Spontaneous Hemorrhage from Central Nervous System Hemangioblastomas

Chibawanye I. Ene, Ryan P. Morton, Manuel Ferreira Jr., Laligam N. Sekhar, Louis J. Kim

Key words
- Hemangioblastoma
- Hydrocephalus
- Intraparenchymal hemorrhage
- Intraventricular hemorrhage
- Oncology
- Subarachnoid hemorrhage
- Tumor

Abbreviations and Acronyms
AVM: Arteriovenous malformation
CNS: Central nervous system
IL: Interleukin
MMP: Matrix metalloproteinase
MRI: Magnetic resonance imaging
VHL: von Hippel—Lindau

From the Department of Neurological Surgery, University of Washington, Seattle, Washington, USA

To whom correspondence should be addressed: Chibawanye I. Ene, M.D., Ph.D. [E-mail: chiba@uw.edu]

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OBJECTIVE: **Hemagioblastomas are highly vascular tumors that rarely present with hemorrhage. To date, the only factor reported to possibly influence the propensity of a tumor to bleed has been its size (>1.5 cm). Here, we present our series of hemorrhagic hemangioblastomas, which includes 2 very small tumors (<1.5 cm). We propose that other factors apart from size may predispose tumors to hemorrhage.**

METHODS: **We conducted a retrospective analysis of 55 cases of central nervous system hemangioblastomas operated on at Harborview Medical Hospital and the University of Washington between 2004 and 2014. Demographical and clinical data were collected and analyzed to determine factors that may predispose these tumors to hemorrhage.**

RESULTS: **Of 55 cases, only 3 patients presented with hemorrhage (5.5%). None of the patients were von Hippel-Lindau positive. Two of the hemorrhagic tumors were less than 1.5 cm, countering previous studies in which authors proposed that hemangioblastomas that are less than 1.5 cm have essentially no risk of hemorrhage. One tumor also rebled after preoperative embolization.**

CONCLUSIONS: **Our series suggests that small hemangioblastomas may represent a hemorrhagic risk. We speculate that other factors, such as genetic predisposition caused by single-nucleotide polymorphisms, may play a role in hemangiobalstomas that present with rupture.**

INTRODUCTION

Central nervous system (CNS) hemangioblastomas are highly vascular tumors typically found in the posterior fossa or medullary substance of the spinal cord and represent approximately 2%—3% of all CNS tumors (13). Hemangioblastomas may be associated with von Hippel-Lindau (VHL) syndrome, where they occur with a prevalence of 20%—30% (21). Presenting symptoms of cerebellar hemangioblastomas typically relate to hydrocephalus (headache, nausea, vomiting, diplopia, etc) whereas spinal hemangioblastomas typically present with focal neurologic deficit related to mass effect. On very rare occasions, hemangioblastomas of the brain or spine may present with spontaneous subarachnoid, intra-ventricular, or intraparenchymal hemorrhage. Fifty-three such cases reports exist in the literature (2-9, 11-17, 19, 20, 22, 24-26, 28, 29), with only one of these studies attempting to systematically evaluate risk factors that may predispose certain hemangioblastomas to spontaneous hemorrhage (13). Glasker et al. (12, 13) postulated that size alone was the most important risk factor for spontaneous hemorrhage, concluding that tumors <1.5 cm pose essentially no risk of hemorrhage. Here, we challenge this hypothesis by presenting our series of hemorrhagic hemangioblastomas, 2 of which were smaller than 1.5 cm in maximal diameter. The potential pathophysiology of hemorrhage in these tumors is also discussed.

METHODS

This study was approved by the institutional review board. We retrospectively reviewed our clinical database of patients with CNS hemangioblastomas from 2004 to 2014. Clinical features such as tumor size, location, VHL status, radiography features, and clinical symptoms at presentation and follow-up were evaluated and correlated to the risk of spontaneous hemorrhage. Statistical analysis was performed with Student *t*-test.

RESULTS

Retrospective Analysis

We encountered pathologically confirmed hemangioblastomas in 53 patients over 10 years. Forty-six were intracranial, 6 were cervical, and 3 were thoracic; one patient had an intracranial and 2 cervical lesions resected. Seven (13%) tumors were designated small tumors with <1.5 cm in maximum dimension (3 intracranial, 3 cervical, 1 thoracic). Three (5.5%) tumors presented with hemorrhage with 1 case of intraparenchymal/tumor hemorrhage (case 1) and 2 cases of combined subarachnoid/intraventricular hemorrhage (cases 2 and 3). The average maximal diameter of the tumors presenting with hemorrhage was 2.1 cm, with 2 hemorrhagic tumors of maximal diameters <1.5 cm (29% of small tumors).

Table 1. Clinical Data of Patients with Spontaneous Bleeding from Hemangioblastoma

Case	Age/Sex	Tumor Size, cm	Tumor Location	VHL Status	Symptoms
1	60/M	3.8 × 4 × 3.5	Right cerebellum	Negative	Headache, nausea, vomiting
2	40/F	1.2 × 0.6 × 1.1	Right medulla	Negative	Altered mental status
3	55/M	1.2 × 0.8 × 0.9	Cervicomedullary junction	Negative*	Headache, nausea, neck pain

VHL, von Hippel-Lindau; M, male; F, female.
*Met clinical criteria for VHL; however, genetic testing results were negative.

One was located in the cerebellum and 2 in the medulla. All 3 patients had confirmed hemorrhage on cross-sectional imaging, a magnetic resonance image (MRI) scan with gadolinium that confirmed an enhancing mass near the area of hemorrhage, and a digital subtraction angiogram to rule out any other potential vascular etiologies of the hemorrhage. Notably, all 3 patients received genetic testing that was negative for VHL. Further clinical and radiographic characteristics are presented in Table 1, and the cases are discussed in further detail in the sections to follow. There were no significant differences in terms of age or tumor size, in those presenting with hemorrhage and those without ($P = 0.47$).

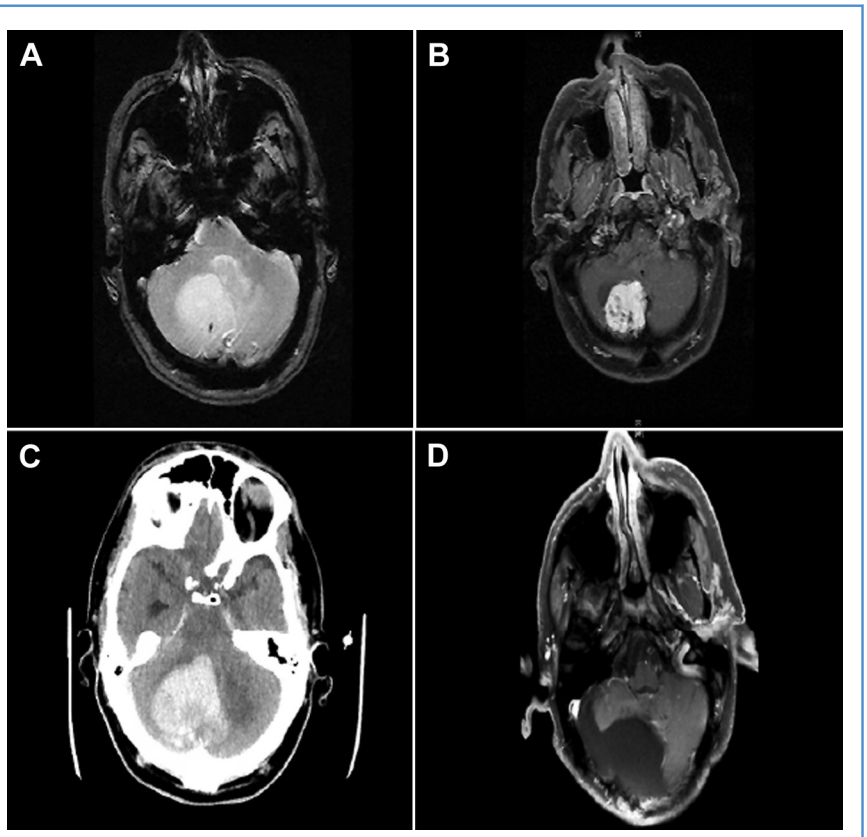

Figure 1. Case 1 (**A**) Gradient echo sequence magnetic resonance imaging (MRI) showing small intratumoral hemorrhage. (**B**) Contrast-enhanced, T1-weighted MRI showing the large solid and slightly cystic hemangioblastoma. (**C**) Noncontrast computed tomography scan of the head demonstrating rehemorrhage after particle embolization. (**D**) Contrast enhanced T1-weighted MRI at 2-year follow-up demonstrating no tumor recurrence.

Case 1

A 60-year-old man presented with severe headache, nausea, vomiting, and gait instability. Findings of an MRI scan demonstrated a giant right cerebellar hemangioblastoma measuring 3.8 cm in maximal diameter with intratumoral and intraparenchymal hemorrhage (Figure 1A shows the GRE sequence; Figure 1B shows T1-weighted imaging with contrast). The tumor underwent preoperative embolization via feeders from the superior cerebellar artery and anterior inferior cerebellar artery/posterior inferior cerebellar artery using 45- to 150-icron particles. This procedure was complicated by a rehemorrhage (Figure 1C), which necessitated an emergent decompression and tumor resection via a suboccipital approach. Pathology confirmed a hemangioblastoma. The patient was discharged to an inpatient rehabilitation facility 2 weeks after his original admission. At longest follow-up (2 years) he has no evidence of recurrent tumor (Figure 1D) and a modified Rankin score (mRS) of 2, having only moderate ataxia and slight dysarthria.

Case 2

A 40-year-old woman presented with a sudden-onset mental status change. A noncontrast CT scan of the head demonstrated intraventricular and mild subarachnoid hemorrhage (Figure 2A, *arrow* shows intraventricular hemorrhage). An external ventricular drain was placed and digital subtraction angiography confirmed a hypervascular lesion with a major arterial contribution from the lateral spinal artery off of the vertebral artery (Figure 2B). Findings of an MRI revealed an avidly enhancing mass in the right medullary foramen magnum region measuring 1.2 cm at maximal diameter (Figure 2C and 2D). Embolization with onyx was performed on hospital day 2, with 100% embolization achieved. This procedure was complicated by a medullary infarction (Figure 2E, *arrowhead*). After embolization, the patient was taken to the operating room for a right far lateral craniectomy for gross total resection of the tumor. She also was discharged to inpatient rehabilitation, and at longest follow-up (3 years) had no evidence of recurrent tumor (Figure 2F). Her mRS was also 2, with