

# Metachronous Pituitary Stalk And Cerebellar Hemangioblastomas In A Patient Without Von Hippel-Lindau Disease: Case Report And Review Of Literature

A Olasunkanmi, R Elliott, K Newman, I Mikolaenko, D Zagzag, J Golfinos

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## Abstract

**Background:** Hemangioblastomas (HBs) are benign neoplasms of the central nervous system (CNS) that account for 10–15% of posterior fossa tumors in adults. HBs most commonly arise in the cerebellum but also occur in the spinal cord and medulla. They occur sporadically as solitary lesions or in association with von Hippel-Lindau (VHL) disease and are usually multiple. HBs can arise in the supratentorial space (>100 reported cases) but only 16 cases of pituitary stalk HBs have been reported—87.5% of which occurred in the setting of VHL disease. Although multiple, metachronous and disseminated HBs can occur in the setting of VHL disease, there are no reported cases of focal, metachronous HBs in patients without this disease. **Case Description:** We report the case of a 61-year old man with no personal or family history of VHL disease who presented with a pituitary stalk HB 9 years after complete resection of a cerebellar HB. He underwent complete resection complicated by diabetes insipidus and visual field deterioration. **Conclusion:** The occurrence of HB at different times and in disparate locations within the CNS is not synonymous with the diagnosis of VHL disease. While diffuse dissemination has been reported following surgery, this is the first reported case of a focal metachronous HBs arising in a patient without VHL disease. Although its unusual location within the pituitary stalk complicated the diagnosis preoperatively, a second HB should be considered in the differential diagnosis and close follow-up may be warranted to identify such lesions prior to irreversible neurological deficits.

## BACKGROUND

Hemangioblastoma (HB) is a benign neoplasm of the central nervous system that accounts for 1 to 2% of primary brain tumors and 10 to 15% of posterior fossa tumors in adults.

<sup>4,17,26</sup> The tumors have a predilection for the posterior cranial fossa, commonly arising in the cerebellum.<sup>4,22,26</sup>

Approximately 20% of cases of HB occur in association with von Hippel Lindau (VHL) disease while the majority (80%) arises sporadically.<sup>10,16,22,26</sup> Whether HBs occur sporadically or as part of VHL disease, they are identical, macroscopically and microscopically, and are seldom seen in the supratentorial compartment of the central nervous system.<sup>16</sup> HBs can arise in the supratentorial space (over 100 reported cases)<sup>9</sup> but only 16 cases of pituitary stalk HBs have been reported—14 (87.5%) of which occurred in the setting of VHL.<sup>4,6,7,15,16,19,25</sup>

The authors describe a 61-year old man with VHL who developed a pituitary stalk HB 9 years after complete

resection of a cerebellar HB. Multiple, metachronous HBs are nearly universal in patients with VHL; however, the leptomeningeal dissemination of hemangioblastomatosis is an infrequently reported phenomenon following surgical resection in patients with and without VHL. To our knowledge, however, this is the first case of discrete metachronous HBs in a patient without VHL.

## CASE DESCRIPTION

### HISTORY AND INITIAL HOSPITAL COURSE: CEREBELLAR HB.

The patient is a 61-year-old right-handed male who initially presented at the age of 52 with blurry vision in the right eye and headache. Ophthalmological exam revealed compromised vision in the right eye (20/200) due to macular degeneration without evidence of tumor or hemangioblastoma. A brain MRI was performed for persistent headache and he was found to have a 3-cm enhancing tumor of the right cerebellar hemisphere (Figure

1A). He underwent a gross-total resection (Figure 1B) and remained neurologically intact following resection.

**Figure 1**

Figure 1.

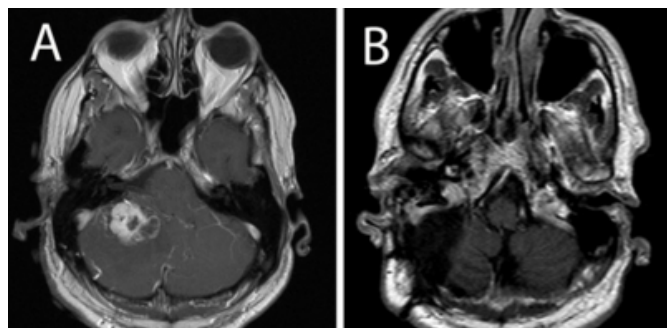


Figure 1. A brain MRI performed for persistent headache demonstrated a 3-cm heterogeneously enhancing tumor of the right cerebellar hemisphere abutting the middle cerebellar peduncle (Figure 1A). He underwent a gross-total resection (Figure 1B) and remained neurologically intact following resection.

His post-operative course was complicated by a wound infection requiring drainage and revision. Pathology was consistent with HB. Genetic testing for VHL disease was negative. He underwent yearly surveillance imaging for 7 years following surgery.

## **SECOND PRESENTATION AND HOSPITAL COURSE: PITUITARY STALK HB.**

Nine years following surgery the patient complained of vertigo, gait ataxia and imbalance. Brain MRI was performed to evaluate for recurrent tumor, but instead, a homogeneously enhancing suprasellar lesion was discovered (Figure 2A). Endocrinological work-up revealed normal anterior and posterior pituitary function. Ophthalmological exam revealed normal visual fields and stable 20/200 visual acuity in the right eye. The differential diagnosis included diaphragma meningioma, solid craniopharyngioma, atypical pituitary adenoma and metastasis. With subsequent growth on a repeat MRI 6 weeks later (Figures 2B-D), he underwent a right pterional craniotomy with orbitozygomatic osteotomy and gross-total resection of this lesion (Figures 2E & F).

**Figure 2**

Figure 2.

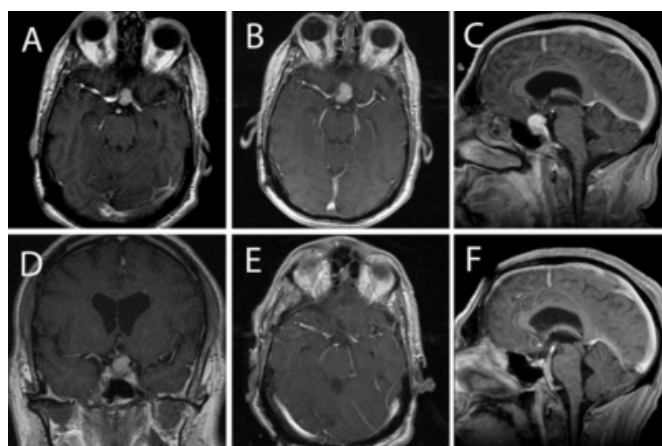


Figure 2. MRI performed 9 years following original resection revealed a homogeneously enhancing suprasellar lesion (Figure 2A). A 6-week follow-up MRI demonstrated growth of the lesion (Figures 2B-D) and he underwent gross-total resection of this lesion via right pterional craniotomy with orbitozygomatic osteotomy (Figures 2E & F).

Intraoperatively, the tumor was extremely vascular, arose from and completely enveloped the pituitary stalk and was adherent to the dorsum sella and the undersurface of the optic chiasm. Post-operatively, the patient developed diabetes insipidus that was controlled with desmopressin. He also developed a bitemporal hemianopsia, whose etiology appeared to be ischemic based on the ophthalmological examination. The former was secondary to stalk section to allow removal of the tumor, while the latter was likely due to interruption of perforators coming from the tumor capsule to the undersurface of the chiasm.

He is now disease-free 16 months following his last surgery and his vision continues to improve. He has no signs of further VNL lesions or HBs elsewhere in the CNS. He has persistent DI but has retained normal function of the adenohypophysis.

## **HISTOPATHOLOGY**

Figures 3 and 4 show the histopathological findings for the cerebellar and suprasellar HBs, respectively.

**Figure 3**

Figure 3.

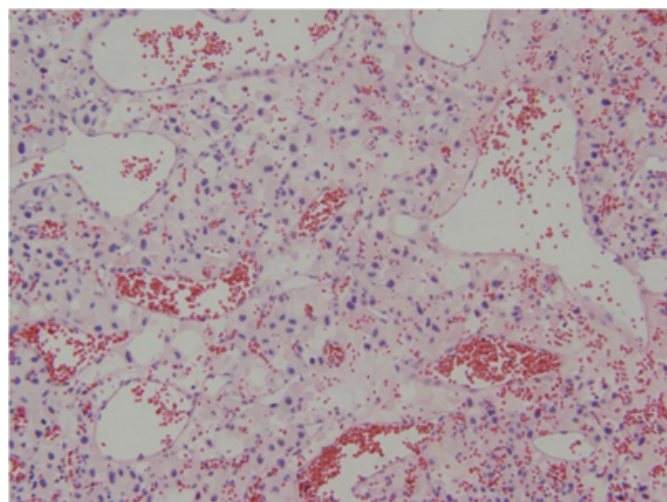


Figure 3. The initial excision shows a highly vascular tumor with stromal cells which are large and vacuolated.

**Figure 4**

Figure 4.

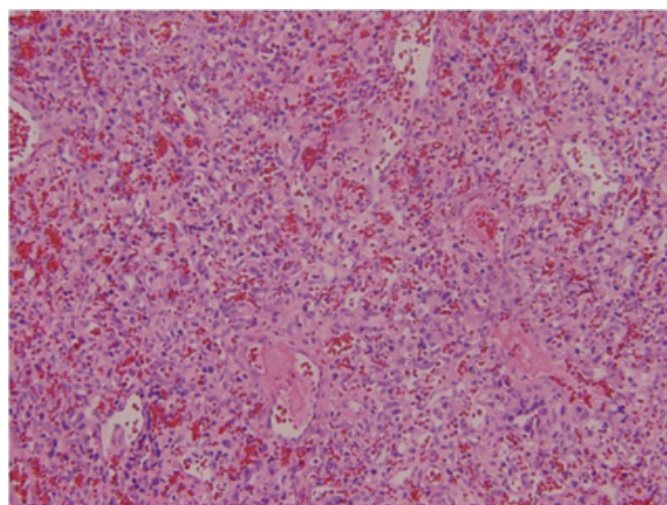


Figure 4. The excision nine years later shows similar findings to the initial excision.

Pathological examination revealed a highly vascular tumor with stromal cells that are large and vacuolated. The differential diagnosis includes HB versus metastatic renal cell carcinoma. Immunohistochemistry was performed to rule out metastatic renal cell carcinoma. The tumor cells were positive for inhibin and negative for CD10 and PAX-2 immunostains. The MIB-1 immunostain which recognizes the ki-67 nuclear proliferation showed a variable labeling index of up to 15%, which was elevated and quite unusual for this tumor. The morphological features and the staining

pattern were consistent with a HB.

## DISCUSSION

Hemangioblastomas are benign vascular tumors of the central nervous system composed of neoplastic stromal cells and blood vessels.<sup>16,24</sup> Most HBs arise in patients without VHL disease, are solitary lesions and develop in the cerebellum.<sup>11,16,26</sup> Recurrence after complete excision is rare<sup>13,21</sup> and developing a discrete, second lesion in patients without VHL has not been reported. We describe a case of metachronous HB in the pituitary stalk 9 years after resection of a cerebellar HB. VHL testing was negative and no further lesions were discovered along the neuraxis or viscera.

The pathogenesis of this second lesion is unknown. Despite genetic testing for an autosomal dominant VHL mutation, the patient could have another, an undefined genetic mutation that confers an increased systemic risk for HB development. Currently, no other mutations have been implicated in HB development. A limited number of cases of hemangioblastomatosis (leptomeningeal dissemination) have been reported,<sup>2,3,8,13,14,18,21,23,27</sup> all of which occurred after surgical resection and more than half occurred in non-VHL patients. Given the lack of de novo development of hemangioblastomatosis, Kim and colleagues<sup>14</sup> contend that spillage and spread of viable tumor cells into the CSF spaces must account for its development. They reported on one of only two cases of supratentorial spread as all other reported cases involved the posterior fossa and spinal cord.<sup>2,3,8,13,18,21,23,27</sup> Weil and colleagues<sup>27</sup> studied the genetic mutations of 4 patients without VHL who experienced hemangioblastomatosis and demonstrated that separate deposits of HB showed evidence of being derived from a single clone with a mutated copy of the VHL gene. They contend that further mutations in one or more other genes account for the malignant behavior and spread, despite the retention of a benign histopathological signature.

Both theories are speculative in this case. The former seems unlikely given the lack of systemic disease and other CNS lesions or laboratory findings are suspicious for VHL disease. The latter theory is not supported by the unifocal pattern of dissemination after surgery. Reported cases of the CNS infiltration usually exhibit diffuse leptomeningeal dissemination, which usually involves the spinal cord and infratentorial space. Kim et al.<sup>14</sup> believe this directionality of spread reflects CSF flow patterns and effects of gravity.

Supratentorial spread and involvement of the pituitary stalk are extremely rare and no cases of non-VHL metachronous HBs have been reported. All of these complicating factors contribute to the difficulty of determining the preoperative diagnosis in this case.

The suprasellar region is anatomically complex and the differential diagnosis of lesions in the area is broad.<sup>5</sup> The overlapping clinical features and the wide range of pathology in the region make preoperative diagnosis of lesions very challenging.<sup>5,20</sup> Diagnostic considerations in this case included craniopharyngioma, atypical pituitary macroadenoma, meningioma and metastasis. The main histopathologic differential diagnosis of HB includes angioblastic meningioma and metastatic renal clear cell carcinoma.<sup>1,4,12</sup> There is considerable disagreement in distinguishing angioblastic meningioma from HB or whether it is a separate entity.<sup>1,12</sup> Although both tumors may share some features, there are differences in anatomical location and gross appearance. Angioblastic meningiomas are usually supratentorial, solid and attached to the dura with the presence of a dural tail, while HBs are usually cystic tumors with mural nodules that lack dural attachment. The diagnostic difficulty in distinguishing HB from a metastatic renal cell carcinoma is due to the similarity in the arrangement of their stromal cells, which appear epithelioid and resemble renal cell carcinoma.<sup>1,17</sup>

Ultimately, the use of appropriate immunohistochemical stains is required to establish the correct diagnosis. Stromal cells of HB variably exhibit immunoreactivity to neuron-specific enolase, vimentin and S100 protein but do not react to endothelial cell markers and usually do not express glial fibrillary acidic protein. These features are not characteristic of meningiomas nor metastatic renal cell carcinoma.<sup>1</sup> The immunohistochemical staining, in this case, is consistent with the diagnosis of HB.

Given the limited numbers of reported cases of pituitary HBs, there is no consensus on their optimal management. Following 25 patients with VHL, Lonser and colleagues reported that pituitary stalk is the most common supratentorial location of HBs, constituting 29% of cases. However, only 16 cases have been reported in the literature, 14 (87.5%) of which arose in patients with VHL.<sup>4,6,7,15,16,19,25</sup> Lonser et al. recommended conservative management of these tumors in patients with VHL given that many tumors remained asymptomatic and the frequent occurrence of panhypopituitarism and DI that occurs with their removal.

<sup>4,7,16</sup> In our patient, lesion growth was documented on the 3-month follow-up MRI with radiographic evidence of compression of the optic apparatus; thus, treatment was recommended.

This case illustrates the difficulty of diagnosing tumors of the suprasellar region, especially in patients with a history of remote HB. Although suprasellar location of HB is rare and unusual, it should be considered in the histopathologic differential diagnosis of tumors of the suprasellar region. This case also argues for the necessity of long-term clinical and imaging follow-up in patients treated for sporadic HB. Such surveillance may identify local or distant HB recurrence, while the lesions are smaller in size and more amenable to safe removal.

## CONCLUSION

To our knowledge, there are no prior reports of cases describing a focal, distant site recurrence of HB in a non-VHL patient. This case illustrates the rare occurrence of metachronous HB in a patient without VHL disease and should be included in the differential diagnosis of second lesions in this population.

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**Author Information**

**Adeolu Olasunkanmi, M.D**

Department of Neurosurgery, New York University Langone Medical Center

**Robert E. Elliott, M.D**

Department of Neurosurgery, New York University Langone Medical Center

**Kia Newman, M.D**

Department of Neuropathology, New York University Langone Medical Center

**Irina Mikolaenko, M.D**

Department of Neuropathology, New York University Langone Medical Center

**David Zagzag, M.D**

Departments of Neuropathology & Neurosurgery, New York University Langone Medical Center

**John G. Golfinos, M.D.**

Department of Neurosurgery, New York University Langone Medical Center