Aggressive dissemination of central nervous system hemangioblastoma without association with von Hippel–Lindau disease: A case report and literature review

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INTRODUCTION

Hemangioblastomas (HBs) account for approximately 2% of central nervous system (CNS) tumors, usually have benign characteristics, and are well-circumscribed and highly vascular neoplasms. They account for 7.5% and 5% of all adult tumors of the posterior fossa and spinal cord, respectively.³

Approximately 66% of CNS HBs occur sporadically, and the remainder occurs in the context of von Hippel–Lindau (VHL) disease, an autosomal dominant neoplasia syndrome caused by a mutation in the VHL tumor suppressor gene.⁹ More than 80% of patients with VHL disease develop a craniospinal HB during their lifetime, and more than 90% of patients with VHL disease and a HB develop multiple CNS HBs. The development and progression of craniospinal HBs are the most frequent causes of morbidity and mortality in VHL disease.⁹

Although the dissemination of HBs in the CNS can occur frequently in patients with VHL disease, it is a rare condition in cases of sporadic HBs, and few cases have been reported in the literature.¹⁰
literature. Herein, we report a case of aggressive craniospinal dissemination of sporadic HB in a previously healthy patient who underwent multiple surgeries and died 4 years after the diagnosis of the first spinal dissemination due to disease progression. We conducted a literature review to identify similar cases and treatment options.

CASE REPORT

A 37-year-old man with no previous medical conditions was diagnosed with a posterior fossa tumor in 2011 and underwent surgery at another institution. Histopathological analysis was consistent with HB. The patient developed recurrence of the cerebellar lesion and underwent a new surgical approach and neoadjuvant stereotactic radiosurgery in 2014. In 2017, he was diagnosed with a lesion at the Th5 level and underwent partial resection of the lesion and subsequent stereotactic radiosurgery. Detailed records of the patient's previous procedures and treatments are not available.

In July 2019, the patient was referred to our neurosurgery facility; he was 45 years of age at the time. On admission, the patient presented with persistent neuropathic pain in the Th6 dermatome, radicular pain in the L1 dermatome, and mild paraparesis. Neuraxial magnetic resonance imaging (MRI) showed multiple contrast-enhancing brain and spinal cord lesions, with leptomeningeal enhancement [Figure 1].

The patient underwent initial screening for VHL disease with fundoscopy and computed tomography of the chest, abdomen, and pelvis, all of which were normal.

In July 2019, the patient underwent gross total resection (GTR) of intradural and extramedullary lesions at Th10 and L1, both with histopathological analysis compatible with HB [Figure 2]. He was discharged without new neurological deficits. In October 2019, he underwent GTR of a C5 lesion and developed quadriaparesis in the immediate postoperative period with progressive improvement.

Serial control examinations during outpatient follow-up showed progression of previously existing lesions and the appearance of new lesions in the neuroaxis [Figure 3]. After a multidisciplinary discussion with the oncology team, it was decided not to perform any adjuvant treatment.

In January 2020, he underwent GTR of a C1 lesion and a small median cerebellar lesion, when he developed worsening quadriaparesis in the immediate postoperative period and CSF leak, which was surgically corrected. In March 2020, he presented with a persistent headache and underwent endoscopic third ventriculostomy for the treatment of hydrocephalus.

He developed vertigo, dysphagia, and right hearing loss in April 2020 when he was hospitalized again for complete resection of a large lesion in the right cerebellopontine angle.

The patient developed postoperative worsening of dysphagia and CNS infection, which was treated with antibiotic therapy. At this time, two genetic tests for VHL gene mutations in blood DNA were performed, both of which were negative. There was no family history of VHL or stigmas suggesting the presence of the disease in other family members.

In June 2020, he underwent ventriculoperitoneal shunt, when he already presented with bradypsychism and...
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quadriplegia after multiple surgical interventions. In October 2020, he underwent the last surgical approach, with the excision of a voluminous right temporo-occipital lesion. There were no intraoperative complications or the need for blood transfusion in any of the surgeries, and all surgeries were performed with intraoperative neurophysiological monitoring.

The patient developed a generalized tonic-clonic seizure at home in early March 2021, which progressed to aspiration pneumonia. He was readmitted for the treatment of the infectious condition, but due to the prior neurological condition and clinical severity, palliative care was chosen together with the family. The patient died in March 2021 at the age of 47 years, 10 years after the first surgery, 7 years after the first local recurrence, and 4 years after the diagnosis of spinal dissemination.

DISCUSSION

HBs are highly vascularized tumors, most commonly located in the posterior fossa, and typically have benign characteristics, accounting for approximately 2% of CNS tumors and 5% of spinal cord tumors.[5,12] The presence of HBs in the CNS is associated with VHL disease in 10–40% of cases.[5]

VHL is an autosomal dominant syndrome caused by a mutation in the VHL tumor suppressor gene, with a prevalence of 1:36,000 births. Patients with VHL may develop visceral lesions such as renal cell carcinomas or cysts, pheochromocytomas, and pancreatic neuroendocrine tumors. CNS lesions include retinal and neuroaxis HB as well as endolymphatic sac tumors.[9,11] The most frequent cause of morbidity and mortality in VHL is the development and progression of craniospinal HBs. More than 80% of patients develop CNS HBs during their lifetime, and more than 90% of patients with VHL and HBs develop multiple lesions.[9]

There are several case reports and case series in the literature regarding multiple CNS HBs in patients with VHL,[7,11,14,18,28,34] however, the dissemination of HB in patients without VHL disease is extremely rare.

After an extensive review of the literature in PubMed and Google Scholar using the terms “Hemangioblastoma,” “Hemangioblastomatosis,” “Leptomeningeal dissemination,” and “von Hippel–Lindau,” we found 30 similar cases reported in the past 46 years [Table 1].[1-4,6,8,10,13,15,17,19,20,22-27,30,32,33]
Table 1: Characteristics of patients with HB dissemination without VHL.

| Author, year | Age at first surgery, sex | Primary site | Spinal involvement | Treatment | Interval to dissemination | Survival after dissemination | Cause of death |
|--------------|--------------------------|--------------|--------------------|-----------|--------------------------|------------------------------|-----------------|
| Mohan et al., 1976[22] | 28, M | Cerebellum | C, Th | Surgery (B + S), RTx (S) | 8 years | 2 years | Bronchopneumonia |
| | 39, M | Cerebellum | C, Th, LS | Surgery (B + S), RTx (B) | 14 years | 3 months | Bronchopneumonia |
| Tohyama et al., 1990[22] | 51, M | Cerebellum | Not present | Surgery (B) | 14 months | N/A* | Intracerebral hemorrhage |
| Hande and Nagpal, 1996[13] | 4, F | Cerebellum | C, Th, LS | Surgery (B), RTx (B + S) | 6 months | Alive* | N/A |
| Raghavan et al., 2000[23] | 36, M | Cervical spine | C | Surgery (S) | 11 years | Alive* | N/A |
| Weil et al., 2002[25] | 43, F | Cerebellum | C, Th, LS | Surgery (B + S), IFN-2α, Minocycline | 7 years | 1 year | Respiratory failure |
| | 47, F | Cerebellum | C, Th | Surgery (B + S), RTx (B + S) | 6 years | 4 years | Respiratory arrest |
| | 34, M | Cerebellum | C, Th, LS | Surgery (B + S), RTx (B + S) | 7 months | 3 years | Progression of prepontine tumor |
| | 41, M | Cerebellum | C, Th, LS | Surgery (B + S), RS (B), RTx (B + S) | 8 years | 2 years | Sudden death |
| Kato et al., 2005[15] | 29, F | Cerebellum | C, Th, LS | Surgery (B + S), RTx (B + S) | 22 years | Alive* | N/A |
| Lightfoot et al., 2007[20] | 71+, F | Cervicomedullary junction | C, Th | Surgery (B + S) | N/A | Alive* | N/A |
| Ramachandran et al., 2008[26] | 75, M | Cervical spine | C, Th, LS | Surgery (S) | N/A | N/A | N/A |
| Kim et al., 2009[17] | 41, M | Cerebellum | C, Th, LS | Surgery (B + S), RS (B), RTx (B + S) | 10 years | 1 year | Septic shock |
| Reyes-Botero et al., 2012[27] | 31, M | Cerebellum | C, Th | Surgery (B), Sunitinib | 5 years | 15 months | Septic shock |
| Chung et al., 2014[6] | 59, M | Cerebellum | Th | Surgery (B + S), RS (B) | 5 years | Alive* | N/A |
| Akimoto et al., 2014[1] | 45, F | Cerebellum | C, Th, LS | Surgery (B + S), RS (B + S), RTx (B + S) | 7 years | 2 years | Respiratory failure |
| | 57, F | Cerebellum | C, Th, LS | Surgery (B), RTx (B + S) | 4 years | Alive* | N/A |
| Seystahl et al., 2014[30] | 54, M | Cerebellum | C, Th | Surgery (B + S), Bevacizumab | 16 years | N/A | N/A |
| Amelot et al., 2015[2] | 40, M | Cerebellum | Not present | Bevacizumab | 32 years | Alive* | N/A |
| Park et al., 2015[24] | 55, F | Cerebellum | C, Th, LS | Surgery (B), Bevacizumab | 1 month | Alive* | N/A |
| Koo et al., 2016[19] | 46, F | Cerebellum | C, Th | Surgery (B + S), Bevacizumab | 5 years | 3 years | N/A |
| | 36, M | Cerebellum | Th, LS | Surgery (B + S) | 17 years | Alive* | N/A |
| | 45, M | Cerebellum | C, Th | Surgery (B), Bevacizumab | 3 years | Alive* | N/A |
| | 54, F | Cerebellum | Not present | Surgery (B), RTx (B) | 4 years | Alive* | N/A |
| Franco et al., 2017[10] | 48, M | Spine | N/A | Surgery (S) | 11 years | Alive* | N/A |
| | 62, M | Cerebellum | C, Th | Surgery (S) | 12 years | Alive* | N/A |
Patient characteristics, treatments, and survival time after the initial diagnosis of CNS dissemination varied among previously reported studies. Surgery was the mainstay treatment in most cases, and adjuvant therapies were variable, including radiotherapy, radiosurgery, and chemotherapy.

The term hemangioblastomatosis is usually referred to as diffuse leptomeningeal dissemination and may be less common in VHL-related HB due to its tendency toward multiplicity. Hemangioblastomatosis has been reported in several studies. The mechanisms by which HBs disseminate in the CNS are still unclear; some authors believe that it may be caused by the spread of tumor cells through the cerebrospinal fluid space after a lesion resection. The first two cases of disseminated sporadic HB were reported by Mohan et al., in 1976. Both patients were young men at diagnosis (28 and 39 years old), and both died from pneumonia after disease progression, similar to our case.

The mean age of patients at the first surgery was 44.8 years old (range, 4–75). In some reports, it was difficult to precisely determine the age of the patients at the first surgery, mainly due to incomplete or unavailable medical records.

In total, there were 18 men and 12 women. Most patients underwent initial resection of a posterior fossa HB; two patients were initially diagnosed with cervical spine HB, one patient with a nonspecified level spinal HB, and one patient with a cervicomedullary junction HB. In most cases, craniospinal dissemination was observed with the involvement of all neuroaxis, but in two cases, the dissemination was restricted to the brain, and in another, to the cervical spinal cord.

There was also great variety among the studies regarding the interval to the diagnosis of CNS dissemination. The interval ranged from 1 month to 32 years. Our patient presented with spinal dissemination 6 years after the first surgery.

In many studies, patients died within 4 years of the diagnosis of CNS dissemination. In one study, the patient survived for 10 years after the dissemination. In some studies, the patients were still alive at the time of publication, but with short follow-up periods or ongoing cases. Some patients who were alive at the time of publication presented with poor neurological status, and some were bedridden. The most common causes of death were infection and respiratory failure due to pontomedullary or cervical spinal cord compression.

Regarding adjuvant treatment, there was great heterogeneity among the studies, probably due to the rarity of this condition and the lack of evidence favoring adjuvant treatment. Surgical treatment was performed in all patients, and brain and spinal radiotherapy or radiosurgery were chosen as adjuvant treatments in many studies but with variable clinical and radiological outcomes. Chemotherapy was used in only five studies. One patient was treated with Interferon-2 and minocycline. Sunitinib was used in one patient, and three patients were treated with bevacizumab.

Vascular endothelial growth factor (VEGF) and VEGF receptors are expressed in HBs, and antiangiogenic therapy

**Table 1: (Continued).**

| Author, year | Age at first surgery, sex | Primary site | Spinal involvement | Treatment | Interval to dissemination | Survival after dissemination | Cause of death |
|--------------|--------------------------|--------------|-------------------|-----------|--------------------------|-----------------------------|----------------|
| Ohba et al., 2017 | 55, F | Cerebellum | C, Th, LS | Surgery (B + S), RTx (S) | 20 months | Alive* | N/A |
| Badran et al., 2018 | N/A, M | Cerebellum | N/A | Surgery (B), RTx (B + S) | N/A | Alive* | N/A |
| Bains et al., 2019 | 34, F | Cerebellum | C, Th, LS | Surgery (B + S), RTx (B + S) | 12 years | 13 months | N/A |
| Cuccarini et al., 2021 | 39, M | Cerebellum | C, Th, LS | Surgery (B + S), RTx (B + S), RS (B + S), Bevacizumab | 10 years | 10 years | Disease progression |
| Present case | 37, M | Cerebellum | C, Th, LS | Surgery (B + S), RS (B + S) | 6 years | 4 years | Pneumonia |

N/A: Not available, M: male, F: female, B: brain, S: spine, RTx: radiotherapy, RS: radiosurgery, IFN: interferon, C: cervical, Th: thoracic, LS: lumbosacral, HB: hemangioblastoma, VHL: von Hippel–Lindau. The patient died of an intracerebral hemorrhage soon after the diagnosis of central nervous system dissemination. At the time of publication, The patient was a 71-year-old woman who had previously undergone biopsy of a benign brain tumor at the same site 48 years earlier, but medical records were not available.
is now being considered as a therapeutic option for some patients.\[^{30}\] In three studies, patients with disseminated sporadic HBS were treated with bevacizumab; two patients had sustained stable disease for 12 months before evolving with progression of the lesions,\[^{8,30}\] and one patient evolved with immediate neurological improvement, but long-term follow-up was not established.\[^{24}\]

Lesions that are not surgically accessible can be treated with stereotactic radiosurgery and radiotherapy.\[^{5}\] Stereotactic radiosurgery has been used as a therapeutic option for CNS HBS, with local control of up to 91% at 2 years' follow-up in cases of VHL-related HBS. Radiotherapy has limited efficacy for tumors with peritumoral cysts and may result in peritumoral edema and cyst progression.\[^{9}\] Some authors suggest that sporadic HB with leptomeningeal dissemination is a radioresistant neoplasm since most of the patients recur despite adjuvant irradiation.\[^{4}\]

In VHL-related HBS, surgical treatment should be reserved for symptomatic lesions due to the unpredictable progression of tumors and to prevent unnecessary neurological dysfunction. Stereotactic radiosurgery can be an option for surgically inaccessible tumors and for patients who cannot tolerate surgery; however, it has shown similar tumor progression when compared to the natural history of untreated tumors after 7 years.\[^{9}\] Anti-VEGF agents have been used in clinical trials for retinal HBS, and more recently, some case reports have described the use of pazopanib hydrochloride, a multityrosine kinase inhibitor targeting VEGF pathways, for the treatment of inoperable or disseminated CNS HBS.\[^{16,21,29,31}\] The anti-tumor effects of pazopanib are thought to arise from inhibition of tumor vascularization by antagonism of proangiogenic receptors,\[^{14}\] but variable responses to treatment have been observed.\[^{31}\] There are no clinical studies on the use of anti-VEGF agents or pazopanib hydrochloride in cases of sporadic HBS, and the benefits of adjuvant therapy remain uncertain.

**CONCLUSION**

Dissemination of sporadic HB is rare and aggressive disease evolution is usually observed. Further studies are necessary to determine the optimal therapeutic options.

**Compliance with ethical standards**

The patient's relatives consented to the submission of the case report to the journal. The case report was written in accordance with the COPE guidelines and complies with the CARE statement. The authors declare no conflicts of interest. The authors have no relevant financial or nonfinancial interests to disclose.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent.

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**Conflicts of interest**

There are no conflicts of interest.

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