

Case Report

Long-Term Follow-Up Clinical Courses of Cerebellar Hemangioblastoma in von Hippel-Lindau Disease : Two Case Reports and a Literature Review

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Although cerebellar hemangioblastomas are histopathologically benign, they yield a degree of malignant clinical behavior in long-term follow-up. We present two cases of long-term progression of renal cell carcinoma, which had been diagnosed as renal cysts during treatment for cerebellar hemangioblastoma. A 14-year-old male with von Hippel-Lindau disease was admitted for a cerebellar hemangioblastoma with multiple spinal hemangioblastomas and a renal cyst. After primary total resection of the cerebellar hemangioblastoma, the patient required two further surgeries after 111 and 209 months for a recurrent cerebellar hemangioblastoma. Furthermore, he underwent radical nephrectomy as his renal cyst had progressed to renal cell carcinoma 209 months after initial diagnosis. A 26-year-old male presented with multiple cerebellar hemangioblastomas associated with von Hippel-Lindau disease and accompanied by multiple spinal hemangioblastomas and multiple cystic lesions in the liver, kidney, and pancreas. He underwent primary resection of the cerebellar hemangioblastoma in association with craniospinal radiation for multiple intracranial/spinal masses. Unexpectedly, a malignant glioma developed 83 months after discovery of the cerebellar hemangioblastoma. At the same time, renal cell carcinoma, which had developed from an initial renal cyst, was diagnosed, and a radical nephrectomy was performed. In the view of long term clinical course, cerebellar hemangioblastoma associated with von Hippel-Lindau disease may redevelop even after primary total resection. In addition, associated lesions such as renal cysts may also progress to malignancy after the passing of a sufficient length of time.

KEY WORDS : Cerebellar hemangioblastoma · von Hippel-Lindau disease · Renal cyst · Renal cell carcinoma.

INTRODUCTION

Cerebellar hemangioblastomas are highly vascular benign tumors that comprise about 2% of all intracranial tumors^{3,12}. They may occur sporadically, but have been found to associate with von Hippel-Lindau (VHL) disease in about 30% of cases. VHL disease includes central nervous system (CNS) hemangioblastoma, renal cell carcinomas or cysts, pancreatic islet cell tumors or cysts, pheochromocytomas, and papillary cystadenomas of the epididymis and broad ligament¹. Existing as a dominantly inherited cancer syndrome, VHL is transmitted in an autosomal dominant fashion with greater than 90% penetrance⁹. Furthermore, it is well documented

that, in spite of complete excision of cerebellar hemangioblastomas, they may develop further as *de novo* lesions in patients with VHL disease, occasionally many years after the initial diagnosis⁸.

We report two cases of cerebellar hemangioblastomas in patients with VHL disease. Both patients had undergone more than two separate procedures for the treatment of a recurring cerebellar hemangioblastoma and through the monitoring of VHL-related systemic disease during a follow-up period of more than eight years, it was found that both had developed subsequent renal cell carcinoma. We considered the possibility of progression from renal cysts, discovered at the initial diagnosis of cerebellar hemangioblastomas with VHL, to renal cell carcinomas.

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CASE REPORT

Case 1

A 14-year-old male presented with headache, dizziness, and



Fig. 1. Serial postcontrast computed tomography (CT) of the abdomen from initial diagnosis. Postcontrast CT of the abdomen at admission demonstrating a renal cyst (double arrow) in the right kidney (A). A two-hundred-and-nine months follow-up post-contrast CT scan of the abdomen revealing a renal cell carcinoma (arrow) in the right kidney (B) and an enlarged renal cyst (arrowheads) (C).

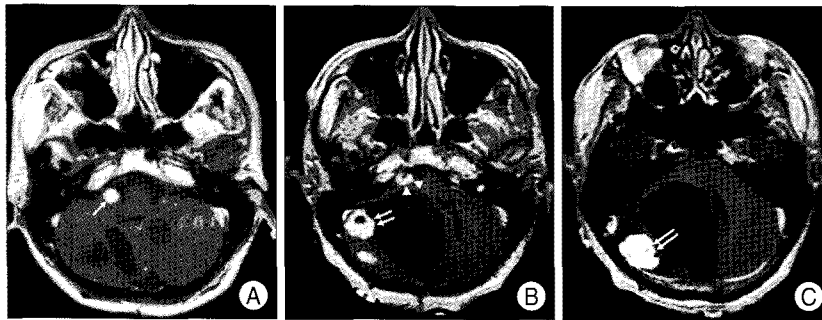


Fig. 2. One-hundred-and-eleven months after the first operation. An axial (A) gadolinium-enhanced MRI showing multiple cysts and a newly developed enhancing mural node (arrow). Axial gadolinium-enhanced MR images obtained 98 months after the second surgery, demonstrating the recurrence of hemangioblastoma with two separated mural nodes (double arrow) (B and C). The mass for which previously radiosurgery was performed, remained unchanged (arrowheads) (B).

vomiting. He had experienced no previous medical problems except for a headache which had gradually worsened over the previous months. Neurological examination disclosed cerebellar signs such as ataxic gait and motor incoordination of the upper and lower extremities. The magnetic resonance imaging (MRI) with a gadolinium enhancement revealed a large cyst, containing two enhancing mural nodes, located in petrous and dorsal side of cerebellar hemisphere. An investigation was initiated to search for systemic manifestation of VHL disease. Multiple small masses located at C4, T3, and T8 level were found on whole spine MR images with gadolinium enhancement. A computed tomography (CT) scan of the abdomen with contrast revealed low density cystic lesions on the right kidney (Fig. 1A), and other abdominal visceral organs showed no abnormalities. Ophthalmologic examination with fundoscopy demonstrated vascular abnormalities of retina compatible with retinal angioma. A diagnosis of VHL disease was made based on both clinical criteria⁸⁾, and his mother's family history of VHL disease.

Surgery was performed to remove the cerebellar hemangioblastoma via a suboccipital craniectomy. A highly vascular mass was found at the posterior petrosal portion of cerebellar hemisphere. Additionally, a cystic portion, filled with yellow fluid, extended into the cerebellar hemisphere. The tumor nodule and cyst wall were all removed completely. Post-

operatively, the patient remained neurologically intact and the postoperative course was uneventful. A decision was made to monitor for spinal hemangioblastomas, renal cysts, and retinal angioma through periodic follow-ups.

One-hundred-and-eleven months after his first surgery, he visited the emergency room with a severe headache, dizziness, and nausea. Brain MRI with enhancement revealed multiple large cysts at the previous surgical site with a newly developed enhanced mass located at the ventrolateral side of the

medulla (Fig. 2A). A cystoperitoneal shunt was performed to control the mass effect of the cyst, and he underwent Gamma Knife radiosurgery for the enhanced mass given that it was small, solitary, and located in a surgically inaccessible area. In the mean time, the renal cyst and retinal angioma had remained quiescent without evidence of progression. He was uneventful until ninety-eight months after the shunt operation until he required additional surgery of mass removal for a recurring hemangioblastoma of two separated enhanced masses attached to lateral petrous portion and transverse-sigmoid sinus junction (Fig. 2B, C). An abdominal CT scan revealed that the renal cyst was transforming into a suspicious renal cell carcinoma (Fig. 1B, C), and he underwent a right radical nephrectomy. Pathological examination of the mass demonstrated a clear-cell carcinoma. Fortunately, in the ventrolateral mass of the medulla, to which gamma knife radiosurgery was performed, multiple spinal masses and the retinal angioma remained unchanged since his last examination. He was discharged and visits our outpatient clinic as part of a regular radiologic follow-up.

Case 2

A 26-year-old male patient was admitted with a headache and dizziness which had developed over one month period. A neurological examination revealed a papilledema, horizontal

nystagmus, difficulty in tandem gait, and ataxic gait. T1-weighted MRI revealed a large hypo-intense mass lesion in the right cerebellar hemisphere associated with a ventral mixed iso-intense area and displacement of the vermis contralaterally. T2-weighted MRI demonstrated a flow void sign in the ventral mass lesion, and high signal intensity in the cerebellar mass lesion. Further MRI with gadolinium enhancement showed a well enhanced mass attached to the cerebellar vermis with a cyst occupying the right cerebellar hemisphere (Fig. 3A). Furthermore, multiple small enhanced lesions were also observed in the left cerebellar hemisphere. A whole spinal MRI with enhancement revealed multiple small enhanced mass lesions at the C1-2, C5, C6, T7, and T8 levels (Fig. 3B). An abdominal CT demonstrated multiple cystic lesions in the liver, both kidneys, and the pancreas.

A midline suboccipital craniectomy was performed to remove the hemangioblastoma. During surgery, as we were opening the dura mater, the cystic component of tumor was observed on the surface of the cerebellar hemisphere. The tumor had a well-defined gliotic plane and gross total resection was accomplished after coagulation of tumor feeders and the tumor surface. Histopathological diagnosis was a hemangioblastoma. For the multiple intracranial and spinal lesions, he underwent whole brain and spinal radiotherapy with 54cGy and 30cGy, respectively. Abdominal multiple cystic lesions were closely observed through periodic radiologic evaluations.

Eighty-three months after craniospinal irradiation, he presented to the emergency department with a disabling headache, dizziness, and nausea, all of which had developed over the previous month. A CT scan revealed a large, poorly delineated enhancing mass at one of the original tumors. The MRI revealed an irregularly well-enhanced mass lesion in the right cerebellar hemisphere at the same location of the previously resected hemangioblastoma (Fig. 4A). The mass exhibited a heterogeneous and irregular-shaped enhancement along the thickened wall. The second operation was performed to excise the irregularly enhanced mass, and a gross total resection was achieved. Pathologic findings of the tumor were large pleomorphic cells with a high mitotic rate, pseudopalisading geographic necrosis, and prominent endothelial proliferation. The histopathological diagnosis was glioblastoma multiforme (GBM). Additionally, a CT scan revealed a renal cell carcinoma which had once existed as cystic lesions of kidney, and therefore, a radical nephrectomy was performed. However, the spinal multiple mass remained quiescent. Four months after this surgery, the patient presented with dysarthria, dysphagia, a severe headache, and vomiting. A more diffuse, irregular enhancing mass extending into brain stem was visualized on MRI with enhancement (Fig. 4B). He declined fur-

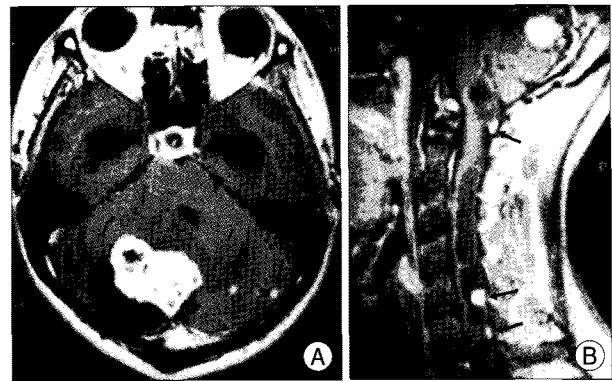


Fig. 3. Axial (A) gadolinium-enhanced magnetic resonance image (MRI) at initial presentation demonstrating hemangioblastoma with mural nodes attached to vermis and tentorium. Multiple small lesions are also observed in the left cerebellar hemisphere (arrows). Sagittal (B) MRI with gadolinium enhancement revealing multiple spinal masses located at C1, C5, and C6 (arrows).

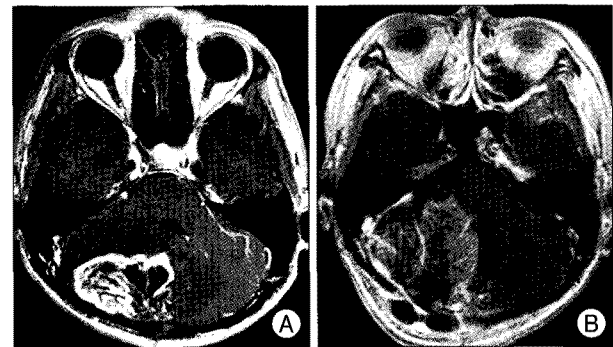


Fig. 4. Axial (A) magnetic resonance image (MRI) with gadolinium enhancement obtained 83 months after the first surgery, revealing a cystic tumor with a heterogeneous irregular enhancement in the thickened walls at previous surgical site. Four months after the last surgery, an axial (B) MRI with gadolinium enhancement demonstrating a more diffuse, irregular enhancing mass extending into the brain stem.

ther treatments, and died eight weeks later.

DISCUSSION

Hemangioblastomas comprise approximately 2% of primary CNS tumors^{4,13,14} and are histologically benign vascular neoplasm composed of endothelial and stromal cells¹¹. They may occur sporadically, but are commonly associated with VHL disease. Up to 72% of patients with VHL disease may have at least one cerebellar hemangioblastoma, and more than 40% with this disease will harbor spinal cord hemangioblastomas¹¹. Further, 5 to 31% of cerebellar hemangioblastomas occur in association with VHL disease, and 80% of spinal cord hemangioblastomas are associated with this disease^{10,15}. As an autosomal dominant disorder, VHL is characterized by multiple hemangioblastomas of the central nervous system and cysts or tumors of abdominal organs such as the kidney, adrenal gland, and pancreas^{2,11}. It occurs as a consequence of mutation in the VHL tumor suppressor gene on

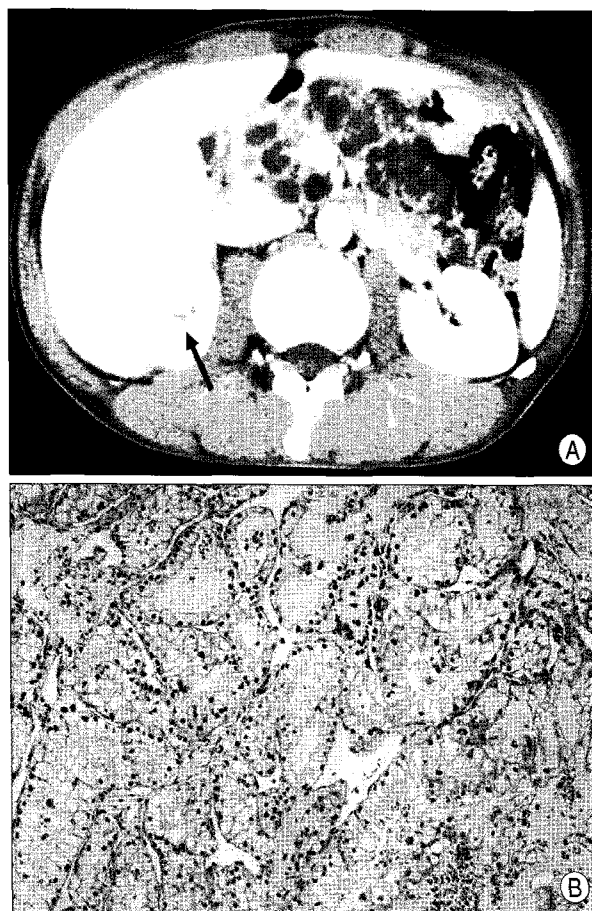


Fig. 5. A : Post-contrast abdominal computed tomography obtained 83 months after the time of initial diagnosis revealing a renal cell carcinoma (arrow) at the upper pole of the right kidney. B : Pathologically, the right kidney contains clear cells with inconspicuous nucleoli forming prominent microcysts, which is typical of clear cell renal carcinoma (H & E \times 100).

chromosome 3, a mutation which can be characterized as an allelic loss at chromosome 3p-25-26. Common manifestations of VHL disease are CNS hemangioblastoma, retinal angioma, renal cyst or carcinoma, pheochromocytoma, pancreatic neuroendocrine tumors, endolymphatic sac tumors, and papillary cystadenomas of the epididymis. The diagnosis of VHL disease can be established by clinical criteria or genetic analysis. Patients with a familial history of VHL disease and a CNS hemangioblastoma, renal cell carcinoma, pheochromocytoma, or endolymphatic sac tumor meet the clinical criteria. If patients have two or more CNS hemangioblastomas or one CNS hemangioblastoma and a VHL-associated visceral tumor, they can also fulfill clinical diagnostic criteria without a familial history of VHL disease^{7,11}.

With respect to natural history of VHL disease, Wanebo et al.¹⁶ reported that, on the basis of a 11 year follow-up period, hemangioblastomas associated with VHL disease have two separate phases of growth. That is to say, there are phases of rapid and quiescent growth, if the condition is observed for a sufficiently long interval. A rapid growth period tends to be followed by a quiescent period which can last more than two

and one-half years. In our first case, of the more than 200 months of surgical follow-up, the cerebellar hemangioblastoma remained quiescently for about 111 months. However, a cystic mass of the cerebellar hemisphere subsequently developed again. Further, 98 months after the second surgery, cerebellar hemangioblastoma recurred along with the development of clear cell renal carcinoma.

Although there have been advances and improvements in microsurgical techniques and an increasing application of radiosurgery, it remains a challenging field particularly with respect to the treatment of recurrent hemangioblastoma that extensively involve the craniospinal area. Also, considering the fact that the optimal management and treatment of choice for a hemangioblastoma is complete microsurgical resection, it is very difficult to determine a further treatment plan when extensive craniospinal involvement is diagnosed. Koh et al.⁶ reported 18 patients with hemangioblastomas who underwent whole brain radiotherapy, and postulated that, in cases of extensive intracranial and/or spinal, residual postoperative, and recurrent hemangioblastomas, whole brain radiotherapy could achieve satisfactory rates of tumor control. We treated one patient with the whole brain radiotherapy for his multiple intracranial and spinal lesions after complete excision of his primary tumor. Unfortunately, it recurred as a form of GBM which had been likely induced by radiation therapy. Radiation-induced GBM, which was first reported in 1978 by Klériga et al.⁵ has recently been increasing in incidence, probably as a result of the improved survival of patients treated for primary malignancy. On the renal involvements, both cases showed small renal cysts which had evolved to renal cell carcinomas. To the best of our knowledge, there has not been a report demonstrating the progression of renal cell carcinomas from renal cysts.

In both cases, follow-up observation was continued for more than 8 years and each had a symptom-free period after their first treatment. However, regardless of the length of time which had passed, both cases exhibited relapsed and were in need of further treatment. These cases have taught some important lessons, including : 1) closely monitored long-term follow-up is mandatory for monitoring the recurrence of primary tumors once cerebellar hemangioblastoma with VHL has been diagnosed and treated; 2) The frequency and length of the follow-up period should be considered when cystic lesions of abdominal organs are known to exist given that this seemingly benign condition can progress into malignancy.

In summary, we would like to emphasize the importance of close follow-ups with radiologic examination of both CNS hemangioblastoma and other organs subsequent to the first for CNS hemangioblastoma associated with VHL disease.

CONCLUSION

We suggest that in the view of the natural history of CNS hemangioblastoma associated with VHL disease, recurrence can occur even after complete treatment of primary lesion if given a sufficiently long time. Additionally, if enough time passes, there is a strong possibility of the progression of renal cysts into renal cell carcinoma. Neurosurgeons should be aware of the importance of the close life-long follow-ups for patients suffering from CNS hemangioblastoma and VHL disease-associated lesions.

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