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CLINICAL CASE

Cerebellar and multiple spinal hemangioblastomas and intraventricular meningioma managed with subtotal resection and external beam radiotherapy; report of a case with literature review

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Summary

Hemangioblastomas are cystic, highly vascular benign neoplasms that constitute 1.5-2.5% of all intracranial tumors and 7-10% of primary posterior fossa tumors. They occur sporadically (80%) or in association with von Hippel-Lindau (VHL) disease (20%). This disease consists of multiple intracranial, retinal and spinal hemangioblastomas, pheochromocytoma, retinal angiomas, pancreatic cysts, renal cell carcinomas and adrenal tumors. Our patient was a 21-year-old male who presented with cerebellar and multiple spinal hemangioblastomas, and intraventricular meningioma. There was a positive family history (mother and brother) of VHL disease. Intracranial and spinal lesions were treated with external beam radiotherapy following subtotal excision of the cerebellar lesion. Three-year follow-up revealed radiologically stable lesions.

Microsurgical resection remains the treatment of choice for the vast majority of symptomatic and sporadic cystic hemangioblastomas. However, since hemangioblastoma is a highly vascular tumor and local invasion of critical structures is frequent and multifocality is often a characteristic of the hemangioblastomas that are associated with VHL disease, subtotal excision is frequent and adjuvant therapies such as external beam radiotherapy or stereotactic radiosurgery represent a reasonable treatment in such cases.

Key words: hemangioblastoma, radiosurgery, radiotherapy, von Hippel-Lindau disease

Introduction

Central nervous system (CNS) hemangioblastomas are solid or cystic, highly vascular benign tumors that present sporadically (80%) or in association with VHL disease (20%) [1-4]. They comprise approximately 1.5-2.5% of primary CNS tumors and 7-10% of primary posterior fossa tumors. Hemangioblastomas also account for 2% of primary spinal cord tumors.

In most of the cases they cause significant morbidity and even mortality through mass effect or invasion of nearby structures. Surgical resection, which confirms the diagnosis, usually controls the tumor and is the treatment of choice for most of hemangioblastomas. However, local invasion of critical structures is frequent and multifocality is often a characteristic of hemangioblastomas that are associated with VHL disease. Subtotal excision is associated with a high incidence of recurrence causing neurological deficit, so adjuvant therapies such as external beam radiotherapy or stereotactic radiosurgery (SR) are considered in most of the cases [5-9].

We present herein a case with cerebellar and multiple spinal hemangioblastomas and intraventricular meningioma and discuss the treatment options in CNS hemangioblastomas by reviewing the relevant literature.

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Case presentation

A 21-year-old male presented with a 2-month history of headache, disequilibrium, gait ataxia, vomiting and numbness. He had a family history of VHL disease (mother and brother). Neurological examination revealed cerebellar findings with decreased sensation in the left L2 and L3 dermatomes. Funduscopic examination and visual fields were normal. Laboratory findings were within normal limits. Magnetic resonance imaging (MRI) of the brain demonstrated oval-shaped masses in the posterior fossa and in the right ventricle, which were hypointense on T1-weighted images and hyperintense on T2-weighted images (Figure 1). MRI of the spinal cord demonstrated multiple lesions that were also hypointense on T1-weighted images and hyperintense on T2-weighted images at D4, D7 and L3 vertebrae (Figure 2). The family history of VHL disease and the presence of multiple spinal lesions bearing the same radiological characteristics with the cerebellar lesion warned us about the possible presence of VHL disease and other tumoral lesions, but the radiological examination of the thorax and whole abdomen revealed no more abnormal findings.

Subtotal resection of the cerebellar lesion and biopsies of the intraventricular lesion, D4 and L3 vertebrae lesions were performed. Histologically, the intraventricular lesion was meningioma. Histological study of the lesions from the cerebellar region and D4 and L3 vertebrae, which were stained with hematoxylin and eosin, showed a rich vasculature that was separated by numerous vacuolated stromal cells exhibiting karyomegaly and pleomorphism with no mitotic activity. Immunohistochemically, the stromal cells were strongly and diffusely positive for vimentin, S100 protein and neuron-specific enolase (NSE), but negative for epithelial membrane antigen (EMA) and

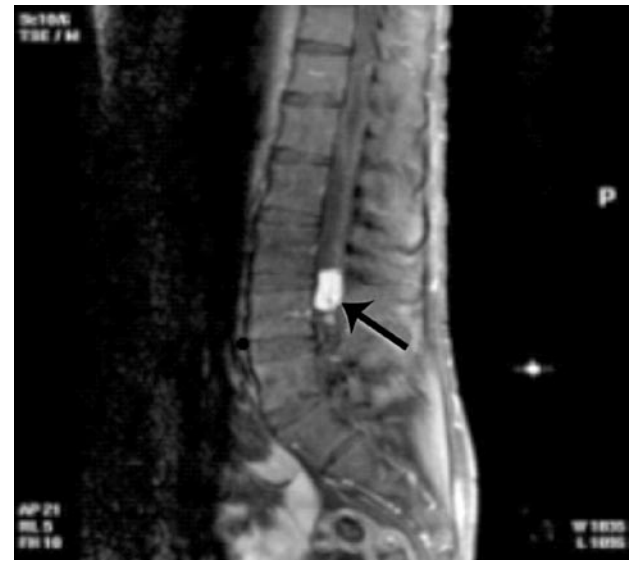

Figure 2. MRI of the hemangioblastoma located at L3 vertebral region in the spinal cord (arrow) before treatment on T2 weighted image.

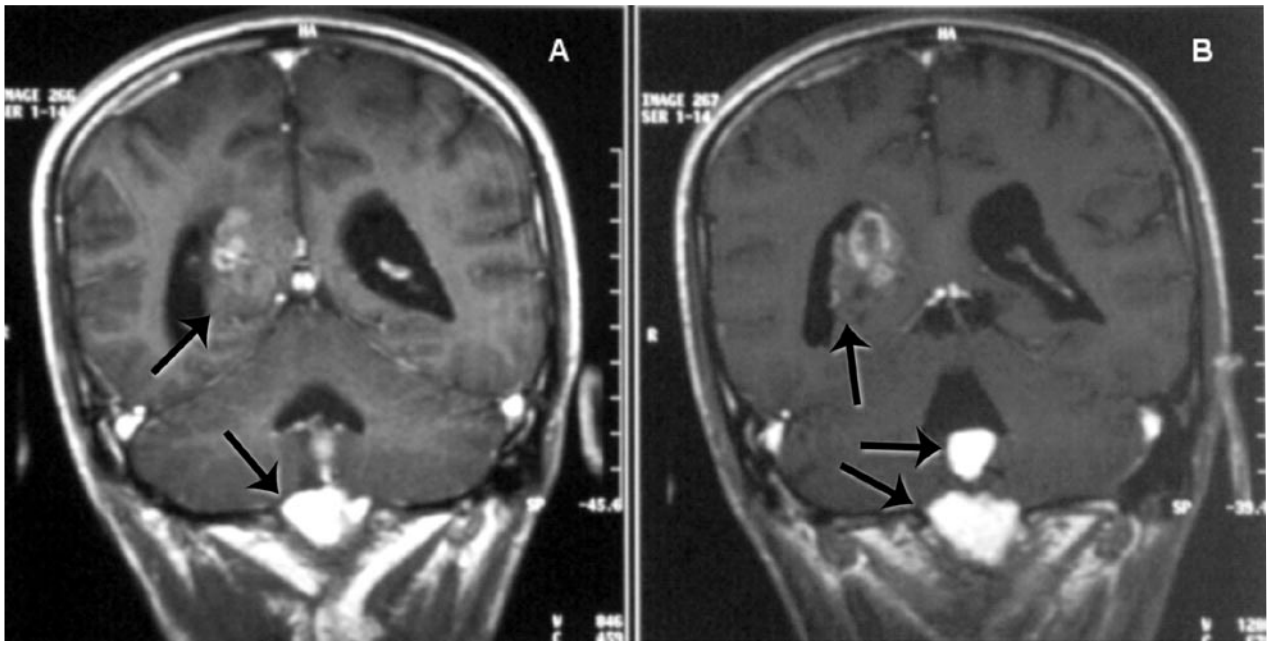

Figure 1. MRI of the brain demonstrating oval-shaped, hyperintense masses in the posterior fossa (arrows, A) and in the right ventricle (arrows, B) before treatment on T2-weighted images.

glial fibrillary acidic protein. Staining the endothelial cells with CD34 highlighted the rich vasculature. The histopathologic and immunohistochemical findings were consistent with hemangioblastoma.

The brain lesions and the hemangioblastomas in D4, D7 and L3 vertebral region were treated with external beam radiotherapy with a total dose of 50 Gy. The neurological symptoms improved dramatically 1 month after the completion of treatment. MRI images taken 3 years posttreatment showed that the cerebellar hemangioblastoma and intraventricular meningioma were stable (Figure 3).

Discussion

Hemangioblastomas mostly occur in the cerebellum, brain stem and spinal cord and rarely in supratentorial regions. The mean patient age at first presentation is the third or fourth decade of life.

VHL disease is an autosomal dominant hereditary tumor syndrome with variable penetrance in which the putative suppressor gene has been mapped to a small region of chromosome 3p [1,2]. This disease consists of multiple intracranial, retinal and spinal hemangioblastomas, pheochromocytoma, retinal angiomas, pancreatic cysts, renal cell carcinomas and adrenal tumors. Approximately 20% of patients presenting with a hemangioblastoma have VHL disease [3,4].

Hemangioblastomas are typically well-circumscribed, highly vascular lesions. While those located in the posterior fossa are frequently cystic and often contain a mural nodule, supratentorial hemangioblastomas are more often solid and only 25-30% have a cystic appearance.

CNS hemangioblastomas in VHL disease are characteristically multiple and present at a younger age than in patients with sporadic disease. So, in all patients who present with a CNS hemangioblastoma, the entire neuraxis should be evaluated for the presence of additional hemangioblastomas using enhanced MRI [5,6]. The National Institutes of Health screening protocol in VHL disease includes a urinary catecholamine evaluation, ophthalmoscopy, and an abdominal CT scan and ultrasound evaluation [7].

Although retinal hemangioblastomas are typically the first manifestation of VHL disease, in most of the patients CNS hemangioblastomas can also be the presenting manifestation [8].

Headache, disturbances of equilibrium and nausea are the most common symptoms at presentation. The mean duration of symptoms is 8 months. The mean size of solid or mural-enhancing lesion at presentation is about 1.5 cm [8].

Morbidity and mortality associated with hemangioblastomas can be reduced significantly if these lesions are appropriately diagnosed and treated.

Regardless of tumor morphology, complete surgical excision is the treatment of choice for all

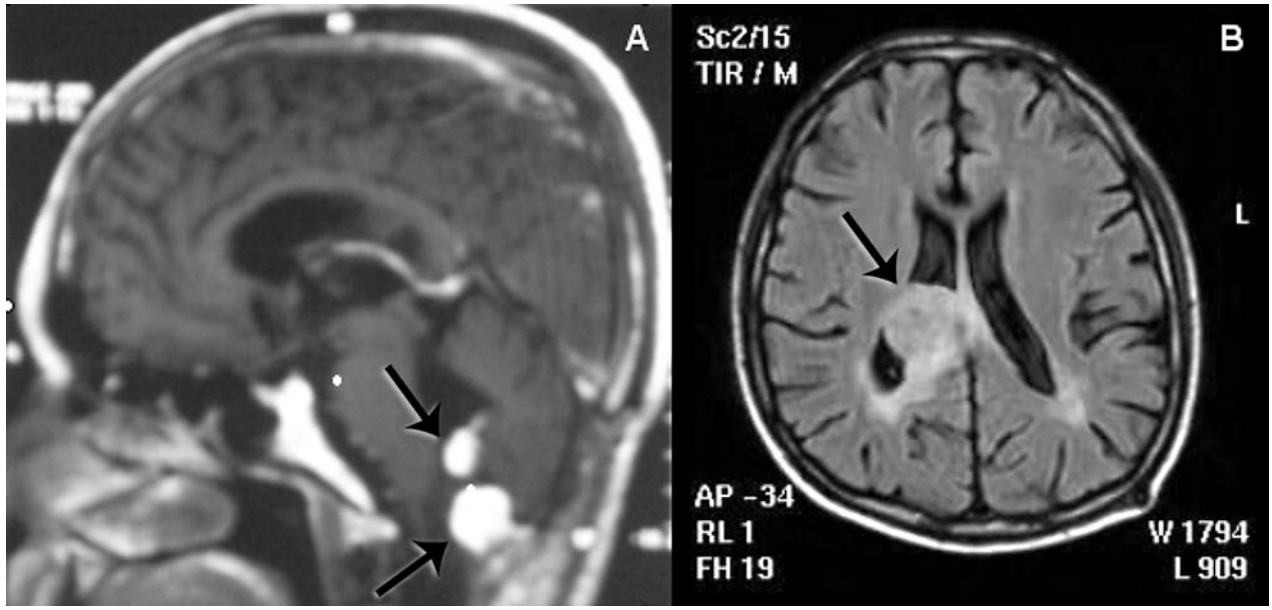

Figure 3. MRI taken 3 years posttreatment showing stable hemangioblastomas in the posterior fossa (arrows, A) and stable intraventricular meningioma (arrow, B) on T2 weighted images.

hemangioblastomas and is curative in most of the cases [9,10]. Surgery is associated with control rates ranging from 75 to 90% in different studies.

Cystic lesions may tend to have a more favorable surgical outcome compared to the more vascular lesions [11]. But, since hemangioblastoma is a highly vascular tumor and local invasion of critical structures is frequent, gross total resection is precluded in many cases. Subtotal excision is associated with a high incidence of recurrence causing neurological deficit, so adjuvant therapies are considered in most of the cases [11,12].

Conventional external beam radiation is the most frequently used adjuvant therapy following subtotal excision. The results of several studies showed that high-dose postoperative irradiation achieves a significant improvement in local control of subtotally resected lesions. Sung et al. reported 24 patients with incompletely resected cerebellar hemangioblastomas. Five- and 10-year survival rates were higher in patients who were treated with 40-55 Gy (91% and 55%, respectively) when compared with patients treated with 20-36 Gy (57% and 27%, respectively) [12]. In a different study, local control and disease-free survival were higher in patients with subtotally resected lesions who were treated with radiation doses more than 50 Gy. Five-, 10- and 15- year disease-free survivals were 76%, 52% and 42%, respectively [13].

The results of these studies show that external radiotherapy has a positive effect in local control and disease-free survival in subtotally resected CNS hemangioblastomas.

SR has also been used as a treatment modality in unresectable or incompletely excised hemangioblastomas. Chang et al. reported 23 hemangioblastomas in 13 patients with VHL disease who were treated with linear accelerator-based radiosurgery. Treatment doses varied between 18 and 40 Gy. Among these 23 tumors, 5 (22%) disappeared, 10 (43%) regressed and 8 (35%) remained unchanged. Tumor responses correlated significantly with increasing radiosurgical doses ($p < 0.0001$). All tumors treated with 30 Gy or more either decreased or resolved and all of the tumors that disappeared completely had been treated with 35 Gy or more. Overall freedom from progression was 97%. The authors concluded that patients with VHL disease who present with small (<3 cm) solid hemangioblastomas are reasonable candidates for radiosurgery. Microsurgical resection remains the treatment of choice for the vast majority of symptomatic cystic and sporadic hemangioblastomas without VHL disease to eliminate mass effects or establish a diagnosis. Although all of the tumors treated with 35 Gy or more had completely disappeared, radiation necrosis was seen as a complication in 3 of these patients, so the authors recommend 20 to 25 Gy as the optimal dose [14].

In a different study 38 hemangioblastomas were treated with SR. Sixteen hemangioblastomas had no prior history of surgical resection and were treated with definitive SR. Two hemangioblastomas were subtotally resected and subsequently treated with SR. Twenty lesions were treated with SR after prior surgical failure (17 patients) or failure after prior surgery and conventional radiotherapy (3 patients). Tumor doses ranged between 12 to 20 Gy (median 15.5 Gy). Two-year actuarial overall survival was 88% and disease-free survival was 86%. The lesions that failed to be controlled by SR received a median minimum tumor dose of 14 Gy compared to 16 Gy for controlled lesions ($p=0.023$). Eighty-seven percent of the surviving patients remained neurologically stable or clinically improved [15]. Zhou et al. evaluated 33 patients with brainstem hemangioblastomas who were treated with microsurgery. Tumors were located on oblongata in 14 patients, ponto-oblongata in 9, pons in 6, and cervicomedulla in 4 patients. These lesions were solid in 29 and cystic in 4 cases. Twelve cases were treated with preoperative embolization. Total tumor removal was achieved in 31 (94%) patients, incomplete removal in 2 (6%) cases and the authors concluded that microsurgical technique and intensive perioperative management were mandatory for removal of these tumors with acceptable morbidity and mortality [16].

Glasker et al. analyzed 6 patients that underwent surgery for spinal nerve hemangioblastomas and reported that most of these tumors arose from the dorsal sensory fascicles and the vascular supply was from extradural circulation. Although the surgical outcome of the lesions was good and permanent neurological deficits were rare, local recurrence rate was relatively high (3 of 6 patients) [17]. In Rajaraman's et al. series, 16 cases of hemangioblastoma secondary to VHL disease were treated with SR. Three patients died and 8 (50%) had progressive disease in 5 years [18].

Multifocality is often a characteristic of hemangioblastomas associated with VHL disease. SR is a very good therapeutic option for these patients since surgical resection of multiple vascular lesions is more complicated and technically challenging than resection of multiple vascular lesions.

Patients with VHL-associated CNS hemangioblastomas may also develop metachronous CNS lesions. SR is also an effective treatment modality in this setting due to its invasiveness and ability to spare normal surrounding brain.

As a result, SR is recommended in surgically unresectable disease or as adjuvant treatment for subtotally resected disease. SR is also used as definitive treatment of multifocal disease and as salvage therapy for radiographically discrete recurrences after surgical intervention.

Endovascular embolization can also be used, especially in the treatment of spinal and medullary hemangioblastomas. The decision to use embolization should be taken after angiography by showing that primarily one or two major feeding vessels supply the tumor. This technique is generally used in conjunction with surgical resection of the tumor.

In conclusion, microsurgical resection remains the treatment of choice for the vast majority of symptomatic and sporadic cystic hemangioblastomas. But, since hemangioblastoma is a highly vascular tumor and local invasion of critical structures is frequent and multifocality is often a characteristic of the hemangioblastomas that are associated with VHL disease, external beam radiotherapy or SR may represent a reasonable treatment in such cases.

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