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Neurosurg Clin N Am 17 (2006) 37–44

NEUROSURGERY
CLINICS
OF NORTH AMERICA

Spinal Cord Hemangioblastomas

Russell R. Lonser, MD*, Edward H. Oldfield, MD

Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 10 Center Drive, Building 10, Room 5D37, Bethesda, MD 20892–1414, USA

Hemangioblastomas can be found throughout the entire central nervous system but are most commonly located in the cerebellum and spinal cord. They occur sporadically (in approximately two thirds of cases) or in association with von Hippel-Lindau disease (VHL) (in approximately one third of cases) [1]. Whether they occur sporadically or in relation to VHL, spinal cord hemangioblastomas are histologically identical, benign, highly vascular tumors that can be cured by complete surgical resection. Despite their benign histologic features, spinal cord hemangioblastomas may be associated with significant neurologic deficits related to their size or location or to the presence of associated edema or syrinx. Recent insights into their natural history as well as improvements in imaging and refinement in microsurgical removal have enhanced the diagnosis and treatment of these tumors.

Clinical, radiographic, and histologic features

Epidemiology

Hemangioblastomas are the third most common intramedullary spinal cord tumor and represent approximately 2% to 5% of primary intramedullary spinal cord neoplasms. They are found approximately 1.5 to 2 times more frequently in men than in women [2,3]. The average age at symptom development from spinal cord hemangioblastomas is between 33 and 35 years of age.

Tumor location

Symptomatic spinal cord hemangioblastomas are found most commonly in the cervical (40%–60%) and thoracic (40%–50%) spinal cord and are infrequently found in the lumbar spinal cord (5%–10%) and cauda equina (less than 1%) [4]. The epicenter of the hemangioblastoma mass is most frequently found in the posterior aspect of the spinal cord (96%) in the region of the dorsal root entry zone (66%) [2]. These tumors can be entirely intramedullary (30%), have intra- and extramedullary components (50%), or be primarily extramedullary (20%) in nature [2].

Natural history

Understanding the natural history of spinal cord hemangioblastomas is critical for optimizing treatment and determining the efficacy of various therapies. It is especially important for patients with VHL with central nervous system hemangioblastomas, because they may have multiple hemangioblastomas along the neuraxis at any point in time and may develop new tumors over their lifetime. Recently, we examined the natural history of central nervous system (including spinal cord) hemangioblastomas in 160 consecutive patients with VHL [5]. Symptoms in patients with spinal cord hemangioblastomas were related to tumor size or syringomyelia-associated mass effect. As a result, symptom formation in patients with spinal cord hemangioblastomas was associated with the presence of syringomyelia and with more rapid rates of hemangioblastoma growth. The pattern of growth seen with spinal cord hemangioblastomas (as well as those hemangioblastomas found elsewhere in the central nervous system) was variable and often marked by

* Corresponding author.
E-mail address: lonserr@ninds.nih.gov (R.R. Lonser).

1042-3680/06/$ - see front matter
doi:10.1016/j.nec.2005.10.005

prolonged (several years) periods of quiescence. No reliable threshold of tumor size or threshold rate of growth could be identified that reliably predicted an association with symptoms or a cyst [5]. Thus, neither tumor size nor rate of growth permitted an argument for early intervention when a tumor is smaller and potentially more easily amenable to surgery or medical therapy. Thus, in the setting of VHL, it is probably best to reserve resection of spinal cord– and other central nervous system–associated hemangioblastomas until the onset of symptoms.

Signs and symptoms

Patients with spinal cord hemangioblastomas present with a variety of signs and symptoms that are related to the spinal level at which the tumor is located, the position of the tumor within the spinal cord (anterior versus posterior), and the presence of edema or a syrinx [2,5–7]. Consistent with their known slow erratic growth and association with edema or syrinxes, spinal cord hemangioblastomas may have a prolonged symptomatic prodrome ranging from several months to years [5,6].

Clinical findings associated with spinal cord hemangioblastomas include sensory changes, weakness, pain, hyperreflexia, gait difficulties, incontinence, and, occasionally, scoliosis (Table 1) [2,3]. The predominance of sensory-related signs and symptoms is most likely the result of an overwhelming preponderance of posterior-located tumors (96% of spinal cord hemangioblastomas) that are often found in the dorsal root entry zone (66%) [2]. Most symptom-producing spinal cord hemangioblastomas have associated syrinxes (95% of symptomatic spinal cord hemangioblastomas) [5].

Imaging characteristics

Postcontrast T1-weighted MRI precisely defines these tumors and their relation to the spinal cord (Fig. 1) [8,9]. Spinal cord hemangioblastomas enhance vividly on T1-weighted MRI after contrast administration (see Fig. 1) [2]. T2-weighted or fluid-attenuated inversion recovery MRI can be used to define peritumoral edema or associated syringomyelia better (see Fig. 1).

Arteriography can be used to define the vascular of anatomy of large hemangioblastomas and provides a vascular "roadmap" during resection. We have found that neither preoperative selective embolization nor diagnostic arteriography is necessary for resection of spinal cord hemangioblastomas, however. Careful adherence to well-described microsurgical techniques [2] obviates the need for adjuvant preoperative selective embolization with its attendant risks.

Table 1
Frequency of signs and symptoms associated with spinal cord hemangioblastomas

Sign or symptom	Percentage of patients presenting with finding
Sensory changes	70%–85%
Weakness	40%–65%
Pain	15%–85%
Hyperreflexia	30%–60%
Gait difficulties	15%–30%
Incontinence	10%–15%
Scoliosis	10%–15%

Data from Roonprapunt C, Silvera VM, Setton A, et al. Surgical management of isolated hemangioblastomas of the spinal cord. Neurosurgery 2001;49:321–7 [discussion: 327–8]; and Wanebo JE, Lonser RR, Glenn GM, et al. The natural history of hemangioblastomas of the central nervous system in patients with von Hippel-Lindau disease. J Neurosurg 2003;98:82–94.

Histologic characteristics

Grossly, hemangioblastomas are bright red or reddish yellow in appearance. The coloring is caused by the highly vascular nature (red) and abundant lipid (yellow) content of these neoplasms. Histologically, hemangioblastomas are benign-appearing tumors that lack mitoses and contain numerous capillaries lined by pericytes and endothelial cells. The capillaries in hemangioblastomas are surrounded by numerous bland lipid-laden stromal cells, which have recently been shown to be the neoplastic cell of origin (Fig. 2) [10–12]. Common histologic patterns seen in hemangioblastomas include cyst and microcyst formation, which is associated with vascular proliferation. These histologic components vary with hemangioblastomas of various sizes and may account for the varied natural history of these tumors.

Special considerations

Because the occurrence of a spinal cord hemangioblastoma is significantly associated with VHL [13], all patients diagnosed with a spinal cord hemangioblastoma should be screened for VHL. Because of the frequent occurrence of pheochromocytomas in VHL (10%–20% of patients with VHL), all patients with VHL who are undergoing surgery should be evaluated before surgery

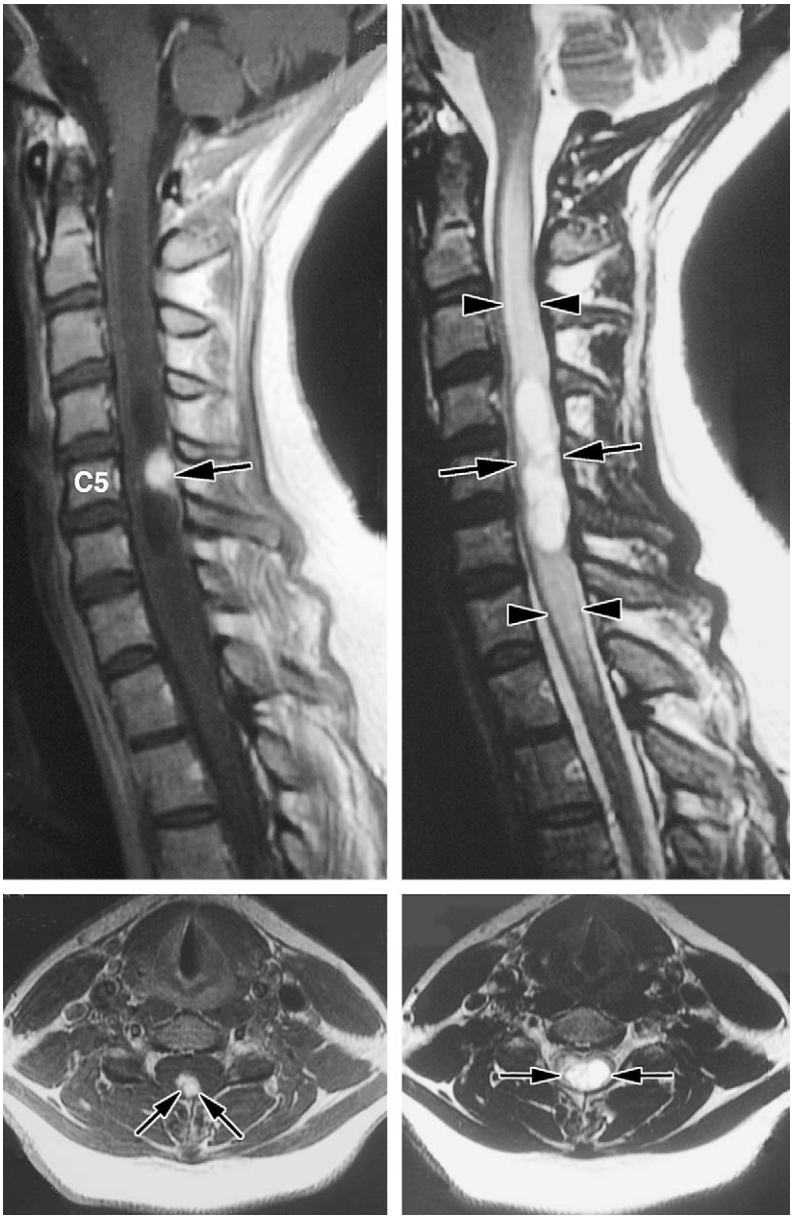

Fig. 1. MRI scan of a 26-year-old patient with VHL and an intramedullary hemangioblastoma at the fifth cervical level (C5). (*Upper left*) Postcontrast, midsagittal, T1-weighted MRI scan of the cervical spinal cord demonstrates the C5 hemangioblastoma (solid enhancing area; *arrow*) with an associated syrinx (dark region intraspinal region). (*Upper right*) Midsagittal T2-weighted MRI scan clearly defines the peritumoral syrinx (*arrows*) and associated edema (*arrowheads*) of the spinal cord, which extends from the cervicomedullary junction to the bottom of the first thoracic vertebrae. (*Lower left*) Postcontrast axial T1-weighted MRI scan of the same hemangioblastoma demonstrates the posterior location within the spinal cord of the tumor (*arrows*). (*Lower right*) Axial T2-weighted MRI scan demonstrates the peritumoral syrinx within the spinal cord (*arrows*). (*From* Lonser RR, Oldfield EH. Microsurgical resection of spinal cord hemangioblastomas. Neurosurgery 2005;57(4):372–6; with permission.)

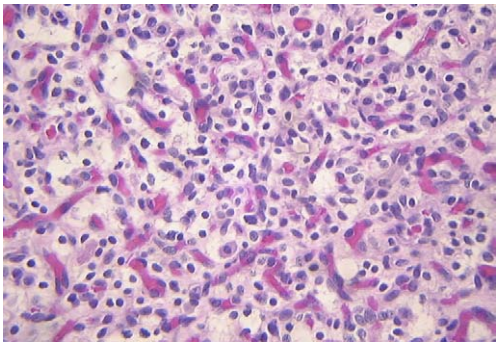

Fig. 2. Hematoxylin and eosin staining of a hemangioblastoma shows the lipid-laden stromal cells distributed within a capillary network (original magnification ×40).

for the presence of a pheochromocytoma that may require priority treatment or perioperative α- and β-adrenergic blockade [4].

Treatment

Surgical resection

Indications

Microsurgical resection is the primary treatment for spinal cord hemangioblastomas. The indications for surgical resection in the setting of sporadically occurring spinal cord hemangioblastomas differ from those occurring in patients with VHL. In patients with sporadically occurring spinal cord hemangioblastomas, resection of the tumor is often necessary for diagnosis and can necessitate removal before symptom formation. Because spinal cord hemangioblastomas have variable patterns of growth (including long quiescent periods) and patients with VHL may require multiple surgeries over a lifetime, the indications for surgery in the patient with VHL are based on the presence of signs and symptoms attributable to the hemangioblastoma or its associated edema or syrinx. Thus, in patients with VHL, asymptomatic spinal cord hemangioblastomas may be followed clinically but should be resected once they become symptomatic. Delay in removal of symptom-producing hemangioblastomas may result in progressive neurologic deficits that are not reversible. Contraindications for removal include medical instability and lack of signs and symptoms that can be attributed to the hemangioblastoma in patients with VHL.

Surgical technique

We have found that an optimal surgical outcome is obtained by directly approaching these neoplasms (Fig. 3) [2,14]. Because most spinal cord hemangioblastomas are located posterior to the dentate ligament, we describe a direct posterior approach to remove these tumors. Hemangioblastomas located anterior to dentate ligament should be approached via a direct anterior or anterolateral approach [14], however, to minimize the rotation and manipulation of the spinal cord during resection inherent to posterior or posterolateral approaches.

To remove posteriorly located tumors, a midline incision is made that extends 1 to 2 (see Fig. 3) spinous processes above and below the rostral and caudal ends of the tumor. Laminectomies are performed to provide wide exposure of the dura over the tumor for at least 1 to 2 cm rostral and caudal to the upper and lower margins of the tumor. Intraoperative ultrasound is used to define the precise location of the highly echogenic hemangioblastoma with respect to the exposed dura and to confirm the adequacy of exposure within the bony opening (Fig. 4). The dura is sharply incised in the midline, with care taken to preserve the underlying arachnoid. The operative microscope is brought into the operative field for illumination and magnification. The arachnoid is opened, and its edges are secured to the edges of the dura.

Vessels crossing the margin of the tumor at its junction with the pia are coagulated with bipolar forceps and divided (see Fig. 3). This permits clear exposure of the margin of the tumor at the pial surface. Because many of these tumors originate in the region of the posterior nerve roots, the spinal cord at the dorsal nerve root entry zone, or both, sensory nerve rootlets imbedded in the tumor must be interrupted at the margin of the tumor if the tumor is to be completely removed. The pia is incised with a diamond knife at its junction with the edge of the tumor. The hemangioblastoma is resected in a circumferential manner at the tumor–spinal cord interface using fine bipolar tips or the tips of microscissors. Microsurgical technique is used to separate the tumor capsule from the spinal cord with discrete visualization, coagulation, and interruption of each of the individual small vessels as they enter and leave the tumor capsule (see Fig. 3). During the dissection of hemangioblastomas with associated syrinxes, it is not necessary to enter the syrinx cavity. Opening a syrinx during hemangioblastoma removal does not enhance resolution of syringomyelia after surgery, because the hemangioblastoma is the underlying cause of syrinx formation [2]. Removal of the hemangioblastoma uniformly results in syrinx

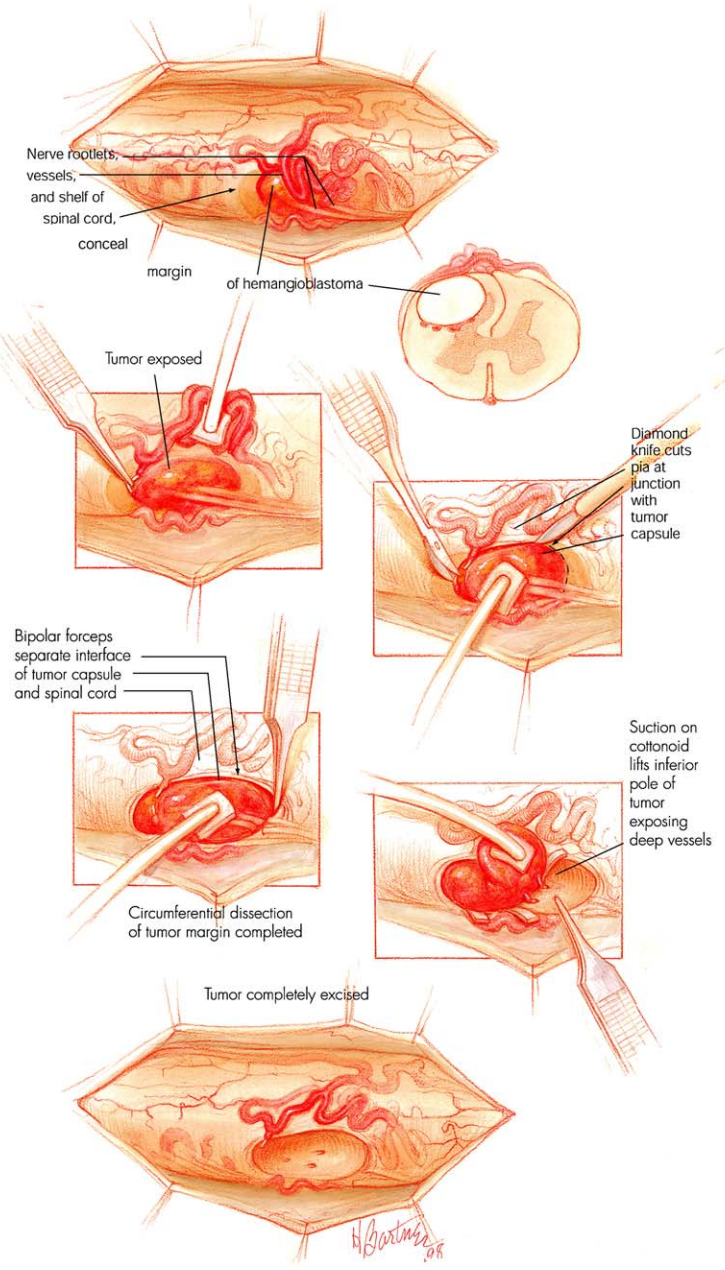

Fig. 3. Illustration of microsurgical resection of spinal cord hemangioblastoma. This drawing depicts the intradural portion of the operation for resection of spinal cord hemangioblastoma. Using an operating microscope, the associated vessels and tumor are identified. The tumor is exposed by reflecting the overlying vessels with gentle traction. The junction between the pia and the tumor capsule is identified and incised with a diamond knife and microscissors. Dissection of the tumor is continued deeper and circumferentially at the tumor capsule–spinal cord interface using bipolar microforceps. After circumferential dissection of the tumor margin is complete, the inferior pole to the hemangioblastoma is reflected with gentle suction on a cottonoid to expose the underlying vessels. (*From* Lonser RR, Weil RJ, Wanebo JE, et al. Surgical management of spinal cord hemangioblastomas in patients with von Hippel-Lindau disease. J Neurosurg 2003;98:106–16.)

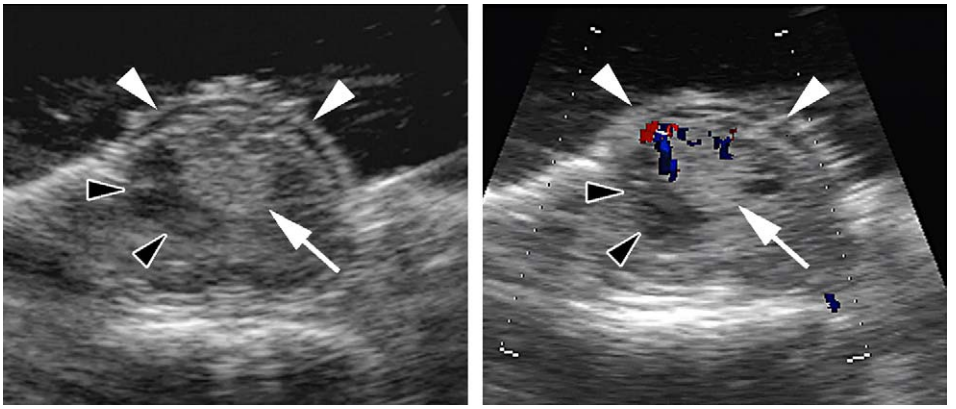

Fig. 4. Intraoperative ultrasound is used to determine the precise location of the spinal cord hemangioblastoma with respect to the exposed dura and to confirm the adequacy of exposure of the tumor within the bony opening. (*Left*) Axial intraoperative sonographic imaging clearly demonstrates the dura (*white arrowheads*), the underlying highly echogenic spinal cord hemangioblastoma (*white arrow*), and an associated syrinx (*black arrowheads*). (*Right*) Corresponding Doppler flow analysis of the same hemangioblastoma in the axial plane demonstrates the high-velocity blood (*colored pixels*) flow to and from the tumor. (*From* Lonser RR, Oldfield EH. Microsurgical resection of spinal cord hemangioblastomas. Neurosurgery 2005;57(4):372–6; with permission.)

resolution (Fig. 5) [2]. Once the tumor is removed, the dura; paraspinous musculature; and fascial, subcutaneous, and cutaneous layers are closed in layers. The incision is covered with antibiotic ointment and a sterile dressing.

Operative results

Many patients (66%) develop new signs and symptoms or have exacerbation of preoperative signs and symptoms in the early postoperative period [2]. These neurologic changes are typically mild in nature (do not limit function) and transient (generally lasting 2–6 weeks). Transient signs and symptoms found in the immediate postoperative period may include sensory disturbances (dysesthesia, pain, and numbness), motor dysfunction (mild weakness, and spasticity), and bladder dysfunction [2].

Generally, the long-term clinical outcome in patients undergoing resection of spinal cord hemangioblastomas is excellent [2]. More than 90% of patients remain clinically stable or improve. Five percent to 10% of patients are clinically worse after removal of a spinal cord hemangioblastoma. Predictors of poor outcome include significant preoperative neurologic deficits, large tumor size (greater than 500 mm^3), and anterior location (defined by the tumor epicenter anterior to the dentate ligament) of the hemangioblastoma [2]. Improved short- and long-term outcomes can be obtained in anteriorly located spinal hemangioblastomas by directly approaching these lesions rather than using a posterior or posterolateral approach [14].

Follow-up studies and recurrence

The frequency of postoperative imaging studies and length of follow-up after resection of a spinal cord hemangioblastoma differ between patients with sporadic and VHL-associated tumors. Generally, all patients should undergo contrast-enhanced spinal MRI 3 to 6 months after hemangioblastoma resection to confirm complete removal of the tumor. Complete resection of spinal cord hemangioblastomas should preclude recurrence and result in inactivation of an associated syrinx or edema [2]. Patients with partially resected hemangioblastomas are at significant risk for progression of tumor growth and recurrence of symptoms that may require additional surgery [13]. Thus, in patients with sporadically occurring spinal cord hemangioblastomas, follow-up after complete resection may be limited to 6 to 12 months after surgery. Because of the potential for development of new hemangioblastomas and continued growth of existing hemangioblastomas, patients with VHL should undergo routine serial screening of the neuraxis at 12- to 24-month intervals (with contrast-enhanced MRI) or sooner if new symptoms develop over their lifetime [4].

Radiation therapy

The role of radiotherapy in the treatment of spinal cord hemangioblastomas remains to be

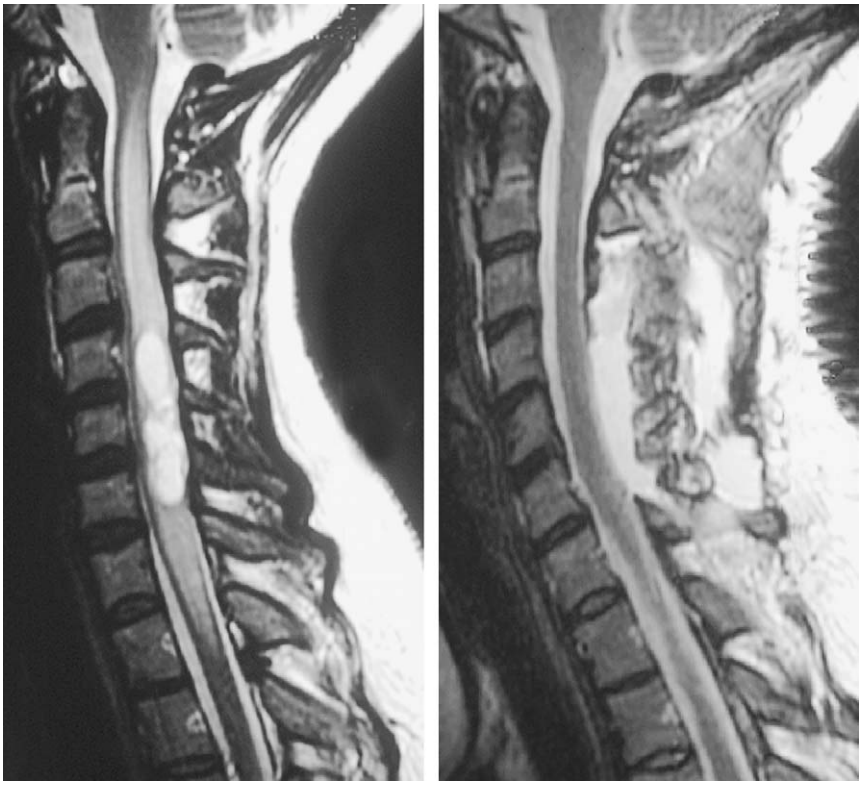

Fig. 5. Preoperative (*left*) and postoperative (*right*) sagittal T2-weighted MRI scans from the patient described in Fig. 1. After successful resection of the cervical spinal cord hemangioblastoma, complete resolution of the associated syrinx and surrounding edema occurs. (*From* Lonser RR, Oldfield EH. Microsurgical resection of spinal cord hemangioblastomas. Neurosurgery 2005;57(4):372–6; with permission.)

defined. Complete or partial craniospinal irradiation may be considered in cases of hemangioblastomatosis in which surgical resection of discrete symptom-producing spinal cord hemangioblastomas is not possible. Stereotactic radiosurgery may play a role in treatment of isolated central nervous system hemangioblastomas (including spinal cord hemangioblastomas) and can avoid some of the potential complications associated with conventional radiation treatment paradigms [15]. Similar to the results for stereotactic radiosurgery of other central nervous system lesions, hemangioblastomas that are large (greater than 3 cm^3 in volume) or associated with cysts are less likely to respond to this therapy [15].

Interpreting the results of radiosurgery and emerging medical therapies must be tempered by the known pattern of growth and quiescence seen in these tumors. Stability of tumor size, which is often used as a criterion for response to radiation or other medical therapies, may be misleading because of the known prolonged intervals of time during which no tumor growth may occur. Thus, absence of growth may only coincide with a quiescent phase of tumor growth and may not represent a response to therapy at all [5].

Emerging medical therapies

Novel medical therapies are beginning to emerge for the treatment of hemangioblastomas, particularly in the setting of VHL. These therapies are targeted at the known molecular abnormalities associated with loss of heterozygosity of the *VHL* gene (chromosome 3p25) [16] in patients with VHL or somatic inactivation of the *VHL* gene that occurs in patients with sporadic hemangioblastoma [11]. The loss of *VHL* gene function results in abnormal protein (pVHL) and loss of pVHL function. pVHL is a tumor suppressor protein that is involved in oxygen-sensing homeostasis and angiogenesis. Abnormal or absent pVHL

function results in enhanced expression of vascular endothelial growth factor (VEGF) through effects mediated by constitutive overproduction of hypoxia-inducible factors (HIFs) [4]. Subsequently, chemotherapeutic treatment paradigms targeted at blocking HIFs and their downstream targets (eg, VEGF) are promising [17].

Summary

Spinal cord hemangioblastomas are histologically benign tumors that can cause significant morbidity because of their size, location, and associated edema or syrinx. They may be found sporadically or in association with VHL. Spinal cord hemangioblastomas in these two settings (sporadic or in VHL) have different indications for surgical treatment and have variable follow-up paradigms. Generally, surgical resection of these tumors is curative and should be performed at the onset of symptoms in patients with VHL or for diagnostic and therapeutic purposes in sporadic cases.

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