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CLINICAL STUDY

Surgical outcomes in spinal cord subependymomas: an institutional experience

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Abstract Spinal cord subependymomas are very rare. Most studies on spinal cord subependymomas have been case reports with literature reviews. This study presented a surgical series of 13 patients with histologically proven spinal cord subependymomas. Their clinical data, radiological findings, operative records, and follow-up outcomes were reviewed. There were 5 male and 8 female patients with a mean age of 39.5 years. The mean follow-up period was 67.8 months. Four tumors were located in the cervical spine, 5 in the cervicothoracic spine, and 4 in the thoracic spine. Gross total resection (GTR) of the tumor with a well-demarcated dissection plane was achieved in 9 cases, and subtotal resection was achieved in 4 cases. The symptoms present before the surgery were improved in 11 cases at last follow-up and the current status of 2 patients had no change compared to the preoperative presentation at last follow-up. The postoperative follow-up magnetic resonance imaging showed no recurrence in the 9 GTR cases during the mean follow-up period of 70.3 months. No recurrence/regrowth of the residual tumors was observed in the 4 STR cases during the mean follow-up period of 62.0 months. Spinal cord subependymomas are amenable to surgical resection. It is possible to achieve GTR of intramedullary subependymomas that have a well-demarcated dissection plane. When GTR cannot be achieved, STR of the lesion for decompression is advised, and follow-up imaging is needed. A good clinical outcome after GTR or STR can be expected.

Keywords Subependymoma · Surgical resection · Spinal cord tumor · Ependymal tumor

Introduction

Subependymomas are rare tumors in the central nervous system (CNS). These tumors compose less than 1 % of all brain neoplasms [1]. Subependymomas are slowly growing indolent benign tumors, corresponding histologically to WHO grade I [2, 3]. These neoplasms are usually found in the floor of the fourth ventricle and on the lateral ventricle walls [3]. Subependymomas rarely occur in the spinal cord, and most are intramedullary lesions located in the cervical and cervicothoracic regions [4].

To our knowledge only 56 cases of spinal cord subependymoma have been described since the publication of the earliest report in 1954 [5, 6], and most previous studies are case reports with an associated literature review. We present the results from a surgical series of 13 patients with histologically proven spinal cord subependymomas and their long-term outcomes from a single center.

Materials and methods

Between the years 2004 and 2010, 13 patients were pathologically diagnosed with spinal cord subependymomas at the Department of Neurosurgery, Beijing Tiantan Hospital. Data related to the clinical presentation, radiological imaging, treatment, and follow-up outcomes were collected with institutional review board approval. Patients who had

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Table 1 Modified McCormick classification [7, 8]

Grade	Definition
I	Neurologically normal
	Gait normal
	Normal professional activity
Ib	Tired after walking several kilometers
	Running is impossible, or moderate sensorimotor deficit does not significantly affect the involved limb
	Moderate discomfort in professional activity
II	Presence of sensorimotor deficit affecting function of involved limb
	Mild to moderate gait difficulty
	Severe pain or dysesthetic syndrome impairs quality of life
	Independent function and ambulation maintained
III	More severe neurological deficit
	Requires cane and/or brace for ambulation or maintains significant
	Bilateral upper-extremity impairment
	May or may not function independently
IV	Severe neurological deficit
	Requires wheelchair or cane and/or brace with bilateral upper-extremity impairment
	Usually not independent

an alternate tumor type or a mixed subependymoma-ependymoma tumor type on pathology were excluded.

Magnetic resonance imaging (MRI) with gadolinium-contrast enhancement was performed as standard radiological investigation before and after surgical treatment. With intraoperative neurophysiologic monitoring of somatosensory and motor evoked potentials, all the patients underwent surgical resection and no evoked potentials were lost during the surgery.

The author performed a structured telephone interview to evaluate the patients' postoperative status. Modified McCormick classification (Table 1) [7, 8] was applied to assess neurological function. This assessment was performed before surgery, at discharge, at 3 months after surgery, and semi-annually thereafter.

Results

There were 486 patients with histologically proven spinal cord ependymal tumors treated at our institute during the same period. Of those, 13 (2.7 %) had intramedullary subependymomas (Table 2). Thus, there were 5 male and 8 female patients included in the study. The mean age at the time of the operation was 39.5 years (range, 20–52 years). The mean duration of illness was 39.7 months (range, 2–120 months). The preoperative presentations included motor deficits (10 cases, 76.9 %) associated with sensory disturbance (13 cases, 100 %) and sphincter dysfunction (5 cases, 38.5 %). The preoperative assessment showed that 3 patients were at Grade Ib of the modified McCormick classification, followed by 8 at Grade II and 2 at Grade III.

Preoperative imaging diagnosis

Tumors were located in the cervical (4 cases, 30.8 %), cervicothoracic (5 cases, 38.4 %), and thoracic (4 cases, 30.8 %) spinal cord regions. Radiological diagnosis indicated the presence of intramedullary spinal cord tumors Based on the T1-weighted MRI results, the tumor had iso-signal intensity in 5 cases and low signal intensity in 8 cases. The T2-weighted MRI results indicated the tumor had high signal intensity in all the cases. Contrast-enhanced T1-weighted MRI revealed 8 cases with no enhancement and 5 cases with partially faint enhancement, which was mixed across all the cases and had no consistency with the imaging findings on T1-weighted MRI. Eccentricity of the lesions in location was noted in 9 cases (Fig. 1), of which 8 cases were misdiagnosed as astrocytomas. Peritumoral edema, tumor cysts, and associated syringomyelia were rarely present. On the basis of preoperative MRI, all the patients were misdiagnosed with ependymomas (5 cases, 38.5 %) or astrocytomas (8 cases, 61.5 %).

Intraoperative findings

All of the tumors were removed through the posterior approach using an operative microscope for tumor dissection, and the completely intact dura mater was opened in the midline. The lesions in all cases were intramedullary and there were extramedullary extensions in 4 patients. Laminectomy was performed in 5 of the cases, and laminoplasty was performed in the other 8 cases.

Intraoperatively, myelotomy was performed for intramedullary exploration. The lesions were yellowish or red-grayish in color, multi-nodular or lobulated in shape, firm or soft in texture, mildly vascular, and mostly eccentric in location. Most of the masses were well demarcated from the spinal cord parenchyma, which facilitated their exposure and dissection. Thus, gross total resection (GTR) of the tumor was achieved in 9 cases (69.2 %) with a well-demarcated dissection plane. Subtotal resection (STR) was achieved in 4 cases (30.8 %) with poor tumor-spinal cord interfaces or densely adhesion to neural tissue. An illustrative example of a case is shown in Fig. 2.

Pathological examination

Microscopically, all tumors showed typical histological indications of subependymoma according to the WHO classification (Fig. 3). Each tumor was composed of scattered clusters of small monomorphic cells arranged in a

Table 2 Summary of clinical presentations and radiological findings of 13 patients

Case	Age (yrs), sex	Duration of illness	Tumor location	Presentations	MRI findings			Surgical methods	McCormick grade			FU (mos)
					T1WI	T2WI	+GA		Preoperative	Postoperative	Last FU	
1	20, F	8 years	C7-T5, IM	Rt leg pain and weakness; lt leg numbness; mild fecal incontinence	Mild hypo	Mild hyper	Patchy	GTR	II	III	Ib	46
2	50, M	2 years	C3-7, IM	Lt limbs pain and numbness; bil upper limbs and lt leg weakness; difficulty in defecation and urination	Mild hypo	Hyper	Mildly patchy	STR	III	IV	II	84
3	33, M	2 months	C7-T6, IM	Rt limbs numbness	Iso	Hyper	No	GTR	Ib	II	Ib	56
4	49, F	1 year	T6-10, IM	Rt leg pain and numbness; bil legs weakness	Hypo	Hyper	Mildly irregular	STR	II	II	Ib	48
5	44, F	5 years	C5-T4, IM+EM	Rt leg hypoesthesia and lt leg weakness	Iso	Mild hyper	No	GTR	II	II	II	44
6	50, M	10 years	T5-8, IM+EM	Bil legs weakness and hypoesthesia; urinary incontinence	Mild hypo	Hyper	No	STR	II	II	Ib	64
7	24, F	4 years	C4-T3, IM	Rt limbs numbness and weakness; fecal incontinence	Iso	Mild hyper	Mildly patchy	GTR	II	III	I	74
8	45, F	4 months	C5-T1, IM	Neck pain and bil legs numbness	Mild hypo	Hyper	No	GTR	Ib	II	I	72
9	28, M	2 years	C1-4, IM+EM	Rt upper limb numbness and weakness	Hypo	Hyper	No	STR	II	II	Ib	52
10	44, F	7 years	C3-6, IM+EM	Neck pain and left upper limb weakness	Mild hypo	Hyper	No	GTR	II	II	I	94
11	24, F	6 months	T7-12, IM	Bil legs numbness and weakness; difficulty in defecation and urination	Iso	Hyper	Mildly irregular	GTR	III	IV	II	66
12	52, M	2 years	C3-5, IM	Neck and rt shoulder pain, rt upper limb numbness	Iso	Hyper	No	GTR	Ib	II	I	73
13	51, F	1 year	T3-7, IM	Rt leg weakness and lt leg numbness	Hypo	Hyper	No	GTR	II	II	I	108

bil bilateral; *EM* extramedullary; *FU* follow-up; *+GA* gadolinium administration; *GTR* gross total resection; *hyper* hyperintensity; *hypo* hypointensity; *IM* intramedullary; *iso* isointensity; *lt* left; *MRI* magnetic resonance imaging; *rt* right; *STR* subtotal resection; *WI* weighted image

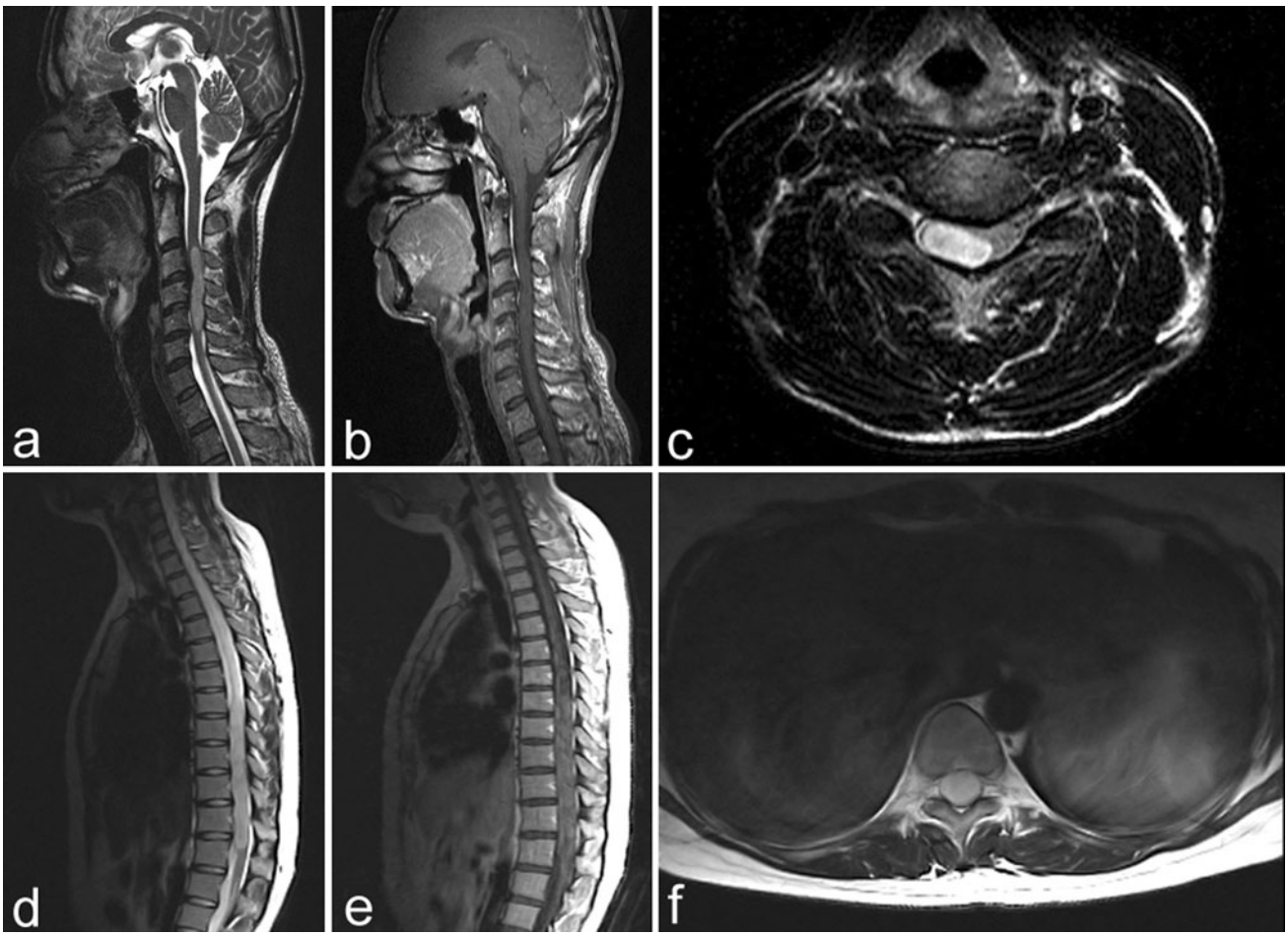

Fig. 1 **a–c** Case 12. Preoperative magnetic resonance imaging (MRI) showed a well-demarcated, hyperintense intramedullary mass at the C3-5 levels on the sagittal T2-weighted image (WI) (**a**), with no enhancement on sagittal T1WI with gadolinium (**b**). The lesion grew eccentrically within the cord on axial T2WI (**c**). **d–f** Case 11. Preoperative MRI showed a hyperintense intramedullary mass at the T7-12 levels on the sagittal T2-weighted image (WI) (**d**), with mildly irregular enhancement on sagittal T1WI with gadolinium (**e**). The lesion was located centrally within the cord on axial T2WI (**f**)

finely fibrillary background. The nuclei were markedly uniform with moderate pleomorphism, and with relative lack of perinuclear cytoplasm. Mitotic activity, ependymal rosettes or perivascular pseudorosettes, and microcystic degeneration were rarely found. Immunohistochemical analysis was performed, and the tumor cells were typically found to be positive for glial fibrillary acidic protein (GFAP) but negative for epithelial membrane antigen (EMA). Ki-67 labeling index in all the lesions was less than 1 %.

Long-term outcomes

The postoperative course in all the cases was uneventful. After surgery immediately, 7 patients had a worsening of neurological deficits. The mean follow-up period was 67.8 months (range, 44–108 months). During the telephone interviews, 11 patients reported their latest status was improved markedly compared to the preoperative presentation, and the current status of two patients had no change at last follow-up. However, some patients did complain of motor deficit (6 cases, 46.2 %), sensory disturbance (5 cases, 38.5 %), and sphincter dysfunction (3 cases, 23.1 %). At the last follow-up assessment, 5 patients returned to Grade I and 5 were at Grade Ib followed by 3 at Grade II.

Postoperative MRI results showed no tumor recurrence in the 9 GTR cases after a follow-up period of 70.3 months on average. In the 4 STR cases, the follow-up MRI showed no regrowth in the residual tumors during the mean follow-up period of 62.0 months. None of the patients underwent second surgery and further adjuvant therapy.

Discussion

Epidemiology and clinical features

Subependymoma is an uncommon benign neoplasm, which can occur throughout the CNS. It accounts for only 0.7 %

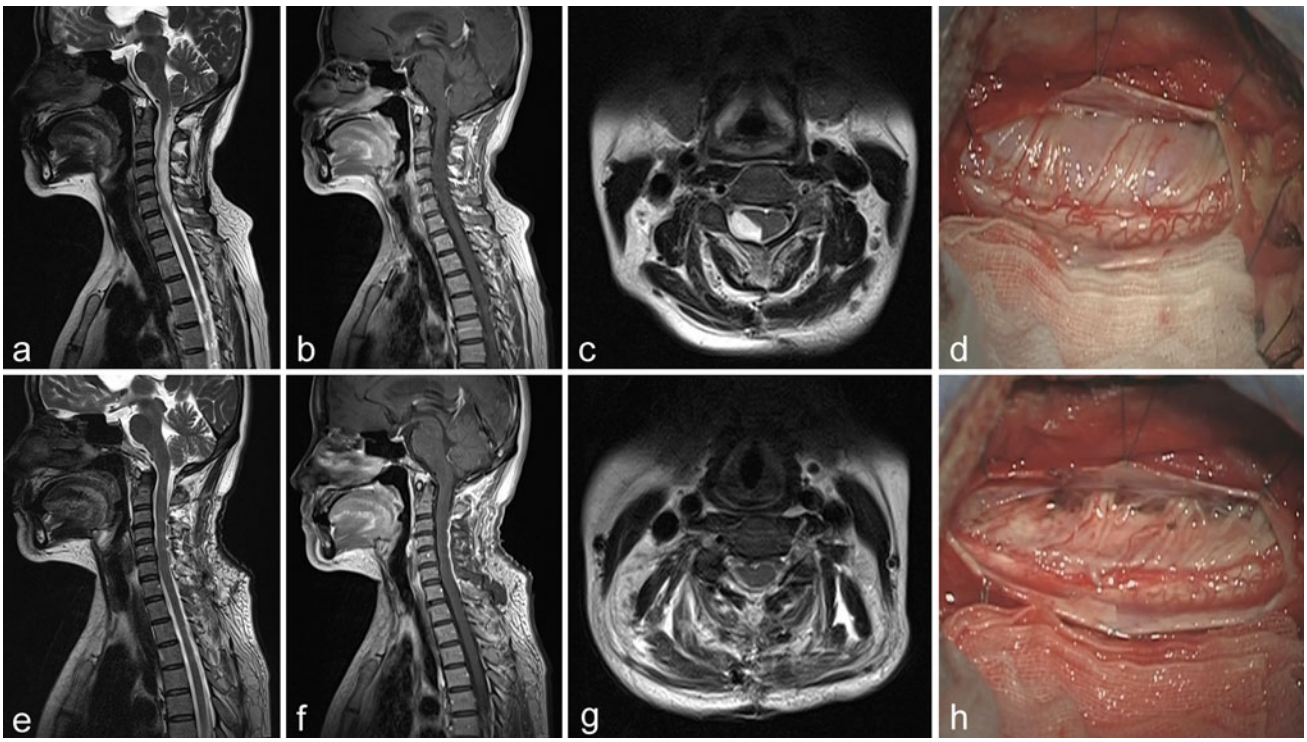

Fig. 2 Illustration of case 10. Preoperative magnetic resonance imaging (MRI) showed a tumor was located at C3-6 without peritumoral edema, tumor cysts, and associated syringomyelia. The lesion showed hyperintensity on the sagittal T2-weighted image (WI) (**a**), and no enhancement on the sagittal T1WI with gadolinium (**b**). Based on axial T2WI (**c**) and intraoperative finding (**d**), the tumor was found to be predominantly subpial eccentric with right exophytic tumor extension, located between the ventral and dorsal rootlets. Postoperative MRI (**e** sagittal T2WI, **f** sagittal T1WI with gadolinium, **g** axial T2WI) and intraoperative finding after surgical removal (**h**) revealed total excision of the tumor

of all intracranial neoplasms and 8.3 % of all ependymal tumors [5, 9]. This entity is rarely encountered in the spinal cord. There have been 56 cases of spinal cord subependymoma reported in the literature. It is known to predominate in males (36 men and 20 women) and the mean age of symptom onset is the fourth decade of life (mean age 44.8 years). The most frequently affected site is the cervical and cervicothoracic spinal regions, and the intramedullary location is the most common except for five extramedullary cases [5, 9–13].

In our series, subependymomas represented 1.3 % of all intramedullary tumors ($n = 988$), 2.7 % of all ependymal tumors ($n = 486$), and 15.5 % of all CNS subependymomas ($n = 84$) during the same period. The mean age was in the expected range (39.5 years). However, the predominance of female (male: female = 5: 8) and the incidence of thoracic location (cervical: cervicothoracic: thoracic = 4: 5: 4) was different as compared to the previous literature. All the lesions involved four or more vertebral segments.

Similar to those of common intramedullary tumors, the clinical symptoms of intramedullary subependymomas are sensory, motor or sphincter dysfunctions, which eventually appear in the late stages of lesion progression. Furthermore, pain and sensory change are the most common initial symptoms. In our series, the mean duration between symptom onset and presentation was 39.7 months (2–120 months), longer than common intramedullary gliomas, which probably reflects the benign nature and slow growth pattern of the tumor.

Pathogenesis

The occurrence of intramedullary spinal subependymomas is exceedingly rare. Compared with common intramedullary tumors, diagnosis and treatment of intramedullary subependymomas is very critical in preventing unnecessary morbidity, providing accurate information with respect to prognosis, and establishing a reasonable schedule for outpatient follow-up. The pathogenesis of this rare lesion is still unknown. Some theories of etiology suggest that the origin may be from ependymal cells with reactive astrocytic proliferation, subependymal zone glial precursor cells, and subpial spinal white matter progenitor cells [5, 10, 14]. Krishnan et al. [14] noted the tumor origin from the outer subpial spinal white matter progenitor cells could better explain the eccentric, subpial, and exophytic locations of spinal subependymomas. However, the glial progenitor cells origin is still uncertain. Thus, various pathogenic mechanisms may cause spinal cord subependymomas.

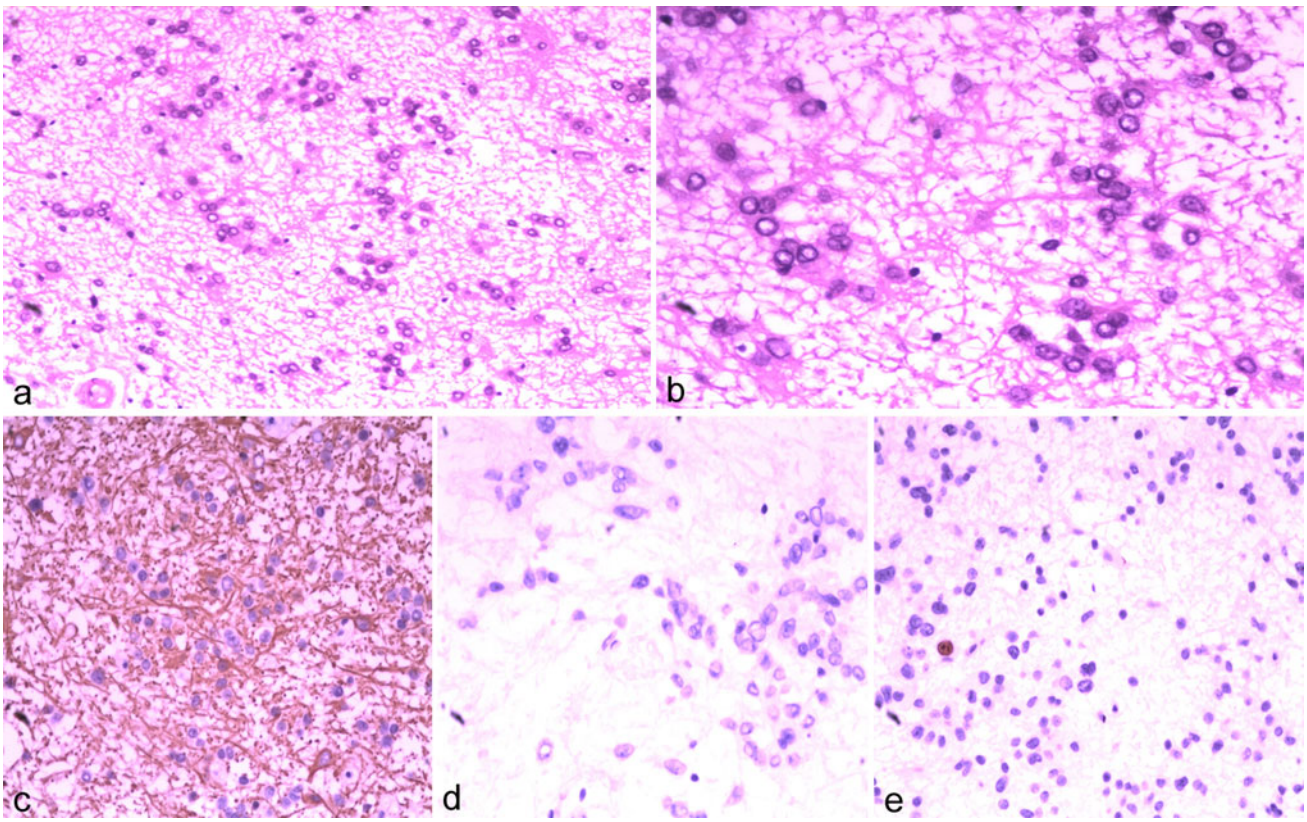

Fig. 3 Pathological feature of spinal cord subependymoma. Each tumor was composed of scattered clusters of small monomorphic cells arranged in a finely fibrillary background (**a**). The nuclei were markedly uniform with moderate pleomorphism (**b**). In the immunohistochemical analysis, tumor cells were positive for glial fibrillary acidic protein (**c**) but were negative for epithelial membrane antigen (**d**). Section stained for MIB-1(**e**) shows a low proliferation index

Radiological features and diagnosis

MRI is the modality of choice for the diagnosis of spinal cord tumors. Preoperative differential diagnosis for intramedullary spinal cord tumors is important when planning surgical strategies and determining the extent of the required resection to avoid overtreatment and unacceptable complications. On MRI, subependymomas are generally hypointense to isointense on T1WI and hyperintense on T2WI, and contrast MRI sequences show little to no enhancement. Segmental fusiform dilatation of the cord is usually noted, and associated syringomyelia is very rare which is usually present in ependymomas. Intraspinal subependymomas tend to grow eccentrically within the cord or show an exophytic component compared to the central location of an ependymoma. Thus, eccentric localization and no enhancement as well as associated syringomyelia in subependymomas may differ from intramedullary ependymomas (WHO Grade II), which usually present as a well-enhanced lesion and are located centrally because of the origin from the ependymal cells of the central canal of the spinal cord. However, subependymomas may develop into huge masses and compress the cord severely, which causes the characteristic of eccentric localization undistinguishable on MRI. Therefore, although the differential diagnosis with other common intramedullary tumors (ependymoma, astrocytoma) is important, definitive preoperative diagnosis of intramedullary subependymoma is difficult based only on MRI due to lack of highly specific appearance.

Treatments and outcomes

Since subependymoma is histologically benign and usually well marginated, a good clinical outcome after complete removal is anticipated. GTR should be attempted with microsurgical technique based on protection of spinal function if a frozen biopsy confirms the subependymoma [15]. In the present study, the lesion surface of most cases was easily found intraoperatively. Most of the lesions showed no adhesion to the spinal cord, and total removal was achieved easily using microsurgical techniques. However, if the lesion is densely adherent to neural tissue or ill-demarcated from the cord, which indicate difficulty in total removal even though the tumors are benign, subtotal removal for decompression of the spinal cord from the

intramedullary lesion is acceptable to improve the myelopathic symptoms and avoid severe operative complications. In the literature, some patients had recurrence or regrowth of the residual tumor with clinical progression, a revision operation was the primary treatment to control the tumor [16, 17]. Other adjuvant therapy options are not recommended for intramedullary subependymoma.

At the mean follow-up of 67.8 months, the postoperative McCormick grades of most patients had significantly improved; moreover, the symptoms did not progress in all the patients. Among our 13 intramedullary subependymomas patients, we achieved GTR with clinical improvement and no recurrence in 9 cases. In the 4 STR cases, adjuvant radiochemotherapy was not recommended because histopathological nature of the tumors was benign, and regular follow-up MRI was performed to determine if there was regrowth of the residual tumor. Satisfyingly, there was no progression and recurrence of the residual tumors after a follow-up of at least 48 months. Therefore, revision operations were unnecessary.

Limitations

The limitation of the present study is its retrospective nature for the last seven years. Microneurosurgical techniques and understanding of intramedullary tumors have been developed during the follow-up period. These developments could help in safely accomplishing tumor removal and therefore have an effect on the surgical outcome. Additionally, detailed operative information in some early cases could not be fully ascertained since their intraoperative findings were based on the medical records without confirmation by operation videos. Although 13 cases in a series seem to be small, the present study included the largest number of intramedullary subependymoma cases yet to be reported.

Conclusions

The present case series and review suggest that spinal cord subependymomas should be considered in the differential diagnosis of a middle-aged patient with intramedullary spinal lesions involving multiple vertebral segments, if the duration of illness is long, and the tumor has eccentric localization and no enhancement on MRI. Total resection using standard microneurosurgical techniques is the goal for treatment of intramedullary subependymomas. When GTR cannot be achieved, STR of the lesion for decompression is advised, and follow-up imaging is needed. Adjuvant radiochemotherapy is unnecessary and a good clinical outcome after GTR or STR can be expected.

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Conflict of interest The authors report no conflict of interest concerning the materials or methods used in this study or the findings described in this paper. No benefits in any form have been or will be received from any commercial party related directly or indirectly to the subject of this manuscript.

Ethical standards This retrospective study was approved by Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University.

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