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Original Article

Spinal cord hemangioblastomas with a focus on clinical presentation, diagnosis, and treatment at a tertiary care hospital of Karachi, Pakistan: A retrospective chart review

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ABSTRACT

Background: Hemangioblastomas are benign neoplasms that consist of stromal cells and small blood vessels. They are highly vascular tumors and can arise throughout the central nervous system. This study aims to provide an overview of our experience with this rare tumor's presentation, radiology, histopathology, and outcomes as literature regarding this pathology is sparse from our country.

Methods: The study is a retrospective review of cases that were histopathology proven cases of spinal cord hemangioblastomas. The clinical characteristics of these patients were examined, and their presentation was recorded. The radiology was also reviewed to describe classic appearance on magnetic resonance imaging. A detailed review of immunohistochemistry was also performed and outcome was described.

Results: A total of 25 cases of spinal hemangioblastomas were found in our records in the period of 2001–2019. There were 20 males (80%) and only 5 female patients (20%). Gross tumor fragments ranged in size from 0.24 cm^2 to 10.5 cm^2 (mean 3.28 ± 2.65). Histologically, tumor was composed of nests of large stromal cells with clear to vacuolated cytoplasm separated by thin-walled capillaries. Focal intratumoral hemorrhage was noted. No significant cytological atypia or mitotic figures were noted. Immunohistochemical stains were performed to confirm the diagnosis and exclude other tumors. Inhibin was tested in 20 cases and it was positive in 16 cases (80%). Neuron-specific enolase was positive in 6/8 cases. Cluster of differentiation (CD) CD68 was positive in 6/6 cases and vimentin in 4/4 cases. Glial fibrillary acidic protein (GFAP) and epithelial membrane antigen were performed in 14 and 8 cases, respectively, and all were negative. Cytokeratin AE1/AE3 was negative in 13/13 cases. CD34 highlighted vasculature in the 8 cases in which it was performed and was negative in tumor cells. Follow-up was available in 17 out of 25 cases and ranged from 12 months to 216 months (mean 61.8 ± 60.6 months). Recurrence occurred in 2 out of 17 (11.7%) patients for whom follow-up information was available.

Conclusion: Our experience shows that spinal cord hemangioblastomas can be surgically removed in most cases with a low risk of recurrence. Most patients in our study were male and unlike other studies, none of our cases showed GFAP positivity.

Keywords: Hemangioblastoma, Spinal cord, Surgery

INTRODUCTION

Hemangioblastomas are benign neoplasms that consist of stromal cells and small blood vessels. They are highly vascular tumors that usually occur in the spinal cord and cerebellum.[14] They

represent about 1.6–5.8% of spinal cord tumors.[5] Their occurrence can be either spontaneous (sporadic) or be associated with the autosomal dominant von Hippel-Lindau (VHL) disease. Most of these tumors in the spinal cord happen to be sporadic comprising 70–80% of total spinal hemangioblastomas. It needs to be emphasized that hemangioblastomas are histologically benign with their significant morbidity related to their location in the central nervous system (CNS). In case of spinal hemangioblastomas, this is translated as possible quadriplegia or paraplegia, depending on the level involved. Morbidity can also be due to associated pathologies such as syringomyelia and pseudocysts.[15]

As for most benign CNS pathologies, treatment is centered on complete surgical resection, with adjuvant methods such as angioembolization and radiosurgery reserved for unresectable disease, residual disease, or as an adjunct to surgery.[2,13,17] Recent literature has thrown light on the epidemiology of this unique pathology as well.[19] Histologically, these tumors are characterized by the presence of vacuolated tumor cells and a rich vascular component. However, their histochemical differentiation from metastatic clear cell renal carcinoma can be cumbersome since both diseases can occupy a niche in the same subset of patients with VHL disease.[3]

This study aims to provide an overview of our experience with this rare tumor's presentation, radiology, histopathology, and outcomes as literature regarding this pathology is sparse from our country.

MATERIALS AND METHODS

The study is a retrospective review of cases whose histopathology was sent to our hospital for analysis. These samples were received from all over the country and included patients who were operated at our hospital as well.

The clinical characteristics of these patients were examined, and their presentation was recorded as well as the location of the lesion in the cord. The radiology was also reviewed to describe their appearance on magnetic resonance imaging (MRI) and angiography in certain cases. The histopathology was reviewed in detail with immunohistochemistry (IHC). The IHC antibodies (DAKO™ and Santa Cruz™) used were against glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA), S100, neuron-specific enolase (NSE), inhibin, cytokeratin (CK), vimentin, cluster of differentiation (CD) 68, and CD34. Tests were validated and involved positive and negative controls in compliance with College of American Pathologists Guidelines. Outcomes were recorded from medical records in terms of postoperative improvement of neurological function, static with no change, and worsening postsurgery. Ethical review committee exemption was obtained.

RESULTS

A total of 25 cases of spinal hemangioblastomas were found in our records in the period of 2001–2019. There were 20 males (80%) and only 5 female patients (20%). Sixteen cases were referrals and nine were in-house cases. Only 1 patient (4%) was a known case of VHL disease although information on all patients being screened for VHL disease was not available. Gross tumor fragments ranged in size from 0.24 cm^2 to 10.5 cm^2 (mean 3.28 ± 2.65). Surgery was carried out by different qualified neurosurgeons using a posterior approach and gross total excision was achieved in each case.

Histologically, tumor was composed of nests of large stromal cells with clear to vacuolated cytoplasm separated by thin walled capillaries. Focal intratumoral hemorrhage was noted. No significant cytological atypia or mitotic figures were noted [Figure 1a-d]. Immunohistochemical stains were performed to confirm the diagnosis and exclude other tumors. Inhibin was tested in 20 cases and it was positive in 16 cases (80%) [Figures 2a and b]. NSE was positive in 6/8 cases. CD68 was positive in 6/6 cases and vimentin in 4/4 cases [Figures 2c and d]. GFAP and EMA were performed in 14 and 8 cases, respectively, and all were negative. CK AE1/AE3 was negative in 13/13 cases. CD34 highlighted vasculature in the 8 cases in which it was performed and was negative in tumor cells. Follow-up was available in 17 out of 25 cases and ranged from 12 months to 216 months (mean 61.8 ± 60.6 months). Recurrence occurred in 2 out of 17 (11.7%) patients for whom follow-up information was available. About 64% of our patients had neurological improvement while 36% remained unchanged. None of our patients with follow-up available worsened. [Table 1] summarizes the demographic, clinical, and immunohistochemical characteristics of these

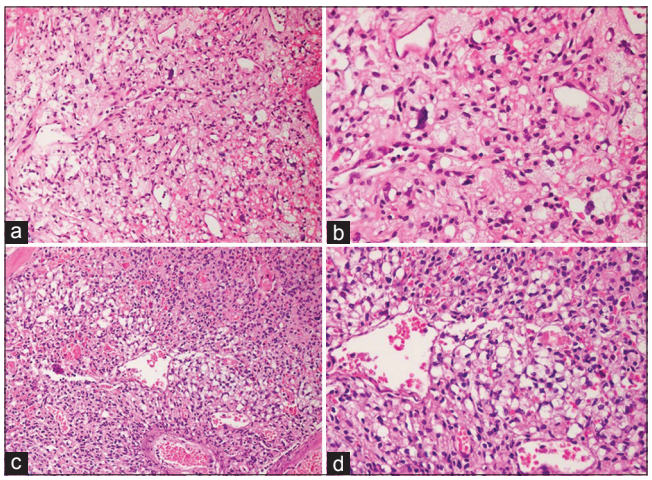

Figure 1: (a and b) Low and medium power examination showed numerous thin-walled anastomosing vessels and scattered variable sized stromal cells. The stromal cells showed microvacuolated cytoplasm and moderate nuclear atypia. (c and d) Histological features from another case showing a predominance of univacuolated stromal cells among fine capillary sized vessels.

Table 1: This table shows the clinical characteristics of the patients and immunohistochemical patterns of the tumors (*n*=26).

S. No.	Age (years)	Sex	Location of tumor	Clinical presentation	Gross size (cm)	Positive immunochemistry	Negative Immunochemistry
1	18	Male	C4-C7	Quadriplegia	4×1.7	S100, NSE, Vimentin	GFAP, EMA
2	31	Male	D6-D10	Paraplegia	2.5×1.5	NSE, CD68	GFAP, EMA, inhibin
3	27	Female	C7-T1,	Paraplegia	0.8×0.3	Inhibin	CK
4	24	Male	C4,	Quadriparesis	1.3×0.8	Inhibin	GFAP, CK
5	40	Male	D11	Known case of Von Hippel-Lindau syndrome. Paraparesis and urinary incontinence	1.3×0.7	S100, inhibin	GFAP
6	34	Female	Cervical spine	Neck pain with B/L upper limb paresis	Not known	Inhibin, vimentin	GFAP, S100, CK
7	38	Male	C3-4 spinal lesion	Progressive weakness of upper extremity R>L	1.8×1.5	Inhibin, CD68	-
8	20	Male	Cervical spine	Progressive right sided paresis	2.5×2	NSE, inhibin	GFAP
9	49	Male	C3-5	Neck pain and paraparesis	3×1.8	S100, inhibin	CK
10	42	Male	Cervical	Quadriparesis	3.3×2	Inhibin	GFAP, CD34
11	36	Male	D4-5	Difficulty in walking and weakness right side of body	1.6×1.1	Inhibin	GFAP, CK, CD34
12	37	Male	Cervical spine	Quadriparesis	1×1	Inhibin	EMA, CK
13	64	Male	C4-C5	Quadriparesis	Not Known	Inhibin, vimentin, CD68	GFAP, EMA, NSE, CK, CD34
14	19	Male	D10	Paraparesis	3×1.5	Inhibin	GFAP, CK, CD34
15	49	Male	D12	Backache for 1 year and paraparesis	2.5×2	Inhibin	GFAP, CK, CD34
16	18	Male	D8-9	Paraparesis	1.7×1.1	NSE, CD68	GFAP, S100, EMA, inhibin, CK, CD34
17	44	Male	D2	Paraparesis	2×1.5	None	GFAP, EMA, inhibin
18	39	Female	D11, D12	Backache, paraplegia	3×2	S100, inhibin	GFAP, EMA, CK
19	31	Male	Dorsal	Paraplegia	3.5×3	NSE, inhibin	-
20	30	Female	cervical	Quadriparesis	0.8×0.5	S100, NSE, CD68	Inhibin, CK, CD34
21	34	Female	Cervical	Back pain and quadriplegia	3×1.5	Not done	Not done
22	36	Male	L2-3	Back pain	1	NSE	-
23	56	Male	Cervical spine	Quadriplegia	NK	S100, vimentin, CD68	CD34
24	46	Male	C7-T1	Bilateral lower limb numbness. Difficulty in walking	1.2×1	Inhibin	GFAP, S100, EMA, NSE, CD34
25	30	Male	C1-2	Right arm numbness	0.6×0.4	S100, inhibin	EMA, NSE, CK

NSE: Neuron-specific enolase, GFAP: Glial fibrillary acidic protein, EMA: Epithelial membrane antigen, CK: Cytokeratin, CD68: Cluster of differentiation 68, CD34: Cluster of differentiation 34, B/L: Bilateral

cases. [Table 2] compares our study with other studies in literature and also reports outcomes in our cases.

DISCUSSION

Our study is the largest case series to be complied from Pakistan and provides important clinical, histopathological, and outcome data for a very rare lesion. The incidence of spinal hemangioblastomas has been estimated by Westwick *et al.* to be 0.014/100,000 population. This study was based on the examination of the surveillance, epidemiology, and end results data set. This was a first effort to establish incidence and prognosis of a population with spinal hemangioblastomas. According to their study, there was a slight female preponderance with a female-to-male ratio of 1.05:1. However, an earlier study by Deng *et al.* had reported a strong male predilection of 1.8:1. This male preponderance holds true for our data with a male-to-female ratio of 4.8:1.[7,19] The association of VHL disease with spinal hemangioblastomas could not be derived from the data but almost half of patients with spinal hemangioblastomas had VHL disease. In our

Table 2: Comparison of previous case series with our study. It should be noted that there was a lack of uniform reporting in our literature search and not all studies reported outcomes while some did not report presentation findings. All these studies included patients who underwent surgery.

Author/year	*n*	Sex, male	Age, average, years	Location			Chief complaint			VHL disease %	Outcome		
				Cervical	Thoracic	Lumbar	Sensory	Motor	Pain		Improved	Stable	Worsened
Deng *et al.*, 2014	92	64	32				65	38	53	35	41	43	15
Serban and Exergian, 2013	5	40	43								80		20
Harati *et al.*, 2012	17	59	43	76	17					64	18	82	
Park *et al.*, 2012	16	59	43					66	66	25	19	56	25
Imagama *et al.*, 2011	26	58	42							23			15
Takai *et al.*, 2010	35	71	45	42	33	25				51	37	53	10
Mehta *et al.*, 2010	108	53	32	47	44		64	36		100		93	6
Clark *et al.*, 2010	20	65	49	45	27	15				55	25	65	10
Parker *et al.*, 2009	34	44	41	38	34	5				73			17
Kanno *et al.*, 2009	48	43	33	40	54	5				100	13	70	17
Shin *et al.*, 2008	20	60	49	30	55					10			15
Bostrom *et al.*, 2008	23	52	44	13	35					35			4
Biondi *et al.*, 2005	4	50	43			100				25	50	50	
Van Velthoven, 2003	28	50	38	54	21	4				64	14	79	
Lonser *et al.*, 2005, 2003	44	59	34							100		84	9
Lefranc and Brotchi, 2003	25	48	40	56	24	76						64	20
Lee *et al.*, 2003	14	79	37								57	21	21
Xu *et al.*	20	76	32	100									5
Malis *et al.*, 2002	19			74	26						100		
Roonprapunt, 2001	19	68	31	68						Excluded			10
Pietila *et al.*, 2000	15	93	27							87			17
Our study, 2020	25	80	37	62	34	4	20	88	36	4	64	36	

data set, there was only one patient known to have VHL disease. As the clinical data for our cases were limited and, we cannot draw definite conclusions. Multiple tumors may be encountered in 60–80% of patients with VHL disease but in only 3% of individuals with sporadic hemangioblastomas.[16]

Spinal hemangioblastoma patients present predominantly with spinal symptoms which depend on the exact location of the tumor in the spine. Even though their histology is benign, their attendant morbidity can be significant. The earliest signs and symptoms are pain and sensory disturbances. Depending on the level at which the tumors are located, symptoms may include hyperreflexia, myelopathy, weakness, abnormal spine curvature, bowel, and bladder issues. Syrinx formation is usually associated with symptomatic lesions and if the lesion is small and symptomatic, there is a significant edema and cord expansion. The presence of an associated pseudocyst strongly correlates with presence of symptoms. The natural history of these tumors usually shows spurts of growth punctuated with stasis but can sometimes follow a linear or exponential growth pattern.[18]

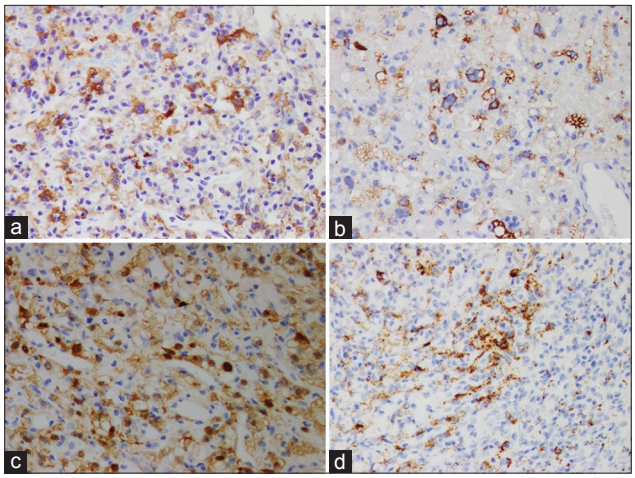

Figure 2: (a and b) Inhibin A positivity in stromal tumor cells. (c) A subset of tumor cells was positive for S100 protein and (d) CD68.

Diagnosis of spinal hemangioblastomas can be quite confusing due to its myriad of variable appearances. They can be associated with the presence of a pseudocyst, syrinx, diffuse spinal cord enlargement, exophytic disease with minimal cord involvement, or entirely extramedullary disease.[1] Gadolinium-enhanced MRI is essential to detect these lesions. They are usually hypo to isointense on T1 imaging and iso to hyperintense on T2-weighted imaging [Figures 3-5]. Multiple lesions should raise suspicion of VHL disease. In the presence of multiple lesions, only one is usually responsible for spinal symptoms. This has been described in literature while we only had one patient with known VHL disease and a single spinal lesion. Larger lesions may demonstrate flow voids and hemorrhage, either subarachnoid or intramedullary is the exception rather than the rule.[6]

The term "hemangioblastoma" was first used by Arvid Lindau in 1926. These were described as nonmetastasizing lesions of the CNS that is characterized by two important features. The first being a dense capillary network separated by stromal cells and the second being a high frequency of pseudocyst formation (approximately 70% of cases). The stromal cells are often lipid laden and give the tumor a yellowish gross appearance. Their radiological appearance may mimic a pilocytic astrocytoma with contrast enhancement and pseudocyst formation. Since this tumor is not invasive, there is always a rim of gliotic tissue surrounding it which may be erroneously reported as an astrocytoma if frozen section is used intraoperatively.[12,20]

The origin of the "stromal cells" in hemangioblastomas is the subject of much debate. Possible derivation may be from glial cells, endothelial cells, embryonal cells, etc. A wide variety of other sources have been proposed. Zhao *et al.* described a

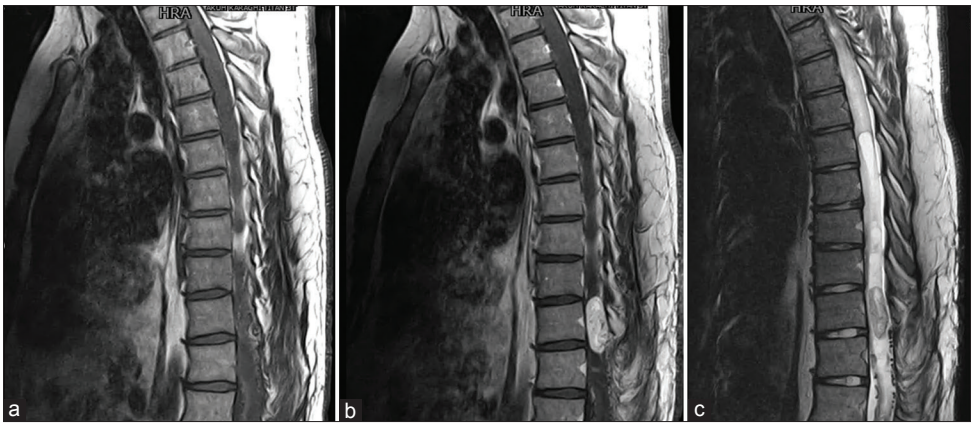

Figure 3: (a and b) Magnetic resonance imaging thoracic spine T1-weighted images, without and with gadolinium contrast demonstrating an intraspinal well-circumscribed lesion with almost homogenous contrast enhancement in sagittal sections. (c) T2-weighted sagittal imaging demonstrating the lesion with hypo to hyperintense internal signals and rostral syrinx formation.

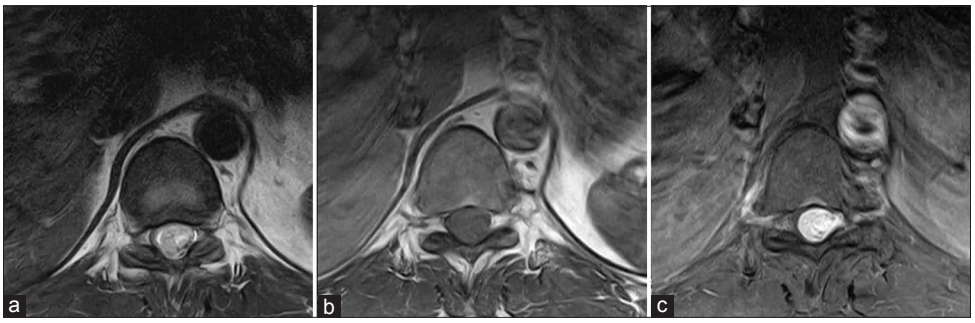

Figure 4: (a) Axial T2 image demonstrating the intramedullary location of the lesion with thinning of the cord around it. (b and c) Axial T1 images, without and with gadolinium contrast, demonstrating avid contrast-enhancing intramedullary lesion projecting to the surface of the cord in the left dorsolateral aspect of the cord.

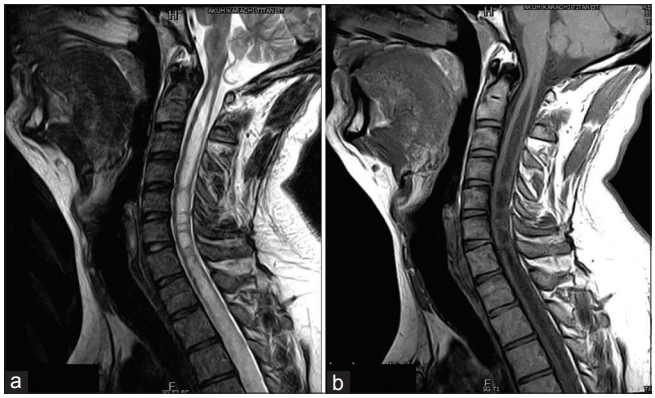

Figure 5: (a and b) Magnetic resonance imaging cervical spine T2- and T1-weighted images from the same patient in Figures 3 and 4, demonstrating rostral syrinx formation from the lower dorsal spine to the cervicomedullary junction.

series of 26 cases of hemangioblastomas (not limited to spinal cord). They described variable expression of neural (S-100, NSE, and CD56), glial (GFAP), and mesenchymal (vimentin) markers. Nonspecific markers that were expressed included epidermal growth factor receptor, D2-40, vascular endothelia growth factor, and CD68. No muscle-derived markers were expressed.[21] Our study group, however, did not show any samples to be positive for GFAP. We believe that GFAP expression represents sampling of the adjacent gliotic tissue. Ki-67 proliferative index is variable. In a study by Imagama *et al*., Ki-67 index was <1% in purely intramedullary tumors while it ranged between 18% and 25% in cases where the tumor was both intra and extramedullary.[10]

Treatment of spinal hemangioblastomas is usually by microsurgical excision. The nature of this tumor necessitates complete excision as partial removal leads to treatment failure and bleeding. The edema and syrinx associated with the tumor may persist with incomplete resection. This may be especially problematic in tumors with both intra an extramedullary component as there can be worsening of neurophysiology during the procedure leading to procedure abandonment and forcing reoperation at a later date.[10] The overwhelming majority of these tumors are dorsally located in the cord and require a dorsal approach with a laminectomy and wide exposure of the dura. A laminoplasty is usually performed in children but its utility in the thoracic spine in adult patients is questionable. For the small minority of more ventrally situated tumors, a carefully selected anterior approach is warranted to avoid morbidity.[11]

During surgery, the tumor appears red to orange in appearance with a well-developed capsule that separates it from the pia mater. The syrinx and pseudocysts associated with the tumor do not require any special diversion or excision as they are filled with fluid derived from the tumor itself and resolve once resection of the tumor is complete. The resection of intramedullary tumors which was pioneered by Sir Victor Horsley was associated with significant morbidity. Over the past 100 years, advances in technique led to the first successful resection by Guidetti and Fortuna in 1967 without significant morbidity. Microsurgical resection is now associated with low morbidity.[9,15]

We employed intraoperative sensory and motor evoked potential monitoring in our patients which is now considered important when resecting intramedullary cord lesions. However, the value of this technique has been questioned in light of historical data and perspective. Minimally invasive techniques may decrease morbidity from the wound but the major morbidity in these cases is from the intradural work performed and we feel the decision to perform minimally invasive versus conventional approaches should be based on surgeon's preference. The surgical approach to these tumors is different from other more common intramedullary tumors which are usually juxtamedullary and instead of a midline myelotomy, the surface projection of the tumor is approached to devascularize and safely separate the tumors from the pia from which they arise.[15] Angiography is useful for evaluating feeding and draining vessels [Figure 6]. Embolization with superselective catheterization may be considered in a very small minority of tumors with a large distinct feeder. Embolization is associated with attendant risk of stressing an already thinned cord and causing ischemia.[8]

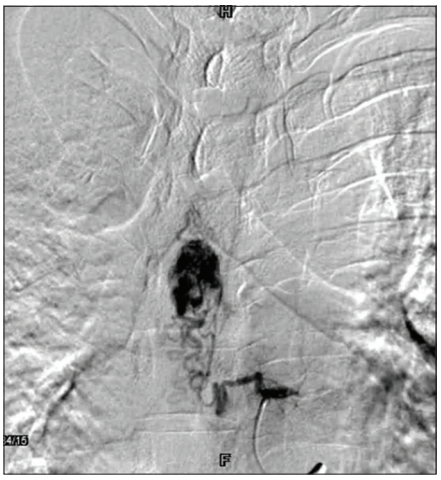

Figure 6: Digital subtraction angiogram with super selective catheterization demonstrating feeding vessels to the tumor with draining vessels not visualized in this image.

A review of literature reveals surgical excision to be the most effective means of treating spinal cord hemangioblastomas. However, recently, stereotactic radiosurgery (SRS) has been used as a noninvasive means of treating these patients. The first evidence for SRS using linear accelerator came in the mid-1990s while in 2001 FDA approval was granted to CyberKnife for extracranial lesions. Bridges *et al.* succinctly summed up the literature on SRS for spinal hemangioblastomas. Based on published studies, SRS achieves either stable or regressive tumors in 98% of cases with only 2% of cases progressing. There were little to no side effects from SRS. At present, patients who have VHL disease and multiple tumors may be treated with SRS.[4]

CONCLUSION

Our experience shows that spinal cord hemangioblastomas can be surgically removed in most cases with a low risk of recurrence. Most patients in our study were male and unlike other studies, none of our cases showed GFAP positivity. Some of these lesions may require endovascular techniques to facilitate surgery. Good planning and timing of surgery can help neurosurgeons treat this tumor with great success.

Declaration of patient consent

Institutional Review Board permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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