlined, and the rate of spontaneous and anticoagulation-associated hemorrhage is compared.

MATERIALS AND METHODS

Following institutional review board approval (15-005543), a prospective VS clinical database was queried, and all patients

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TABLE I.
Baseline Patient Demographics and Disease Presentation.

Case	Sex	Age	Preexisting VS Diagnosis?	Risk Factors	Symptoms
1	M	39	N	AntiCoag (INR 2.8), HTN	HA, Diz, HL, ataxia, hemiparesis
2	M	66	N	HTN	HA, Diz, HL, ataxia, hypoesthesia
3	M	68	N	AntiCoag (INR 2.3), HTN	HA, Diz, HL, FN paresis (HB 4), hypoesthesia
4	F	72	N	HTN	HA, Diz, HL, ataxia, hemiparesis, hypoesthesia
5	M	61	Y	None	HA, Diz, HL, FN paresis (HB 4)

AntiCoag = anticoagulation; Diz = dizziness; F = female; FN = facial nerve; HA = headache; HB = House-Brackmann; HL = hearing loss; HTN = hypertension; INR = international normalized ratio; M = male; N = no; VS = vestibular schwannoma; Y = yes.

with a documented history of clinically significant ITH were identified. Specifically, only subjects with acute change in symptoms and radiological evidence of ITH with or without subarachnoid hemorrhage were included. Patients with prior treatment were excluded. Details regarding baseline patient demographics, presenting symptoms, comorbidities, systemic anticoagulation (i.e., warfarin, heparin, dabigatran, rivaroxaban, apixaban, and edoxaban), tumor characteristics, radiological findings, treatment strategy, and clinical outcome were reviewed. Facial nerve function was reported according to the House-Brackmann (HB) grading system, and hearing capacity was presented according the American Academy of Otolaryngology–Head and Neck Association reporting guidelines.[15,16] Gross total resection (GTR) was specified when all visible tumor was removed, and near-total resection (NTR) was specified when less than a $2 \times 5 \times 5$-mm pad of adherent tumor was intentionally left in situ in order to preserve facial nerve integrity or minimize the risk of stroke. Subtotal resection (STR) was designated when any tumor remnant greater than NTR was left.[17] Data were presented using the median and range or frequency count and percentage. The Fisher's exact test was used to compare rates of ITH between populations. P values less than 0.05 were considered statistically significant.

RESULTS

Five VS with clinically significant ITH were evaluated between 2003 and 2015, representing 0.4% of all newly diagnosed VS evaluated at the authors' center during this time. The median age at time of ITH was 66 years (range 39–83 years), four of five cases occurred in men, and all had sporadic unilateral tumors. Four patients reported a history of hypertension, and none reported antecedent trauma. In total, two of five were taking anticoagulation at time of hemorrhage. Of these, the first patient was a 39-year-old man who had been on warfarin for over 9 years for treatment of a complex cardiac condition involving an atrial septal defect, hypertrophic nonobstructive cardiomyopathy, and severe pulmonary hypertension. At time of hemorrhage, the international normalized ratio (INR) was 2.8. The second patient was a 68-year-old diabetic man with hypertension, on long-term low dose aspirin, who was started on warfarin and enoxaparin only 2 weeks earlier for treatment of pulmonary embolism. At the time of hemorrhage, the INR was 2.3. None of the remaining three patients were receiving antiplatelet or anticoagulation therapy at the time of presentation (Table I). During the study period, 36 of 1,392 (2.6%) newly evaluated VSs were receiving systemic anticoagulation at the time of consultation. Thus, the frequency of ITH among patients receiving anticoagulation was 5.6% (2 of 36), compared to only 0.2% (3 of 1356) in non-anticoagulated patients ($P = 0.006$), representing a 25-fold increased risk.

The median tumor size at diagnosis of hemorrhage was 3.1 cm (range 2.4–4.2 cm), three patients had radiological evidence of hydrocephalus, two tumors exhibited macrocystic features, and two demonstrated moderate peritumoral vasogenic edema. Imaging features of intratumoral and subarachnoid hemorrhage included focal areas of precontrast T1-hyperintense signal within the tumor in two cases, hypointense T2 signal within the tumor in four cases, blood sediment in the lateral ventricles in three cases, and fluid–fluid levels within tumoral cysts in one case (Table II) (Figs. 1–4). Three of five patients had preoperative head computed tomography (CT) imaging available for review, demonstrating intratumoral hyperintensity on noncontrast CT consistent with acute blood product.

Only one of the five index patients had a known diagnosis of VS prior to hemorrhage despite harboring relatively large tumors, whereas the remaining four experienced acute neurologic change from tumor hemorrhage as their heralding presentation. The single patient with a preexisting diagnosis of VS was a 61-year-old man who presented to an outside facility 2 years prior with a 1-cm VS. Between his second and third surveillance scan, separated by 15 months, the tumor demonstrated rapid cystic expansion to 2.4 cm with accompanying ITH. At time of hemorrhage, all patients had acute onset of headache, disequilibrium, and progression of hearing loss to nonserviceable hearing, three reported trigeminal symptoms, and two exhibited acute moderate facial paresis (both HB grade 4 of 6).

All five patients underwent microsurgical resection, three via retrosigmoid craniotomy and two through a translabyrinthine approach. Two of the three patients with hydrocephalus had external ventricular drain placement prior to tumor resection for control and monitoring of perioperative intracranial pressure. Three received GTR, whereas two were managed with aggressive STR, where over 95% of the tumor volume was removed. In one patient with a 4.3-cm VS,

TABLE II.
Tumor Characteristics and MRI Features Associated With Hemorrhage.

Case	Tumor Size (cm)	Hydrocephalus	Macrocystic	Fluid-Fluid Level	T1-Signal	T2-Signal	Vasogenic Edema	Blood in Lateral Ventricles
1	4.2	Y	N	N	Hyper	Hypo	Y	N
2	2.4	N	N	N	Iso	Hypo	N	Y
3	3.1	Y	Y	Y	Iso	Iso	Y	Y
4	3.5	Y	N	N	Hyper	Hypo	N	Y
5	2.4	N	Y	N	Iso	Hypo	N	N

cm = centimeters; Hyper = hyperintense; Hypo = hypointense; Iso = isolated; N = no; Y = yes.

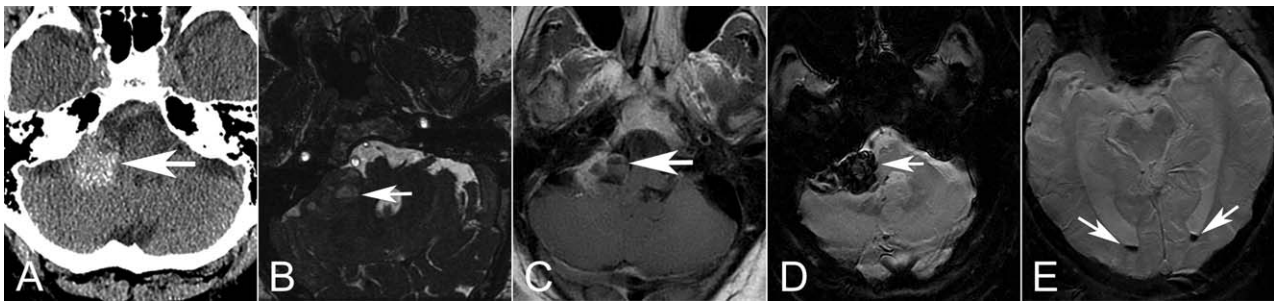

Fig. 1. A 68-year-old man, with a history of hypertension and on anticoagulation, presented with acute headache, vertigo, facial paresis, and diplopia. (A) Axial computed tomography without contrast demonstrates increased attenuation within the vestibular schwannoma consistent with intratumoral hemorrhage (arrow). (B) Axial FIESTA image demonstrates hematocrit level (arrow) within cystic portion of the large vestibular schwannoma. (C) Axial T1 image with contrast reveals a nonenhancing cystic portion of tumor with fluid level (arrow). (D) Axial SWI demonstrates marked hypointense signal (arrow) within the tumor consistent with hemorrhage. (E) Axial SWI image at level of occipital horns of the lateral ventricles demonstrates dependent layered hemorrhage (arrows).
SWI = susceptibility-weighted image.

hydrocephalus, and significant peritumoral edema, the facial nerve plane was poor and facial nerve continuity was ultimately lost during surgery.

Histological sections from all five cases were available for review. In all cases, there were well-preserved areas showing diagnostic features of schwannoma (Fig. 5A). In close association with these were areas of hemorrhage (* in Fig. 5B) and golden-yellow hematoidin pigment (arrowhead in Fig. 5B), indicating recent hemorrhage and early hemoglobin breakdown, respectively. Other areas also showed dark-brown hemosiderin pigment within macrophages and in the stroma (Fig. 5C), indicating hemoglobin breakdown in older episodes of hemorrhage.

Of the two patients with preoperative HB grade 4 paresis, one has recovered normal function over the course of 25 months following surgery, whereas the second patient has HB 4 paresis at his 9-month postoperative appointment, with long-term outcome pending. Two patients with preoperative hydrocephalus exhibited persistent postoperative hydrocephalus and required ventriculoperitoneal

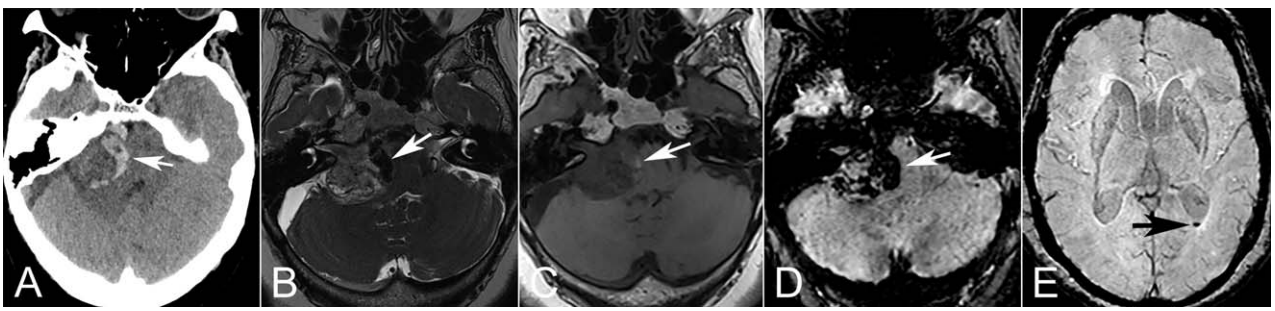

Fig. 2. A 72-year-old woman with hypertension presented with acute headache, nausea, vomiting, and lower extremity weakness. (A) Axial noncontrast computed tomography shows crescent-shaped intratumoral hemorrhage on medial aspect of VS (arrow). (B) Axial 3D T2 fast spin echo image demonstrates marked T2 hypointensity (arrow) along the medial margin of the large VS consistent with hemorrhage. (C) Axial 3D T1 fast spin echo image demonstrates punctate focus of T1 hyperintensity (arrow) consistent with hemorrhage. (D) Axial SWI demonstrates extensive hypointense signal (arrow) confirming presence of hemorrhage identified on T2 and T1 sequences. (E) Axial SWI image at level of the atria of the lateral ventricles demonstrates layered intraventricular hemorrhage (arrow).
3D = three-dimensional; SWI = susceptibility-weighted image; VS = vestibular schwannoma.

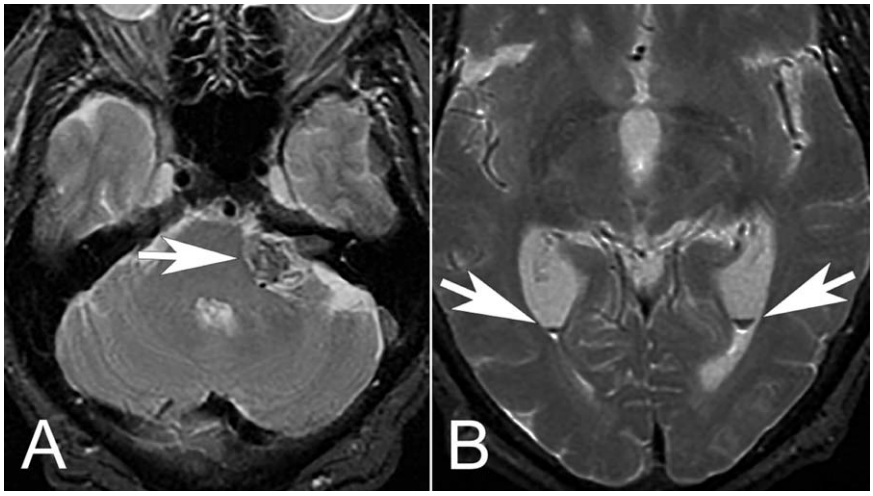

Fig. 3. A 66-year-old man with long-standing hypertension who presented with acute headache, vertigo, facial hypoesthesia, and hearing loss. (A) Axial T2 image demonstrates multifocal areas of hypointense signal within the left vestibular schwannoma (arrow) consistent with hemorrhage. (B) Axial T2 image at level of occipital horns of the lateral ventricles demonstrates layered intraventricular blood products (arrow).

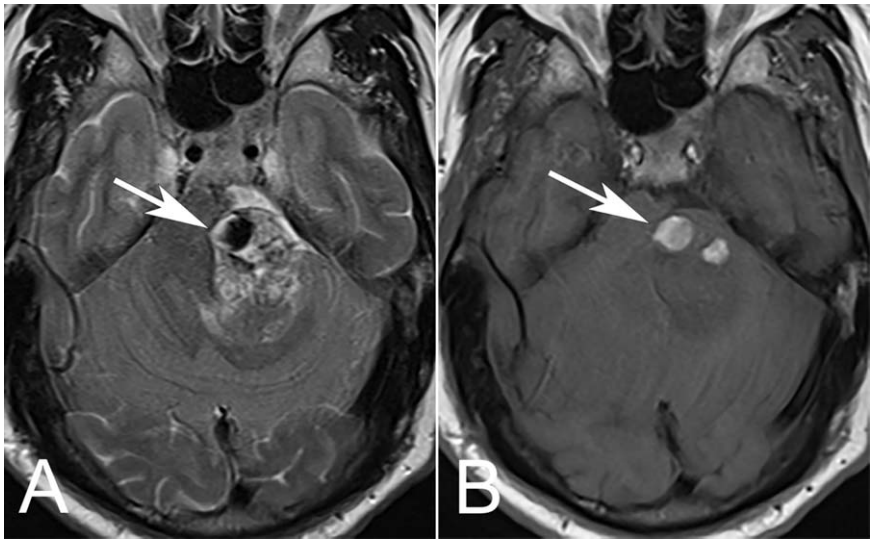

Fig. 4. A 39-year-old man on long-term anticoagulation presented with headache, ataxia, hearing loss, and mild right-sided hemiparesis resulting in falls. (A) T2 image demonstrates focal T2 hypointensity (arrow) consistent with intratumoral hemorrhage within the large left vestibular schwannoma. (B) T1 image demonstrates corresponding T1 hyperintensity (arrow) confirming the presence of intratumoral hemorrhage.

shunt placement. One developed a recurrent deep vein thrombosis after surgery, and anticoagulation was resumed without event. There were no perioperative deaths, and at a median follow-up of 25 months (3–70 months), no patient has experienced tumor recurrence (Table III).

DISCUSSION

To date, fewer than 50 cases of hemorrhagic VS have been reported in the English literature.[4–7,18–29] In 2014, Niknafs et al. performed a review of the literature and identified 39 cases from 18 published articles.[7] Within

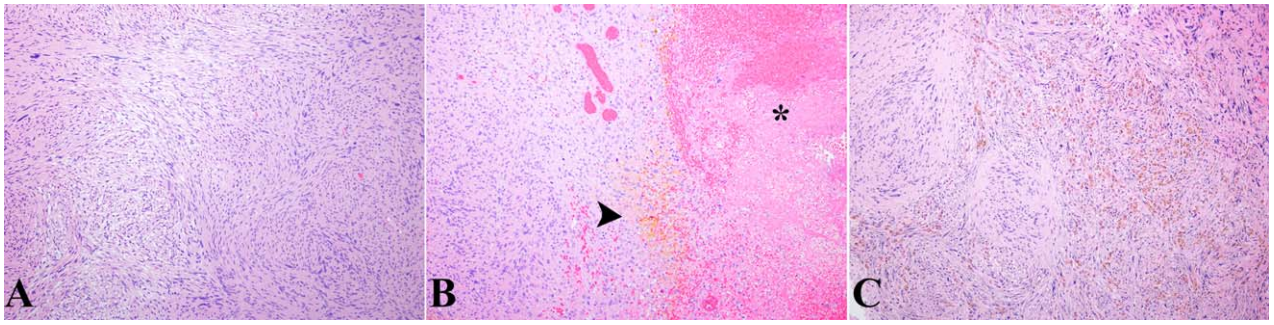

Fig. 5. Histopathology of hemorrhagic vestibular schwannoma. (A) Many of the resection fragments showed well-preserved schwannoma. (B) Some areas showed viable schwannoma adjacent to recent hemorrhage (*) and the golden-yellow hemoglobin degradation product hematoidin (arrowhead), indicative of early hemoglobin breakdown. (C) Other areas also had numerous macrophages containing abundant dark-brown hemosiderin pigment, indicative of further hemoglobin degradation in areas of older hemorrhage. (All Hematoxylin and Eosin stained sections, 100× magnification)

TABLE III.
Surgical Approach and Outcome Following Resection of Hemorrhagic VS.

Case	Surgical Management	Extent of Resection	Complications	HB Function	Improvement of Ataxia and Disequilibrium	Length of Follow-up (months)
1	EVD, then TL	GTR	Hydrocephalus requiring VPS	6*	Y	25
2	RS	GTR		2	Y	69
3	RS	STR (>95%)	CSF leak, hydrocephalus requiring VPS	1**	Y	25
4	EVD, then RS	GTR		5	Y	4
5	TL	STR (> 95%)		4**	Y	9

*Facial nerve was not anatomically preserved during surgery.
**Presenting with HB grade 4 paralysis, prior to operation.
EVD, external ventricular drain; GTR, gross total resection; HB, House-Brackmann; RS, retrosigmoid; STR, subtotal resection; TL, translabyrinthine; VPS, ventriculoperitoneal shunt; Y, yes.

this group, there was no apparent difference in age or sex distribution between hemorrhagic VS and nonhemorrhagic tumors. Although the five index patients in the current study were older than the average VS demographic and four of five were men, no strong conclusions can be made given the small number of cases and wide range of ages represented in this group.

Corroborating prior reports, we found that patients with hemorrhagic VS frequently present with abrupt symptom progression compared to the more indolent course of nonhemorrhagic tumors.[7,21,22,24,26–28,30] Specifically, sudden progression of hearing loss, facial paresis, trigeminal symptoms, and headache are common findings—with facial paresis occurring in approximately a third of cases. The mechanism underlying acute cranial neuropathy and neurologic decline presumably relates to rapid tumor expansion and consequent compression or traction of coursing cranial nerves and brainstem compression. This is further supported by the observation that early surgical decompression, via tumor removal, permits improvement or resolution of cranial neuropathy in many cases.

In the current series, no tumor or treatment-associated mortalities were encountered. However, seven reports of fatal hemorrhage have been published, suggesting that approximately 10% of hemorrhagic VS result in death.[4,6,24,28,29,31,32] Clinically significant subarachnoid or intracerebral hemorrhage occurs in less than 25% of cases where ITH hemorrhage is seen[28]; however, five of the seven reported mortalities occurred in this manner. Thus, not surprisingly, the overall prognosis of isolated ITH is significantly better than in cases with extensive subarachnoid and intracerebral hemorrhage. Presumably, intratumoral containment and self-tamponade explain the difference in clinical outcome between patients with isolated ITH and subjects with significant extratumoral bleeding.

The majority of cases of hemorrhagic VS require prompt surgical intervention because observation and radiosurgery do not alleviate mass effect and risk repeated hemorrhage.[4,23,25] Prior to surgery, a focused history and laboratory testing should be obtained to evaluate for primary or acquired bleeding diathesis. When possible, any underlying hypocoagulopathy should be corrected prior to surgery to reduce the risk of intraoperative or delayed postoperative hemorrhage. Patients with evidence of hydrocephalus may also require perioperative external ventricular drain placement for monitoring and control of intracranial pressure. The primary goal of surgery is early brainstem decompression. The decision to pursue GTR, NTR, or STR must be determined according to patient status at time of surgery, tumor size, age, and favorability of surgical planes between the tumor, brainstem, and cranial nerves. Subtotal resection may be required in unstable or frail patients in order to limit anesthetic time. The primary benefit of complete tumor removal is the reduced theoretical risk of catastrophic postoperative hemorrhage that may occur after STR, particularly if a large tumor remnant is left.[4,23]

The mechanism of hemorrhage in VS remains unknown. In a histological study, Sughrue et al. reported that varying levels of microhemorrhage occur in nearly all VS, with approximately 4% exhibiting diffuse microhemorrhage spanning more than 50% of the tumor volume.[30] Park et al. compared radiological and histological features between solid and cystic VS and concluded that intratumoral microhemorrhage may underlie the development of cyst formation.[33] Specifically, cystic VS more commonly demonstrate fluid–fluid levels and hemosiderin on imaging. It is noteworthy that the single patient in our series with prehemorrhage imaging available experienced ITH in a rapidly growing cystic tumor that increased by 14 mm in only 15 months.

How do we reconcile the observation that tumor hypervascularity and subclinical microhemorrhage is common in VS but clinically significantly hemorrhage is not? We speculate that microhemorrhage provides the inciting spark; however, persistent bleeding generally requires a secondary factor that promotes greater arteriovenous pressure or impaired coagulation. Prior reports have outlined several potential secondary triggers, including hypertension, pregnancy, excessive straining (e.g., weight lifting), minor head trauma, and antiplatelet or anticoagulant therapy.[4–7,18–25,27–29] The issue of head trauma is particularly relevant to the VS population since older age and disequilibrium may increase fall risk.[34] Paralleling the 10-fold greater risk of hemorrhagic stroke in

anticoagulated patients within the general population, our series identified a 25-fold increased risk of clinically significant hemorrhage in patients taking therapeutic levels of anticoagulation.[35] In reviewing the literature, we identified only five other reports of anticoagulation use contributing to VS hemorrhage.[4,6,28,29,36] Of the four cases for which clinical outcomes were reported, three died despite urgent surgical decompression and the fourth experienced fatal hemorrhage several years following radiation therapy.[4,6,28,29]

It is helpful to review our findings in the context of the general neurooncology literature. Overall, ITH occurs in 4% of all intracranial neoplasms and is the heralding symptom of many occult primary and metastatic intracranial neoplasms.[8–10,14] Interestingly, in the current series, four of five VS were only discovered after hemorrhage, despite all having larger sized tumors. Prior studies demonstrate that the risk of ITH varies significantly by tumor type.[10,11,13,14] These inherent differences in hemorrhage rates have led to divergent recommendations for anticoagulation therapy. For example, the risk of hemorrhage with glioma is generally less than 3%, and this risk does not appear to increase with anticoagulation use.[12] In contrast, the risk of intracranial hemorrhage with metastatic tumors, such as renal cell carcinoma, is very high. For these reasons, anticoagulation for venous thromboembolism is often withheld for metastatic central nervous system tumors, whereas it is generally given to patients with glioma.[14]

Because the risk of hemorrhage in VS is significantly greater with systemic anticoagulation, and because prior reports have demonstrated poorer clinical outcomes while on anticoagulation therapy, the management of this subset of patients becomes a critical point of discussion. How should the potential need for anticoagulation be managed, and what is the best initial treatment for the tumor when long-term anticoagulation is required? Unfortunately, given the limited data, strong conclusions regarding optimal medical management cannot be established. However, we offer several recommendations regarding the use of anticoagulation in VS patients: 1) tight management of INR is critical to avoid supratherapeutic levels that may increase the risk and severity of hemorrhage; 2) the need for anticoagulation should be frequently re-evaluated, and alternatives to systemic anticoagulation such as cardioversion or ablation for arrhythmia should be considered when feasible; 3) a low threshold for intracranial imaging following any change in neurological symptoms should be maintained, with the assumption that earlier recognition can result in improved outcome. Ultimately, each patient must be evaluated individually, weighing the risks and benefits of anticoagulation against potential alternatives (e.g., ablation, Watchman Device, inferior vena cava filter).

What is the optimal management strategy for VS in patients requiring long-term anticoagulation therapy? In patients with larger tumors or those with growing cyst formation, our strong preference remains microsurgical resection. However, in our practice, most patients on long-term anticoagulation with small- to medium-sized VS are treated conservatively with observation or radiotherapy, given the attendant risks associated with surgery and the frequent separate comorbidities this patient population keeps. Of the 36 patients who were receiving systemic anticoagulation at time of presentation in our series, 17 were managed with initial observation; 17 underwent radiation therapy; and two underwent surgery. None of the patients who received radiosurgery or surgical resection experienced any adverse events attributable to anticoagulation, such as hematoma or delayed hemorrhage. Paralleling the other tumor pathologies, several groups have reported that radiation therapy itself increases the risk of delayed hemorrhage.[5,6,37,38] However, many of these cases are also complicated by larger tumor size, prior surgery, and cystic degeneration. Based on the limited available data, and what is known regarding management of VS in the general population, we believe that observation is the best initial treatment strategy for anticoagulated patients with small- or medium-sized tumors. Further data are necessary to evaluate choice selection between microsurgery and radiosurgery for growing, noncystic, small- to medium-sized VS. Ultimately, treatment must be individualized according to tumor size, age, comorbidities, necessity of anticoagulation, and patient wishes.

In closing, several limitations warrant discussion. First, the current study only analyzed patients with clinically significant hemorrhage; cases with presumed subclinical hemorrhage, based on radiological findings, were not evaluated. Second, data regarding ITH following radiation therapy and surgery were not analyzed. Curiously, Niknafs et al. found that almost 20% of hemorrhagic VS cases reported to date developed following stereotactic radiosurgery.[7] Also, there have been reports of likely de novo aneurysm formation in patients with VS treated with stereotactic radiosurgery.[39] Additional reports of tumoral hemorrhage following prior subtotal resection have also been described.[4,23] Third, given the retrospective nature of study, details regarding duration of anticoagulation use in the 33 patients was not known. However, of the two index patients on anticoagulation who developed hemorrhage, one had been on 9 years of anticoagulation, whereas the second had only received 2 weeks of therapy before hemorrhage, suggesting that duration of anticoagulation is not necessarily a strong predictor of hemorrhage risk with VS. Last, the risk of hemorrhage with antiplatelet therapy was not evaluated because none of the five index patients in this report were solely taking antiplatelet therapy at time of hemorrhage. This topic is particularly relevant to VS since recent data has suggested that cyclooxygenase inhibitors, such as aspirin, may reduce the probability of future tumor growth in conservatively managed VS.[40]

CONCLUSION

Tumor-associated hemorrhage occurs in 0.4% of untreated VS. The frequency of ITH while receiving systemic anticoagulation is 5.5%, representing a 25-fold increase over the general VS population. In most cases, management of hemorrhagic VS requires prompt surgical intervention to alleviate mass effect and mitigate further neurological decline. The prognosis of isolated ITH is significantly better

than cases with concurrent intracerebral or subarachnoid hemorrhage. Decisions regarding the management of systemic anticoagulation should be made on an individual basis, balancing the effectiveness of treatment with the risk of intracranial hemorrhage and other associated complications.

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