

## “When the Benign Bleed” Vestibular Schwannomas with Clinically Significant Intratumoral Hemorrhage: A Case Series and Review of the Literature

### Abstract

Vestibular schwannomas (VSs) are slow-growing benign neoplasms commonly located at the cerebellopontine angle. Although clinically significant hemorrhagic VSs are rarely encountered with only 75 patients previously reported, they could be life threatening. We discuss the presentation and outcomes of three patients with hemorrhagic VS as well as review the literature for this phenomenon. Consecutive adult patients with a histologically proven diagnosis of VS over a 9-year period were retrospectively reviewed. Fifty adult patients were identified with three (6%) having clinically significant intratumoral hemorrhage. This was defined as patients having acute to subacute symptoms with frank radiological evidence of hemorrhage. The mean age of diagnosis was  $62 \pm 9$  years and the male-to female ratio was 2:1. The mean duration of symptoms, namely headache, vertigo, and sensorineural hearing impairment, was  $26 \pm 4$  days with one patient presenting with acute coma. Retrosigmoid craniotomy for tumor resection was performed for all patients. Histopathological examination revealed extensive areas of microhemorrhage with considerable macrophage infiltration. All three patients were discharged with no additional neurological deficit and good functional performance. Clinically significant hemorrhagic VSs are rare, and patients may present with acute to subacute (i.e., within a month) symptoms of hearing loss headache, facial, or trigeminal nerve palsy. Macrophage infiltration is frequently encountered in tumor specimens and reflects the pivotal role of chronic inflammation in their pathophysiology. Surgical resection can lead to good outcomes with timely intervention.

**Keywords:** Acoustic neuroma, intratumoral hemorrhage, vestibular schwannoma

### Introduction

Vestibular schwannomas (VSs) are benign neoplasms that generally arise from the superior division of the vestibular cranial nerve. VS represents approximately 8% of all primary intracranial neoplasms and 75% of cerebellopontine (CP) angle tumors.<sup>[1,2]</sup> The clinical presentation of VS may vary from prolonged dormancy to subacute symptoms, including unilateral hearing loss, tinnitus, gait ataxia, and vertigo.<sup>[3]</sup>

Brain tumor-related intracranial hemorrhage is a well-described phenomenon, yet intratumoral hemorrhage (ITH) occurring in benign tumors such as VS is rare with fewer than a hundred cases reported in the literature.<sup>[2-4]</sup> While most VSs have an insidious clinical course with slow tumor growth, hemorrhagic lesions can result in sudden neurological deterioration ranging

from facial nerve palsy to severe disability and mortality.<sup>[5]</sup>

Due to the rarity of clinically significant hemorrhagic VS, its pathophysiology and prognosis remain unclear. Understanding the natural course of ITH in VS may assist in patient counseling and clinical decision-making. Here, we describe the presentation, management, and outcomes of three patients with hemorrhagic VS. A comprehensive review of the literature regarding ITH in VS was also performed.

### Case Report

All adult patients with a histologically proven diagnosis of VS and evidence of clinically significant ITH were reviewed at a single neurosurgical center from January 1, 2012 to March 31, 2020. Clinically significant hemorrhagic VS was

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defined as patients having acute to subacute symptoms with frank radiological evidence of acute ITH as exhibited by either a Hounsfield unit reading of 40–70 at the region of interest on noncontrast enhanced computed tomography (CT) or hyperintense signal changes on T1-weighted sequences with corresponding hypointense changes on T2-weighted and susceptibility-weighted magnetic resonance imaging (MRI) sequences. Clinical, radiological, histological, and treatment data were reviewed. In particular, the presence of pre- and postoperative facial palsy (House–Brackmann grading) and hearing impairment was documented.<sup>[6]</sup> Imaging studies were reviewed to assess the size of the tumor, the degree of brainstem compression, and the presence of hydrocephalus. The neurosurgical approach was recorded and the extent of tumor resection was evaluated by postoperative MRI scans. The functional performance of each patient was determined by the Eastern Cooperative Oncology Group (ECOG) grading.<sup>[7]</sup> The database from the US National Library of Medicine and National Institutes of Health (PubMed) was queried to identify ITH in VS. The key search terms “intratumoral hemorrhage” or “hemorrhagic” and “vestibular schwannoma” or “acoustic neuroma” were used. Only English-language articles published after 1970 that described histologically proven VS were included in our review.

In our institution, 50 adult patients were diagnosed with VS during the 9-year study period and three (6%) were identified to have clinically significant ITH. The mean age of diagnosis was 62 years ( $\pm 9$ ; range: 52–69 years) and the male:female ratio was 2:1. The mean symptom duration was  $26 \pm 4$  days. None of the patients were on long-term antiplatelet or anticoagulant medication, and there was no history of neurofibromatosis type II.

### Patient 1

A 69-year-old man presented with intermittent vertigo and progressive left hearing impairment for 6 months. He subsequently experienced a 4-week history of subacute global headache. Apart from a history of hypertension, there were no other significant comorbidities. The patient was fully conscious and did not have facial nerve palsy. There was complete left sensorineural hearing loss and preoperative brainstem auditory-evoked potentials could not be detected.

A CT scan and a subsequent MRI scan revealed a 3.7 cm  $\times$  3.1 cm  $\times$  3.5 cm left heterogeneous gadolinium-contrast enhancing hemorrhagic multicystic CP angle tumor with intratumoral fluid levels [Figure 1]. The tumor exerted considerable mass effect against the pons and was causing early obstructive hydrocephalus. A retrosigmoid (RS) craniectomy for subtotal tumor resection was performed 13 days after admission. Intraoperatively, the tumor was vascular with prominent feeding capsular vessels. Apart from the intratumoral

hematoma, there were multiple cysts containing xanthochromic fluid within the medial side of the tumor, indicating additional intracystic hemorrhage as well. Intraoperative trigger electromyography was utilized to identify the facial nerve, and motor-evoked potential monitoring was performed to confirm its integrity. The final histological diagnosis was VS with diffuse hemosiderin deposits and there were no malignant features.

A week after the operation, there was secondary surgical site hemorrhage that required hematoma evacuation. The patient was discharged home with no facial nerve palsy and an ECOG performance status of 0. There was no improvement in hearing. A 1-year follow-up MRI scan revealed tumor recurrence (2.0 cm  $\times$  1.2 cm  $\times$  0.9 cm) that required stereotactic radiosurgery (SRS).

### Patient 2

A 62-year-old Nepalese woman with a history of hypertension experienced syncope and was comatose on admission with a Glasgow Coma Scale score of 3/15. In the preceding 4 weeks, she complained of right-side hearing impairment, and a day before admission, she also experienced vertigo with recurrent vomiting. Upon hospitalisation her pupils were equal and reactive to the direct light reflex. There was no evidence of facial nerve palsy. A CT brain scan showed a 5.5 cm  $\times$  3.1 cm  $\times$  3.1 cm hematoma over the right CP angle with significant compression against the brainstem, causing acute obstructive hydrocephalus [Figure 2a and b]. There was also an associated widened internal acoustic meatus that suggested the underlying lesion was a VS [Figure 2a]. An urgent RS craniectomy for brainstem decompression, hematoma evacuation, and subtotal tumor resection was performed. Intraoperatively, a vascular tumor was encountered with an intratumoral hematoma and evidence of arachnoiditis [Figure 3a and b]. No attempt was made to identify the facial nerve since the main aim of the operation was for urgent brainstem decompression, and intraoperative neurophysiological monitoring was not available at the time. The histological diagnosis was VS with areas of hemorrhage, thrombosed vessels, and aggregates of hemosiderin-laden macrophages [Figure 3c].

Postoperatively, the patient regained full consciousness. Apart from right complete sensorineural hearing loss, there was no additional focal neurological deficit. In particular, there was no facial nerve palsy. The patient was discharged home 2 weeks after rehabilitation with an ECOG performance status of 1. A 1-month postoperative MRI brain scan showed a residual 2.5 cm  $\times$  1.2 cm  $\times$  1.3 cm tumor and SRS was arranged.

### Patient 3

A 56-year-old man with a history of hypertension presented with acute vertigo with recurrent vomiting a day before admission. He also complained of intermittent

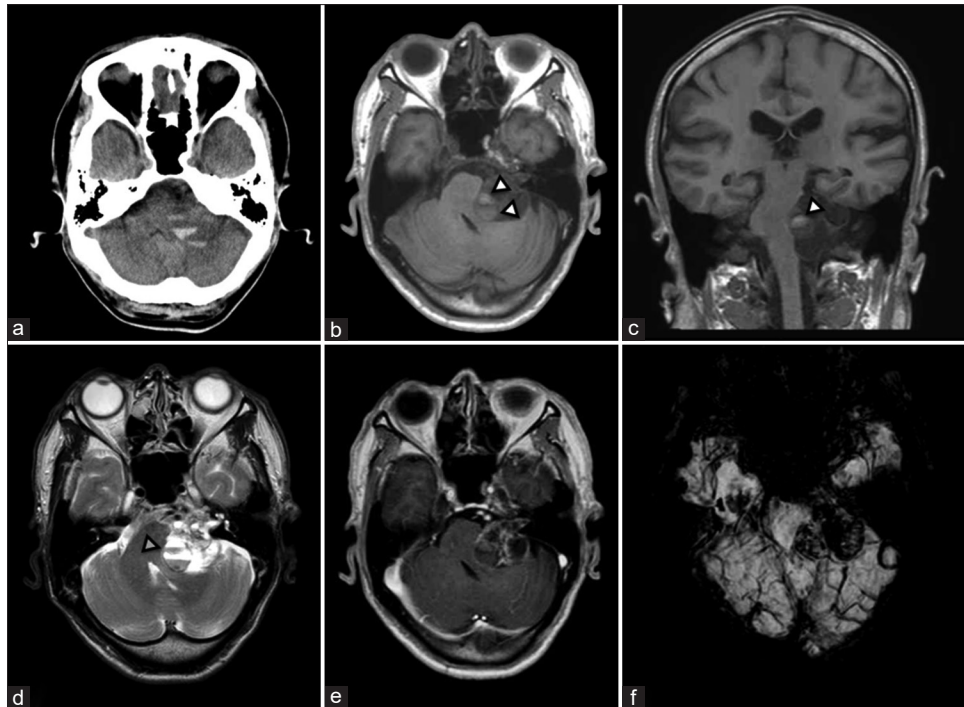


Figure 1: Patient 1. Computed tomography scan showing left cerebellopontine angle lesion hemorrhage (a). T1-weighted magnetic resonance imaging revealed a widened internal acoustic meatus and intratumoral hyperintense signal changes (white arrowheads) suggestive of hemorrhagic vestibular schwannomas compressing the brainstem (b, axial; c, coronal). The corresponding areas are isointense (gray arrowhead) on T2W imaging indicating subacute (6–9 days) methemoglobin blood (d). Contrast-enhanced T1-weighted scan demonstrated heterogeneous enhancement with widening of the internal acoustic meatus indicative of a multicystic vestibular schwannoma (e). Susceptibility-weighted imaging revealed diffuse hypointense signal changes reflecting blood product deposition (f)

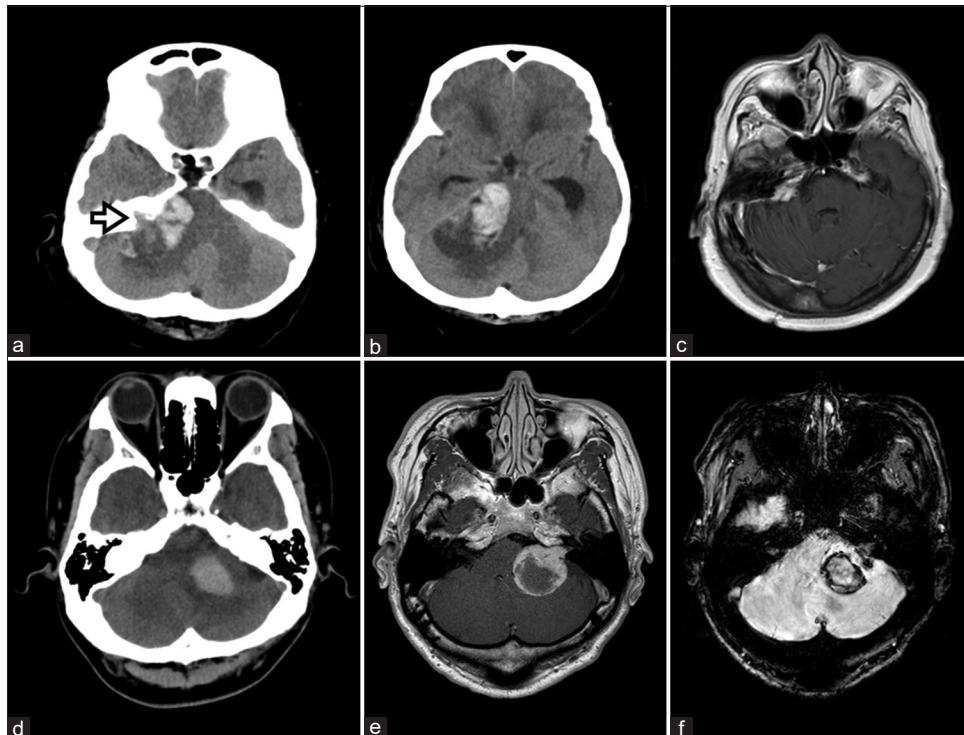
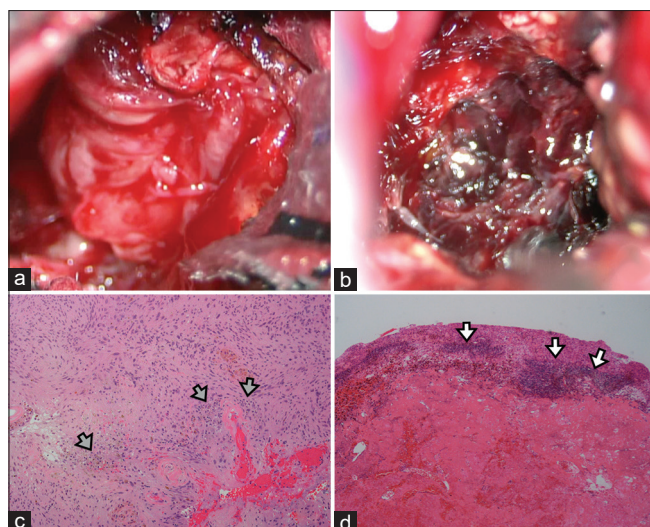


Figure 2: Patient 2. Computed tomography scan revealing acute intratumoral hemorrhage at right cerebellopontine angle causing brainstem compression (a) and acute obstructive hydrocephalus (b). The widened IAM is suggestive of vestibular schwannomas (a, white arrow). One-month postoperative contrast-enhanced T1-weighted magnetic resonance imaging showing residual tumor extending into the IAM (c). Patient 3. Computed tomography scan showing a left cerebellopontine angle hemorrhagic tumor (d). Contrast-enhanced T1-weighted magnetic resonance imaging revealing a widened IAM and heterogeneous enhancement (e). SWI depicting intratumoral blood product deposition (f)



**Figure 3:** Intraoperative photographs of Patient 2. A vascular cerebellopontine angle tumor with prominent arterial feeders was encountered (a). The intratumoral blood clot was evacuated (b). Histopathology revealed a vestibular schwannoma with infiltrating macrophages within both Antoni A and Antoni B regions (c, gray arrows, H and E,  $\times 50$ ). Tumor arterial occlusion is noted in the right lower corner of the microphotograph. Patient 3's vestibular schwannoma revealed extensive microhemorrhage within the Antoni B regions. Infiltrating macrophages are identified at the border with Antoni B regions (d, white arrows, H and E,  $\times 10$ )

headache, left facial numbness, and left hearing impairment in the preceding 4 weeks. A preoperative pure tone audiogram (PTA) did not detect any sensorineural hearing loss. An MRI brain scan revealed a  $3.4 \times 3.2 \times 4.0$  cm hemorrhagic left CP angle extra-axial cystic tumor. The lesion was heterogeneously contrast-enhancing and was causing brainstem compression with obstructive hydrocephalus [Figure 2d-f].

A RS craniotomy for gross tumor excision was performed 13 days after admission. The tumor was vascular and an intratumoral hematoma was encountered with an accompanying cyst containing xanthochromic fluid suggestive of prior hemorrhage. The trigeminal and facial nerves were identified with motor-evoked potential monitoring, confirming their integrity. The histological diagnosis was VS with several focal areas of microhemorrhage, hemosiderin deposits, and tumor-infiltrating macrophages [Figure 3d]. Postoperatively, the patient's symptoms gradually improved and he was discharged 5 days later with an ECOG functional performance status of 0. There was no facial nerve palsy and a repeat PTA showed no deterioration in his hearing. An MRI scan performed 6 months later showed no residual tumor.

A literature review identified a total of 48 articles documenting 75 patients with clinically significant ITH in VS. Including the additional three patients described in this report, 53% (41/78) were women and the mean age was  $51 \pm 17$  years (range: 15–77 years) [Table 1]. Among the patients where relevant clinical data were documented,

**Table 1: Clinical, radiological, treatment characteristics, and outcomes of reported vestibular schwannoma patients with clinically significant intratumoral hemorrhage since 1970**

Characteristics	n (%)*
Patient features	n=78
Age (years), mean $\pm$ SD	51 $\pm$ 17
Male (%)	37 (47)
Hypertension	15 (19)
Antiplatelet or anticoagulant medication	8 (10)
Clinical presentation	n=73
Auditory symptoms or signs	
Hearing impairment	58 (79)
Tinnitus	17 (23)
Raised ICP symptoms	
Headache	49 (67)
Reduced conscious level/coma	8 (11)
Cerebellar symptoms or signs	
Ataxia/nystagmus	38 (52)
Vertigo	18 (25)
Cranial nerve palsy	
Facial nerve palsy	34 (47)
Trigeminal nerve palsy	22 (30)
Vagal/glossopharyngeal/hypoglossal nerve palsy	3 (4)
Hemiparesis	2 (3)
Duration of symptoms (days), mean $\pm$ SD	27 $\pm$ 42
Radiological features	n=72
Largest diameter (cm), mean $\pm$ SD	3.4 $\pm$ 1.0
Cystic changes	19 (30)
Intracystic hemorrhage	7 (10)
Hydrocephalus	
Obstructive	32 (62) <sup>†</sup>
Communicating	1 (2) <sup>†</sup>
Treatment	n=77
Craniotomy NOS	20 (26)
RS approach	47 (61)
TL approach	4 (5)
Combined RS and TL	1 (1)
SRS alone	1 (1)
Adjuvant SRS	4 (5)
Ventriculoperitoneal shunt alone	1 (1)
Conservative treatment	3 (4)
Outcome	n=44
Hearing loss	19 (43)
Facial nerve palsy	22 (50)
Death	8 (18)

\*In accordance with the total number of patients reported in literature where such features could be determined; <sup>†</sup>50 patients were analyzed. The remaining reports had insufficient data to confirm the presence or absence of hydrocephalus. NOS – Not otherwise specified; RS – Retrosigmoid; TL – Translabrynthine; SRS – Stereotactic radiosurgery; SD – Standard deviation; ICP - Intracranial pressure

the most common presenting symptom was hearing impairment (79%, 58/73), followed by headache (67%, 49/73), ataxia (52%, 38/73), facial nerve palsy (47%, 34/73), and trigeminal nerve palsy (22%, 30/73). The mean

duration of symptoms was 4 weeks, i.e.,  $27 \pm 42$  days. For 72 cases where radiological data were available, the mean tumor size was  $3.4 \pm 1.0$  cm (range: 1.5–6 cm). Discernible cystic tumor changes were noted in a third of the patients (30%, 19/72) and intracystic hemorrhage was detected in 10% (7/72). Of the 77 patients who had treatment details described, 94% (72/77) underwent definitive tumor resection with the majority undergoing RS craniotomy (61%, 47/77) and a single patient underwent a combined RS-translabyrinthine approach. Four patients (5%) had adjuvant SRS and one received SRS alone.

## Discussion

Although VS is the most frequently encountered tumor of the CP angle region, clinically significant ITH rarely occurs. Patients with VS typically present with gradual progressive auditory symptoms such as unilateral high-frequency sensorineural hearing impairment and tinnitus. One of the largest single-institution VS case series to date comprising 1000 patients observed that over 90% had unilateral hearing impairment. Trigeminal nerve and facial nerve palsies are relatively rare occurring in 9% and 6% of patients, respectively.<sup>[8]</sup> In contrast, for hemorrhagic VS, more than a quarter of reported patients experienced trigeminal nerve palsy and 47% had facial nerve palsy [Table 1]. Rapid tumor expansion secondary to ITH could result in acute stretching of an already tenuously splayed vestibulocochlear, facial, or trigeminal nerve resulting in a higher incidence of such deficits on presentation.<sup>[9,10]</sup> This observation is further supported by the shorter duration of symptoms among patients with hemorrhagic VS. Including our three described cases, the mean symptom duration described in the literature was  $27 \pm 12$  days and nine patients experienced acute symptoms within a week. In contrast, for 89% of patients with typical VS, the duration from symptom onset to diagnosis was  $>6$  months.<sup>[11]</sup>

The exact pathophysiological mechanisms for why VS would undergo clinically evident ITH while other histologically benign tumors seldom exhibit this phenomenon are unclear. Several theories have been proposed, including arterial tumor invasion, microvascular proliferation of thin-walled tumor arterial feeders lacking tunica media, and necrosis resulting from unbridled tumor growth.<sup>[3,12-16]</sup> Yet, ITH in VS may occur more commonly than previously believed. A histological review of 274 VS specimens revealed that nearly all exhibited varying levels of intratumoral microhemorrhage, and more extensively involved tumors were independently associated with preoperative unserviceable hearing.<sup>[13]</sup> It has also been suggested that multiple hemorrhagic events could account for the existence of cystic VS that comprise 5%–10% of tumors and are widely described as demonstrating rapid growth, shorter symptom durations, and worse outcomes after resection.<sup>[17-19]</sup> Two of our

three patients had tumors with cystic degeneration with evidence of prior intracystic hemorrhage in addition to the presence of an intratumoral hematoma. This is corroborated by the higher incidence of cystic changes among reported VS with ITH (30%, 19/72) compared to typical nonhemorrhagic tumors [Table 1]. High levels of the proteolytic enzyme, matrix metalloproteinase-2, a potent inflammatory mediator that stimulates vascular permeability and enables monocyte infiltration, has been identified in VS cyst fluid suggesting their important pathogenetic role.<sup>[20,21]</sup> There is an increasing body of evidence to suggest that inflammation and angiogenesis play crucial roles in maintaining sporadic noncystic VS “growth” despite the absence of classical histological biomarkers for malignancy such as conspicuous cellular proliferation or mitoses.<sup>[22,23]</sup> The concentrations of intratumoral vascular endothelial growth factor and fibroblast growth factor have been shown to correlate with VS growth rates.<sup>[24,25]</sup> This observation suggests that sporadic VS can elicit an immune response resulting in chronic inflammation with enhanced vascular permeability and is supported by the frequent presence of tumor-infiltrating macrophages, especially within Antoni B areas.<sup>[23,26]</sup> A recent study prospectively investigating the relationship between tumor growth and inflammation utilized positron-emission tomography with the inflammatory cell tracer <sup>11</sup>C-(R)-PK11195 and dynamic contrast-enhanced MRI to compare tumors of differing growth rates.<sup>[26]</sup> With subsequent histological examination, Lewis *et al.* demonstrated that with enlarging VS, tumor-infiltrating macrophages rather than tumor cells accounted for the major portion of the tumor mass.<sup>[26]</sup> This revelation of pseudo-tumoral growth can explain why tumor size ( $>2$  cm), rapid growth, and mixed Antoni A/B cellularity are commonly identified risk factors for clinically significant ITH.<sup>[3,4,12]</sup> In support of this observation, Patient 1, who had the longest duration of symptoms, had radiological evidence of multicystic changes with intraoperative findings of both ITH and intracystic blood indicating that the lesion had undergone several prior episodes of hemorrhage [Figure 1].

In our study, all patients had large tumors with the mean maximum diameter of  $3.7 \pm 1.0$  cm (range: 3.7–5.5 cm) which was comparable to the mean size of  $3.4 \pm 1.0$  cm (range: 1.5–6.0 cm) for other hemorrhagic VS reported in the literature. This is considerably larger than the mean size of a typical VS of  $2.0 \pm 1.0$  cm.<sup>[27]</sup> Antoni A and B regions are characteristic of all VS, but histological examination of our tumor specimens revealed more extensive areas of Antoni B regions microhemorrhage were detected.

With regard to the timing of resection, most patients with hemorrhagic VS could be closely observed, to allow an opportunity for the arrangement of preoperative MR imaging and neurophysiological intraoperative monitoring. Life-threatening hemorrhagic VS, as illustrated by Patient

2 who was comatose upon admission, is uncommon. Only eight (11%) of all hemorrhagic VS patients described had a depressed conscious level on presentation and among them, four (5%) required emergency neurosurgical resection. Should acute obstructive hydrocephalus be the underlying cause for neurological deterioration, urgent external ventricular drainage can be considered as a temporary relieving measure before definitive resective surgery.<sup>[28-30]</sup>

In general, postoperative complications for typical VS include sensorineural hearing loss (>60%), facial nerve palsy (<10%), surgical site hemorrhage (<3%), and meningitis (<2%).<sup>[31,32]</sup> In our study, two patients had worse sensorineural hearing impairment, while the remaining patient did not experience deterioration. Otherwise, none had a permanent focal neurological deficit. Although Patient 1 required a subsequent reoperation for surgical site hematoma evacuation, long-term postoperative functional performance for all three patients was satisfactory. Including our current cases, 19 (43%, 19/44) ITH VS patients had postoperative hearing loss and 22 (50%, 22/44) had facial nerve palsy which are considerably higher than the frequency of procedure-related complications for nonhemorrhagic VS [Table 1]. There is likely to be an underreporting of such complications since 44% (34/78) of case reports did not describe posttreatment outcomes. The presence of dense peritumoral adhesions resulting from chronic inflammation akin to the arachnoiditis encountered intraoperatively in Patient 2 may have contributed to these outcomes. A total of eight (18%, 8/44) patients had fatal hemorrhagic VS resulting from residual hypervascular tumor rebleeding and constituted a significantly higher mortality rate than that observed for nonhemorrhagic VS operations, which is generally cited at <2%.<sup>[32]</sup>

## Conclusion

Clinically significant ITH in VS is rare but potentially life threatening. Most patients can be initially closely observed to allow time for the preparation of early definitive surgery and urgent resection is often not required. Neurosurgeons should be aware that such tumors are hypervascular and carry a risk of postoperative rebleeding after subtotal resection. In contrast to the literature, our experience indicates that surgical outcomes can be comparable to nonhemorrhagic VS.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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