Case Report

Disseminated cerebellar hemangioblastoma in two patients without von Hippel–Lindau disease

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Abstract

**Background:** Two patients who had received a total resection of cerebellar hemangioblastoma developed cerebrospinal fluid dissemination during a long-term follow-up period. We present this rare disease with discussion based on the literature.

**Case Description:** The patients were two women aged 45 and 57 years. In the cerebellar hemisphere, one patient had cystic hemangioblastoma of mural nodule type and the other had solid type. Both the patients successfully underwent total resection by craniotomy. They presented no mutations in the von Hippel-Lindau (VHL) gene or lesions in the other organs. One patient developed local recurrence 38 months after the initial surgery, and received stereotactic radiosurgery. Three spinal cord tumors developed 91 months later, and the tumors were disseminated to the entire cerebrospinal cavity 107 months later. The other patient developed hydrocephalus 53 months after the initial surgery with tumor tissues disseminated in the intracranial subarachnoid space. The conditions of the two patients gradually aggravated despite treatment with ventriculo-peritoneal shunt and irradiation to the whole brain and whole spinal cord.

**Conclusion:** Cerebrospinal fluid dissemination of cerebellar hemangioblastoma was found dominantly in non-VHL patients. The diagnosis was made 10 years after the initial surgery. Irradiation therapy was performed, but the patients died about 2 years after the diagnosis was given. Molecular targeted therapies including vascular proliferation suppression have been attempted lately, but no effective therapy has been established. Early diagnosis of dissemination as well as combination of aggressive excision and stereotactic radiosurgery are considered to be appropriate for current interventions.

**Key Words:** Cerebellar hemangioblastoma, cerebrospinal fluid dissemination, von Hippel-Lindau disease

INTRODUCTION

Cerebellar hemangioblastoma is a vascular tumor with a clear border that develops intramedullary to extramedullary. Solitary hemangioblastomas are for the most part considered benign, curable by total resection, except in those cases associated with von Hippel-Lindau (VHL) disease.
We report our experience of cerebrospinal fluid dissemination in two patients who underwent total resection of cerebellar hemangioblastoma that was assessed as sporadic, non-VHL type to account for 62-75% of hemangioblastomas by the direct sequence of genomic deoxyribonucleic acid (DNA).\(^{[4,13]}\)

**Case 1**
A 45-year-old female had no remarkable findings in her medical or family history. She started to have the symptoms of sudden headache and nausea. At the time of visit to our hospital, she presented with right dominant gaze rotatory nystagmus and right cerebellar hemisphere symptoms. Head computed tomography (CT) scan and magnetic resonance imaging (MRI) showed a highly contrasted cystic tumor with a mural nodule in the right cerebellar hemisphere [Figure 1a]. The cerebral angiography showed an intense tumor stain from the anteroinferior cerebellar artery and draining into the petrosal vein [Figure 1b]. The blood biochemistry findings showed no abnormalities such as polycythemia. No abnormal finding was found by a whole body scan including the retina. No VHL gene mutations were found by direct sequence of DNA 3p25 region using whole blood. Total tumor resection by craniotomy was conducted, and a pathological diagnosis of hemangioblastoma was made [Figure 1c]. The symptoms disappeared and she was discharged on foot. Thereafter, recurrence of a nodular tumor developed at the site of the initial tumor 38 months after the initial surgery [Figure 1d]. Since she did not wish to receive surgery, local stereotactic radiosurgery (SRS) at 20 Gy was performed. As a result, the tumor gradually shrank over a period of 2 years. [Figure 1E]. However, paraplegia developed in the legs 91 months later. MRI showed the presence of three spinal cord tumors at the levels of C7, Th7, and L2 [Figure 1f]. The tumor at Th7 was resected and diagnosed as hemangioblastoma. The tumor at C7 was treated with cyberknife at 17 Gy in five fractions. The tumor at L2 was also resected 107 months later during follow up because the tumor enlarged. During this surgery, microvascular proliferation was observed in the arachnoid around the tumor, for which the presence of hemangioblastoma cells was confirmed by pathological examination. The general condition of the patient rapidly deteriorated thereafter, and MRI revealed disseminated foci in the subarachnoid space in the cranium as well as over the spinal cord. Ventriculo-peritoneal shunt (VP shunt) and irradiation at 36 Gy to the whole brain and whole spine were performed, but no improvement was obtained [Figure 1g,h]. The patient died due to respiratory failure after the course of 120 months. Autopsy findings showed the foci restricted in the cerebrospinal region. There was multicentric nodular dissemination of hemangioblastoma in the cerebrospinal subarachnoid space, and compression of the medulla oblongata was considered to be the cause of death [Figure 1i-k]. The initial tumor treated by SRS became fibrosis foci accompanied by hyalinization with a maximum diameter of 15 mm, and no viable tumor tissues were observed [Figure 1l].

**Case 2**
A 57-year-old female whose mother had multiple renal cysts had a medical history including a diagnosis of a renal cyst and surgery of coxarthrosis. She visited our hospital with complaints of photophobia and unstable gait. She presented with left cerebellar hemisphere symptoms and scanning speech. Head CT showed a solid tumor highly enhanced in the left cerebellar hemisphere [Figure 2a]. Cerebral angiography revealed tumor stain from the postero-inferior cerebellar artery and draining to the cerebellar vein [Figure 2b]. The blood biochemistry findings showed no abnormalities. No abnormal findings were found by a whole body scan including the retina. No VHL gene mutations were found using whole blood. Total resection of the brain tumor by craniotomy was performed, and a pathological diagnosis of hemangioblastoma was made [Figure 2c, d]. Histological VHL analysis showed a mutation from CAA to TAA at exon 2 and codon 132. She visited the hospital 53 months later due to brain contusion from a fall. Head CT and MRI showed no tumor recurrence at the site of the initial surgery, but diffuse disseminated foci were observed in the subarachnoid space, accompanied by hydrocephalus [Figure 2e, f]. VP shunt was performed to treat hydrocephalus. A neuroendoscopy examination showed a yellowish orange colored tumor attached to the third ventricle floor with a definite draining vein [Figure 2g]. The presence of hemangioblastoma cells was confirmed by a cytological examination of the cerebrospinal fluid [Figure 2h]. Spinal MRI showed an extensive spinal dissemination. Therefore, irradiation at 30.6 Gy to the whole brain and whole spine was performed. She was discharged with an aid for walking. The disseminated foci gradually proliferated during the 90 months after the initial surgery, and the patient remains bedridden due to quadriplegia [Figure 2i, j].

**DISCUSSION**
The guidelines for the diagnosis and treatment of VHL were published in Japan in 2011.\(^{[13]}\) This guideline indicate the incidence of development of hemangioblastoma in cerebellum is 44-72%, in brain stem is 10-25%, and in spinal cord is 13-50% of the VHL patients.\(^{[13]}\) However, the guidelines contain no entries on the possibility of cerebrospinal fluid dissemination.

Literature review revealed only 12 patients reported with cerebrospinal fluid dissemination of cerebellar hemangioblastoma.\(^{[14,11,14,15]}\) With our report, the total number of patients described in literature would be 14.
The demographic characteristics and various other factors been delineated in the Table 1. The number of male and female patients was equal, and the age ranged from 17 to 71 years (median: 44 years). The duration from initial diagnosis of cerebellar hemangioblastoma to identification of the disseminated disease ranged between 4 and 22 years (median: 114 months). As a result, nine patients had no germline VHL mutations, and they were given a diagnosis of a non-VHL sporadic tumor. There was no significant difference between three VHL patients and nine non-VHL patients in terms of age, sex, and time to diagnosis of dissemination, etc., All patients underwent cytology of cerebrospinal fluid or resection of nodular spinal lesions demonstrated on MR images, and a definite diagnosis was made in each case. Almost all patients received irradiation to the whole brain and spine after diagnosis of disseminated disease, and additional SRS was performed if indicated. VP shunt was performed in six patients. Twelve patients died. The survival period after the initial diagnosis was between 74 and 171 months (median: 127 months), and the survival period after diagnosis of dissemination was between 3 and 37 months (median: 24 months). The period until diagnosis of dissemination was about 10 years after initial diagnosis, and the survival period following dissemination was 2 years. Mechanisms of recurrence and dissemination of cerebellar hemangioblastoma have been discussed. De la Monte et al. [7] argued that local recurrence after a total resection was likely to occur in male patients with the initial onset at the age of <30 years, with VHL, with multiple tumors, with small and solid tumors, and with many eosinophilic stromal cells in the tissues. However, the presence of multiple tumors and abundant eosinophilic stromal cells also suggest
tumor features associated with VHL. \[1\] Moreover, no reports have demonstrated that local recurrence and disseminated tumors have the same histological features as the initially isolated tumor. Kim et al. \[4\] considered that spillage of tumor cells during resection was one of the causes of dissemination. However, in principle, vascular rich hemangioblastoma is resected as a single tumor mass by repeating a careful detachment process from the surrounding brain, and therefore spillage of tumor tissues is very unlikely to occur. In the two cases described earlier, no local recurrence was observed when extensive dissemination was confirmed. If tumor cells were spilled during tumor resection, local recurrence would have been observed in a relatively short period. However, in the two cases, a median of 10 years elapsed until confirmation of dissemination. From these

Figure 2: Clinical and pathological images of Case 2. (a): A contrast-enhanced CT scan image at the initial examination. A homogenously enhanced solid type tumor was observed in the left cerebellar hemisphere. (b): Cerebral angiography showed pronounced tumor stain and venous drainage. (c): The tumor consisted of capillary proliferation and proliferation of interstitial foamy stromal cells (H and E, ×200). (d): Total resection of tumor was performed at the initial surgery. (e): Gadolinium-enhanced T1-weighted MRI showed enhanced diffused dissemination at the basal cistern and ambient cistern of the brainstem 53 months after the initial surgery. (f): Dissemination image in the ambient cistern of the brainstem and in the suprasellar cistern with a complication of severe hydrocephalus. (g): Neuroendoscopic examination of the third ventricle during ventriculo-peritoneal shunt showed a clear ventricular wall and a yellowish brown colored nodular tumor at the ventricle floor. The presence of an obvious draining vein was confirmed. (h): A small number of large tumor cells with foamy cytoplasm were observed in the cerebrospinal fluid. (Giemsa stain, original magnification ×100) (i): VP shunts improved hydrocephalus, but there was a gradual increase in tumor tissues contrasted in the subarachnoid space. (j): The entire subarachnoid space of spinal cord was filled with tumor tissues.
findings, local recurrence seems unlikely to be the origin of spinal dissemination.

When dissemination is associated with VHL, a new tumor focus may develop at any site of the central nervous system and dissemination may be one of the phenotype of tumor development. However, no VHL gene mutations were confirmed in 75% of the patients with dissemination. Regarding the accuracy of the analysis of VHL gene mutation, DNA direct sequence achieves diagnosis in 75% of VHL patients.\cite{Weil2002, Courcoutsakis2008, Mohan1976} By combination with multiplex ligation-dependent probe amplification (MLPA), it will enable diagnosis in 84% of VHL patients.\cite{Kim2009} This means that 16% of VHL patients cannot be detected with the currently available techniques. Therefore, most of the patients with dissemination in this analysis are not assurred to be definitely non-VHL.

Weil et al.,\cite{Weil2002} who reported dissemination in four non-VHL patients, found no germline alteration of the VHL gene, but observed a somatic mutation of one copy of the VHL gene. Actually, 33–67% of hemangioblastoma tissues showed an allelic loss of the VHL gene, which was also observed in one of our two patients (Case 2). Based on the results of the comparative genomic hybridization (CGH), Weil et al.\cite{Weil2002} suggested that a somatic mutation of the VHL gene involving loss of the NF1 gene in 17q12 and loss of p15 and p16 genes in 9p21 was highly associated with dissemination of hemangioblastoma. An overlooked VHL mutation at the germline level or the addition of multi-stage gene mutations to a somatic mutation may be a cause of dissemination.

The autopsy findings of Case 1 and endoscopic findings of Case 2 attracted interest scientifically. Disseminated hemangioblastoma cells behaved as if they were implanted in the subarachnoid space, and then formed a new nodule of hemangioblastoma. The findings in Case 1 (three spinal cord tumors, a draining vein attached to the tumor, and tumor nodules around the brain stem observed at the autopsy) and the findings in Case 2 (a tumor mass formation with a draining vein at the third ventricle floor, etc.) are different from the patterns of accumulation of tumor cells observed in patients with dissemination of glioblastoma or metastatic tumor. In fact, spinal fluid examination of the present two cases showed very few floating cells and a slight increase in protein. In addition, a cytological examination showed a small number of stromal cells. These findings do not support a mechanism by which abundant tumor cells are disseminated to form extensive foci, but they suggest a pattern by which a small number of tumor cells implant at some locations, and then form tumors at the locations, which subsequently proliferate to form extensive foci. Therefore, interventions such as early detection of dissemination, surgical removal of the local tumor, and stereotactic radiation may prevent widespread dissemination.

The effects of therapies for cerebospinal fluid dissemination of hemangioblastoma were disappointing. Most of the patients received irradiation to the whole brain and whole spine. Moreover, they were treated with angiogenesis inhibitors such as interferon-alpha,\cite{Hanse2007} thalidomide,\cite{Kato2005} sunitinib\cite{Kato2005} and an EGFR selective inhibitor erlotinib.\cite{Reyns2003} However, no therapy has shown clinical efficacy. It is assumed that the early detection of dissemination and the performance of aggressive therapies for local tumors are key to preventing the progression of dissemination.

Table 1: Summary of reported cases of disseminated hemangioblastoma

| Author      | Age, Gender | Duration | Treatment                          | VHL   | OS    | Autopsy |
|-------------|-------------|----------|------------------------------------|-------|-------|---------|
| Mohan J (1976) | 28, M       | 8 y      | Surg, WB/WS-RTx                    | Not examined | 10 y  | (+)     |
|             | 39, M       | 14 y     | Surg                               | Not examined | 14 y 3 m | (+)     |
| Weil RJ (2002) | 43, F       | 7 y      | Surg, VPS, IFN-2a                   | (−)   | 8 y   | (+)     |
|             | 47, F       | 6 y      | Surg, VPS, FB/FS-RTx               | (−)   | 10 y  | (−)     |
|             | 34, M       | 7 m      | Surg, WB/WS-RTx                    | (−)   | 3 y 8 m | (−)     |
|             | 41, M       | 8 y      | Surg, VPS, WB/WS-RTx               | (−)   | 8 y   | (−)     |
| Reyns N (2003) | 50, M       | 7 y      | Surg, VPS                          | (+)   | 7 y 6 m | (−)     |
| Kato M (2005) | 50, F       | 22 y     | Surg, VPS, WB/WS-RTx               | (−)   | 23 y+ | Not described |
| Hanse MC (2007) | 17, F       | 10 y     | Surg, WB/WS-RTx                    | (+)   | 10 y 3 m | (−)     |
| Lightfoot NJ (2007) | 71, F     | 12 y     | Surg, WB/WS-RTx                    | (−)   | 13 y  | (−)     |
| Courcoutsakis NA (2008) | 43, M      | 12 y     | Surg, WB-RTx                       | (+)   | 14 y  | (−)     |
| Kim HR (2009) | 51, M       | 10 y     | Surg, WS-RTx, GK, VPS              | (−)   | 11 y  | (−)     |
| Zhang Q (2011) | 46, F       | 11 y     | Surg, VPS, GK                      | (+)   | 12 y 3 m | Not described |
| Presented cases | 45, F      | 7 y 7 m  | Surg, SRS/CK, WB/WS-RTx, VPS       | (−)   | 10 y  | (+)     |
|             | 57, F       | 5 y 3 m  | Surg, WB/WS-RTx, VPS               | (−)   | 7 y 6 m+ | Still alive |

VHL: von Hippel-Lindau disease, VPS: Ventriculo-peritoneal shunt, IFN: Interferon, FB/FS-RTx: Focal brain and spine radiotherapy, GK: Gamma knife, SRS: Stereotactic radiotherapy, CK: Cyber knife, y:Years, m:Months, OS: Overall survival
CONCLUSION

Dissemination of cerebellar hemangioblastoma is mostly found in non-VHL patients. Since dissemination is confirmed at approximately 10 years following the initial resection of the tumor, long-term follow-up of these tumors may be necessary. It is strongly suggested that routine screening of these patients for any neurological signs and early imaging of the cerebrospinal axis and providing an appropriate treatment will lead to better prognosis. Development of a more accurate screening method for VHL gene mutations and new therapies including molecular targeted therapy for hemangioblastoma are expected.

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Commentary

Akimo et al. report their treatment of two patients with sporadic intracranial hemangioblastomas (HBs) treated with surgery, who were found to have disseminated disease via cerebrospinal fluid over a follow-up of 10 years. Central nervous system HBs are considered indolent vascular tumors, with ill-defined cellular lineage being presently classified as World Health Organization (WHO) Grade I tumors. They occur either sporadically or associated with von Hippel–Lindau (VHL) disease. About 7-10% of all adult posterior fossa neoplasms and 4% of spinal neoplasms will be HBs. In turn, 75% of the HBs will be sporadic in origin with over 90% of them occurring in the cerebellum.

VHL is an autosomal dominant inherited syndrome and a systemic disease requiring a multidisciplinary approach. Sporadic HBs have been associated with allelic losses and mutations in the VHL gene, however, in the absence of familial inheritance, an identified genetic mutation, retinal hemangiomas and other associated tumors, they are considered sporadic tumors alone. The goal of surgery is directed toward devascularizing the tumor followed by a total neurosurgical resection, recurrences usually being associated with subtotal or incomplete resections. There are no guidelines for the follow-up of patients with sporadic HBs but recommendations are to monitor patients up to 10 years. Histology appears to correlate with the recurrence rates, a 25% recurrence with the cellular subtype and 8% recurrence with the reticular subtype. Various targeted antiangiogenic therapies have been used to control disseminated tumor without any guidelines or recommendations for their use for HBs.

Why does the phenomenon of tumor dissemination occur in some cases, whereas in others there appears to be good tumor control? Our understanding of the primary DNA sequencing has progressed significantly since identification of the human genome over a decade ago. The ability to deep sequence metastatic clones has revealed that tumor cells possess varying mutations, differing in both the primary and secondary tumor. Studies on leukemia have revealed that the clones harboring the most complex genetic alteration may not be the dominant mutation and may not be the clones responsible for relapses after treatment. We now have the initial evidence to support a high prevalence of genetic heterogeneity being observed at various stages of cancer evolution. Different cancer types have now
been found to have clones that are able to metastasize early as well as a clonal subset capable of metastasizing in a delayed manner and this depends on factors like the cancer cell pool, genetic instability, intratumoral heterogeneity, and proliferation rates.[4] Are there subsets of indolent tumors such as sporadic HBs that are evolving with differing genomic profiles? How do we identify and stratify these variants? How do we target these evolving subsets with molecular targeted therapies?

Akimo et al. in their report clearly brings out the need for long-term follow-up for the so called ‘benign’ or indolent pathology. As we advance with the identification of interactions between tumor cells and the microenvironment,[1] use of network biology and mathematical, computational models to further our understanding of genetic interactions and global networks in human cells, our ability to visualize tumor biology as a kaleidoscope of interactions will enhance. In turn, we can hope that this results in therapeutic strategies for a variety of intracranial tumors and their variants.

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