Journal of Neuro-Oncology (2005) 74: 47–52
DOI 10.1007/s11060-004-3348-9

Clinical Study

Primary neurocytoma of the spinal cord: a case report and review of literature

Suash Sharma[1], Chitra Sarkar[1], Shailesh Gaikwad[2], Ashish Suri[3] and Mehar C. Sharma[1]
[1]*Department of Pathology, All India Institute of Medical Sciences, New Delhi, India;* [2]*Department of Radiology, All India Institute of Medical Sciences, New Delhi, India;* [3] *Department of Neurosurgery, All India Institute of Medical Sciences, New Delhi, India*

Key words: brain, central nervous system, neurocytoma, neuronal tumors, spinal cord

Summary

Most central neurocytomas (CN) and spinal neurocytomas (SN) have a bland well-differentiated histologic picture and uneventful clinical course. However, rare examples showing histologic atypia, recurrence and even CSF dissemination have been reported. Herein we report a case of recurrent spinal neurocytoma in a 24-year-old male who presented with a 2-month history of weakness and numbness of the left upper and lower limbs, and was previously operated at the same site 10 months ago. MRI revealed a contrast enhancing intramedullary mass involving C5-T1 region. Radiologic and operative impression at both surgeries was that of a glioma, possibly anaplastic. Histologic and immunohistochemical features in both resections were those of an atypical neurocytoma. The tumor showed rare mitoses, focal mild vascular proliferation in both specimens, and necrosis in the initial specimen. MIB1 labeling indices were 9 and 10%, respectively. Based on the analysis of this case and limited data from the literature, it is hypothesized that SN shows a histopathologic picture, immunoprofile and biologic behavior very similar to CN. However, the presence of histologic atypia and increased MIB1 index in SN appear to more closely correlate with tumor recurrence and a worse overall outcome, in part due to their location in the critical region of cervical spinal cord. Therefore, we hypothesize that SN with atypia requires a close clinical follow up. As in CN, radiation therapy is perhaps best reserved for atypical, progressive and recurrent SN.

Introduction

Central neurocytomas are uncommon primary central nervous system tumors that are typically located in the supratentorial ventricular system, occurring in young adults and often presenting with symptoms of increased intracranial pressure. Histologically, the tumor is usually well differentiated and composed of small round cells with neuronal differentiation. The entity first described by Hassoun et al. [1,2] is now a well-established diagnosis included in the latest WHO classification [3,4]. Genetic abnormalities in neurocytomas have recently begun to be recognized [5,6]. Primary tumors resembling central neurocytomas have been reported at locations outside the ventricular system including the cerebral hemispheres, thalamus, cerebellum, pons [7–11] and rare examples in spinal cord [12–18]. Herein we report a rare case of primary spinal cord neurocytoma and discuss the clinicopathologic features associated with its atypical location and histology.

Case report

A 24-year-old male initially presented 10 months ago at an outside hospital with a history of weakness and numbness of the left upper and lower limbs for the past 3 months. Physical examination at that time showed mild to moderate decrease in power of the left upper and lower limbs, greater decrease in the upper limbs along with 10–15% sensory loss in the left C4-T1 dermatomes. An MR imaging demonstrated an intramedullary space occupying lesion in the C5-T1 spinal segments (Figure 1a–d). The tumor was isointense on T1 weighted image (Figure 1a) and hyperintense on T2 (Figure 1b). The tumor showed homogenous enhancement with contrast injection (Figure 1c and d). Radiologic diagnosis was of a glioma with a differential diagnosis of hemangioblastoma. The patient was operated upon, a cervical spinal cord tumor was detected at surgery and a gross total removal was performed. Operative impression was that of a glioma. A post-operative MR scan showed no evidence of residual tumor.

The patient subsequently presented 10 months after surgery at our hospital with similar complaints of weakness and numbness of the left upper and lower limbs for the past 2 months. On examination, he was found to have moderate decrease in power of the left upper and lower limbs, more significant in the upper limbs. In addition, there was 20–25% sensory loss in the left C2-T1 dermatomes with 80–90% sensory loss in the C4 spinal segment. Radiologic diagnosis was a recurrent glioma. At surgery, a grayish vascular intramedullary tumor mass was noted in the C6-T1 spinal segments expanding the spinal cord in the region. No definite plane of resection could be made out between the tumor

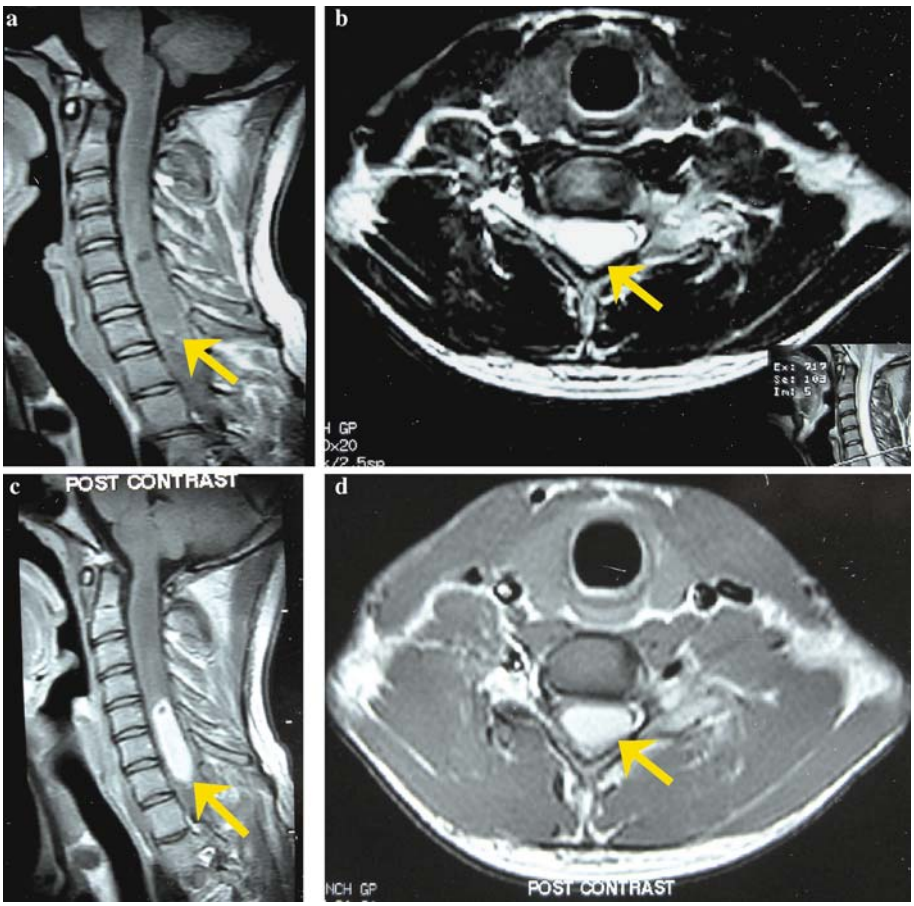

Figure 1. (a) T1 weighted sagittal MR image showing an isointense intramedullary ovoid mass (arrow) seen in the cervical region from C5 to C7 lower border. (b) The intramedullary mass (arrow) is hyperintense on T2-weighted axial MR image. (c) Post contrast sagittal MR image showing homogenous enhancement of the intramedullary mass (arrow). (d) Post contrast axial MR image showing homogeneous enhancement of the intramedullary mass (arrow).

and the non-neoplastic cord tissue. The operative impression was that of a glioma, possibly anaplastic glioma.

The histopathologic diagnosis of the specimen removed at first surgery at an outside hospital was ependymoma with an outside consultation diagnosis of oligodendroglioma. In our hospital, we received the slides and representative paraffin blocks of the first surgery for consultation and detailed evaluation. The specimen of the second surgery performed at our hospital was received in 10% buffered formalin, routinely processed and paraffin embedded. Five-micron sections were cut from blocks of both specimens for H&E staining and immunohistochemistry.

The tumor from first resection consisted of well differentiated round to oval cells with scant to moderate slightly vacuolated cytoplasm and round nuclei with slight chromatin condensation. No significant nuclear pleomorphism was seen. Fine neuropil type fibrillary matrix was prominent with occasional ill defined neuropil islands, however well formed rosettes were not conspicuous. Ganglion cell differentiation was not present. A fine reticular vascular network was present interspersed between tumor cells (Figure 2a–c). Focal mild vascular proliferation and a tiny focus of necrosis were seen (Figure 3a). Rare mitotic figures were present (Figure 3b). Immunohistochemistry revealed diffuse immunoreactivity for synaptophysin in the tumor cells and the neuropil like fibrillary matrix (Figure 4a and b). MIB1 labeling index was about 9% on the original resection specimen (Figure 4c). Focal positivity for GFAP was also seen (Figure 4d).

The histopathologic picture of the surgical specimen obtained at our hospital was identical, except that no necrosis was seen and the MIB1 labeling index on the recurrent tumor was 10%. The diagnosis of atypical neurocytoma was made independently on both specimens based on the histologic features and MIB1 labeling indices.

Discussion

Primary tumors resembling central neurocytomas (CN) have been reported at locations outside the ventricular system including the cerebral hemispheres, thalamus, cerebellum, pons [7–11] and spinal cord [12–18]. The clinicopathologic features of spinal neurocytomas (SN) are summarized in Table 1. In addition, three cases of SN are mentioned in the literature, however their details are not available [18]. The data is obviously very limited to draw any conclusions, however certain interesting observations come to light. Most intramedullary neurocytomas occurred in the cervical or cervico-thoracic

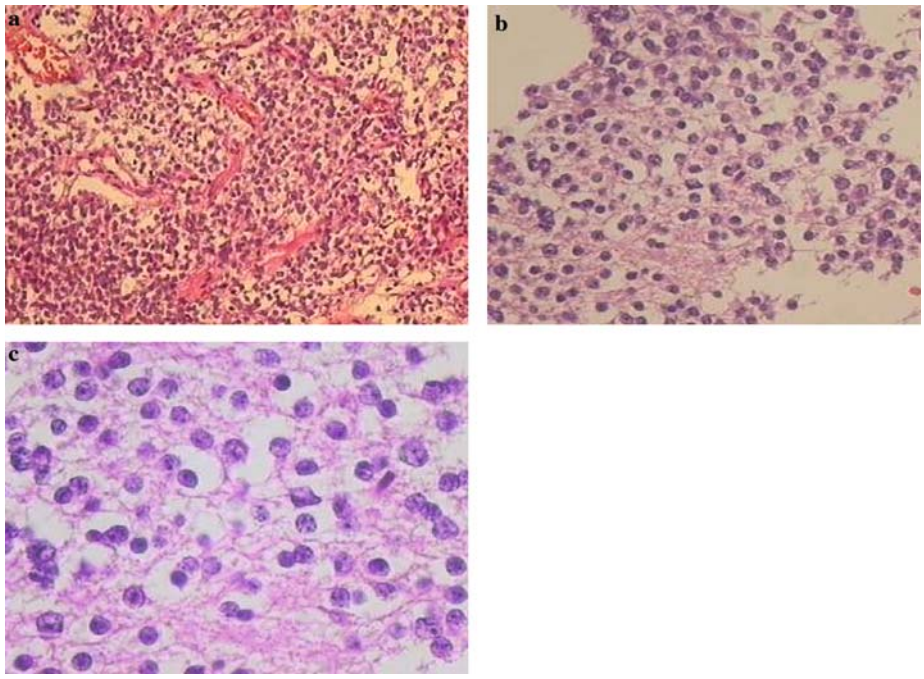

Figure 2. (a) Moderately cellular small round cell tumor with a thin walled capillary like vascular network (H&E×100). (b) Well-differentiated small round cell tumor with a fine fibrillary neuropil like stroma and scattered cells with perinuclear halo (H&E ×200). (c) Well differentiated small round cell tumor with cells showing regular nuclear outlines, fine uniformly dispersed chromatin, and a fine fibrillary neuropil like stroma (H&E ×400).

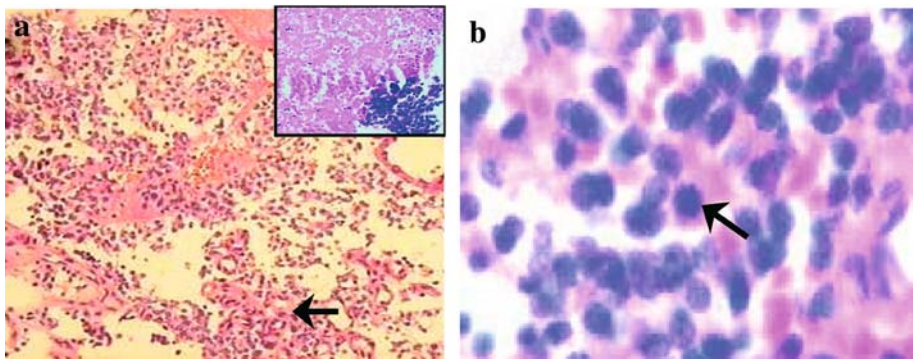

Figure 3. (a) Focus of micro-vascular hyperplasia (arrow) is seen (H&E ×200). Inset shows a tiny area of necrosis (H&E ×100). (b) Rare mitotic figures (arrow) are seen.

region, these patients had relatively short duration of symptoms and were operated upon within 1.5 years of their first symptom. While most reported cases of CN occur in adolescents or young adults, SN shows a wider age range (Table 1).

The most striking feature of the current case is the presence of histologic atypia, high MIB1 labeling index and tumor recurrence within 10 months. Histologic atypia in central neurocytomas (recognizably a bland tumor with excellent prognosis) is an uncommon event and not a predictor of survival. The histologic diagnosis of atypical neurocytoma is based upon the presence of atypical histologic features, such as focal necrosis, vascular proliferation, and increased mitotic activity, or MIB1 labeling index of more than 2%, and thus constitute about 25% of central neurocytomas [19–21]. Studies evaluating the proliferative potential of central neurocytomas have reported MIB1 labeling indices varying between 0.1 and 8% [2,22–24]. The MIB1 labeling index of 9% in the present case, the only reported case of SN with documented MIB1, is more than the reported range for CN. The presence of atypical histologic findings in those cases of SN that recurred (Table 1) is in contrast to CN in which despite the presence of histologic hallmarks of malignancy, a correlation with worsened clinical outcome has not been established [9,13,25]. MIB1 labeling index though not an independent predictor [22] correlates better with recurrence and survival in CN than histologic atypia alone [24,26]. On the contrary, the rare tendency of CN to recur or show CSF dissemination despite bland histology [23] was not seen in the reported cases of SN (Table 1). While most cases of SN had bland histology and low proliferative potential, two cases including the present case showed atypical features on histology and were associated with tumor recurrence. The case

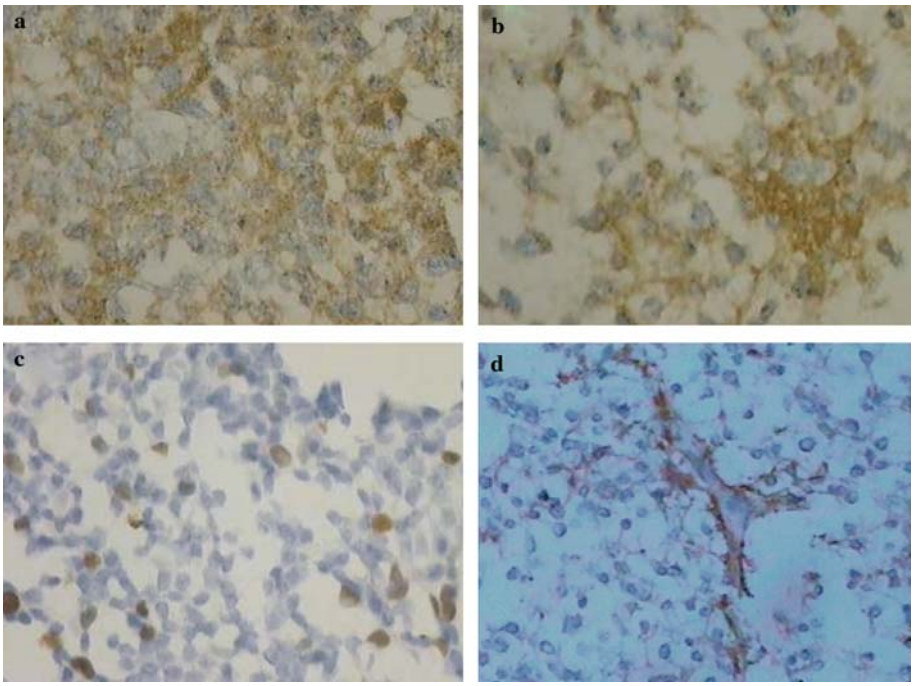

Figure 4. (a) Immunostain for synaptophysin shows positivity in the fine neuropil like fibrillary background within the tumor (×200). (b) Immunostain for synaptophysin highlights the neuropil like islands within the tumor (×400). (c) Immunostain for MIB1 stains a few scattered tumor nuclei (×400). (d) Focal immunoreactivity for GFAP is seen (×200).

Table 1. Spinal neurocytoma: clinicopathologic features of the reported cases

S.No.	Age/Sex	Site	Clinical features	Duration (months)	Histopath	Treatment	Follow up	Reference no.
1.	65/M	C2-6 IM	Arm weakness, sensory loss	18	Ty	Bx + XRT	120, NR	9,12
2.	67/M	T10-11 IM	Foot numbness	48	Ty	TR	30, NR	14
3.	49/M	C3-4 IM	Progressive myelopathy	72	Aty	STR + XRT	72, R, D	12,13
4.	12/M	C4-T1 IM	Myelopathy	2	Ty	TR	33, NR	15.
5.	46/F	T12-L1 EM ID	Leg weakness numbness	2	Ty	TR	12,NR	16
6.	50/M	T2-T5 IM	Myelopathy	3	Ty	STR	24, NR	17
7.	24/M	C5-T1 IM	Weakness and numbness	10	Aty	STR	18, R	Present case

Abbreviations: M – male, F – female, C – cervical, T – thoracic; IM – intramedullary; EM/ID – intradural extramedullary; Ty – typical; Aty – atypical; Bx – biopsy; TR – total resection; STR – subtotal resection; XRT – radiotherapy; NR – no recurrence; R – recurrence; D – died from recurrent tumor.

reported by Tatter et al. [13] contained a single mitosis and hemosiderin suggestive of old hemorrhage on histology. The patient had tumor resection twice and irradiated, and succumbed to tumor recurrence at the craniocervical junction associated with obstructive hydrocephalus after 6 years [12,13]. This patient's tumor recurrence after total resection and histology suggested possible clinicopathologic correlation. The present case similarly showed rare mitoses along with focal mild vascular proliferation, a tiny focus of necrosis and a high MIB1 labelling index, and was associated with tumor recurrence within a year of gross total resection.

Another issue of considerable importance is the histologic resemblance of neurocytomas to many other tumors. The differential diagnosis of SN, just like supratentorial CN, typically includes ependymoma and oligodendroglioma. Both these possibilities were raised by the pathologists at the outside hospitals in the current case. The striking features of neurocytomas are a neuropil type fine fibrillary matrix that is more delicate than the coarse glial fibrillary matrix of astrocytomas and ependymomas, best seen in the nuclei-free zones [12]. Perinuclear halos may be present just like oligodendrogliomas, however the vasculature is delicate and sometimes dilated [27] but without complex branching [12]. Rosettes are of Homer-Wright type; perivascular pseudorosettes and ependymal type true rosettes are not seen. The nuclei of neurocytoma cells are round unlike angulated nuclei of ependymomas, and the chromatin is more delicate than either ependymoma or oligodendroglioma cells [12]. An unusual feature in our case was

the focal GFAP positivity mostly at the periphery of the tumor, an observation described in the literature in CN, possibly reflecting their bipotential characteristic [19,28] but not in SN [12–18]. A rare case of spinal glioneural tumor with 'rosetted' neuropil islands has been described that showed well differentiated histology with MIB1 labeling index of less than 1%. Unlike reported cases of SN, the tissue in glioneural tumor with 'rosetted' neuropil islands showed clear astrocytic differentiation interspersed between the neuropil islands in a 'stroma' like distribution [29].

It has been suggested that similar to CN, that likely arise from the periventricular germinal matrix, SN also arise from neuronal precursor cells surrounding the region of central canal in fetal life [12]. Complete resection appears to be the key to management just like in CN [30]. Radiation therapy is perhaps best reserved for atypical, progressive and recurrent SN just as in CN [20,30]. Since long-term responses for chemotherapy used in some of the recurrent unresectable CN have not been reported [30], its role in SN remains unclear.

Thus based on the analysis of this case and the limited data available from the review of literature, we hypothesize that SN shows a bland histopathologic picture, immunoprofile and indolent biologic behavior very similar to the CN. The degree of atypia seen in this case and reported in the literature is within the spectrum of CN. However, the presence of histologic atypia and high MIB1 labeling index in SN appears to more closely correlate with tumor recurrence and a worse overall outcome, that may in part be because most SN are located in the critical region of cervical spinal cord. Therefore SN with atypia, though extremely rare, require a close clinical follow up. Despite these observations and apparent differences, it appears that radiation therapy is best reserved for atypical, progressive and recurrent SN just as in CN.

Acknowledgments

Authors wish to extend their sincere gratitude to Dr David Louis, MD at the department of pathology (neuropathology), Massacheutts General Hospital, Harvard Medical School for his consult opinion regarding this case.

Addendum

Patient presented 14 months after the second surgery with headache, vomiting, and weakness of all four limbs for two months. MRI showed leptomeningeal seeding and a contrast enhancing intraparenchymal cerebellar mass with obstructive hydrocephalus. A midline suboccipital craniotomy with gross total excision of a soft, vascular, cusa suckable, well defined tumor in the inferior vermis was performed with good post-operative recovery. Microscopic examination of the cerebellar tumor showed an atypical neurocytoma morphologically similar to the original spinal tumor.

Present case is unusual in being the first case of spinal neurocytoma showing CSF dissemination (in the rarely described retrograde caudo-cranial pattern), and showed histologic atypia in addition to high MIB1 LI, unlike previously reported CSF disseminated central neurocytomas.

References

1. Hassoun J, Gambarelli D, Grisoli F, Pellet W, Salamon G, Pellissier JF, Toga M: Central neurocytoma: an electron microscopic study of two cases. Acta Neuropathol 56: 151–156, 1982
2. Hassoun J, Soylemezoglu F, Gambarelli D, Figarella-Branger D, von Ammon K, Kleihues P: Central neurocytoma: a synopsis of clinical and histologic features. Brain Pathol 3: 297–306, 1993
3. Kleihues P, Cavanee WK: World Health Organization Classification of Tumors of the Nervous System. WHO/IARC, Lyon, France, 2000
4. Kleihues P, Louis DN, Scheithauer BW, Rorke LB, Reifenberger G, Burger PC, Cavanee WK: The WHO classification of tumors of the nervous system. J Neuropathol Exp Neurol 61: 215–225, 2004
5. Tong CYK, Ng H-K, Pang JCS, Hu J, Hui ABY, Poon W-S: Central neurocytomas are genetically distinct from oligodendrogliomas and neuroblastomas. Histopathology 37: 160–165, 2000
6. Jay V, Edwards V, Hoving E, Rutka J, Becker L, Zielenska M, Teshima I: Central neurocytoma: morphological, flow cytometric, polymerase chain reaction, fluorescence in situ hybridization and karyotopic analyses. J Neurosurg 90: 348–354, 1999
7. Giangaspero F, Cenacchi G, Losi L, Cerasoli S, Bisceglia M, Burger PC: Extraventricular neoplasms with neurocytoma features. A clinicopathological study of 11 cases. Am J Surg Pathol 21: 206–212, 1997
8. Enam SA, Rosenblum ML, Ho K-L: Neurocytoma in the cerebellum: case report. J Neurosurg 87: 100–102, 1997
9. Louis DN, Swearingen B, Linggood RM, Dickersin GR, Kretschmar C, Bhan AK, Headley-White ET: Central neurocytoma and neuroblastoma in adults – report of eight cases. J Neurooncol 9: 231–238, 1990
10. Soontornniyomkij V, Schelper RL: Pontine neurocytoma. J Clin Pathol 49: 764–765, 1996
11. Rabinowicz AL, Abrey LE, Hinton DR, Couldwell WT: Cerebral neurocytoma: an unusual cause of refractory epilepsy. Case report and review of the literature. Epilepsia 36: 1237–1240, 1995
12. Tatter SB, Borges LF, Louis DN: Central neurocytomas of the cervical spinal cord: report of two cases. J Neurosurg 81: 288–293, 1994
13. Tatter SB, Borges LF, Louis DN: Correction: central neurocytomas of the cervical spinal cord. J Neurosurg 82: 706, 1994
14. Coca S, Moreno M, Martos JA, Rodriguez J, Barcena A, Vaquero J: Neurocytoma of spinal cord. Acta Neuropathol 87: 537–540, 1994
15. Stapleton SR, David KM, Harkness WFJ, Harding BN: Central neurocytoma of the cervical spinal cord. J Neurol Neurosurg Psychiatr 63: 119, 1997
16. Stephan CL, Kepes JJ, Arnold P, Green KD, Chamberlin F: Neurocytoma of the cauda equina: case report. J Neurosurg 90: 247–251, 1999
17. Martin AJ, Sharr MM, Teddy PJ, Gardner BP, Robinson SFD: Neurocytoma of the thoracic spinal cord: case report. Acta Neurochir 144: 823–828, 2002
18. Miller DC, Kim R, Zagzag D: Neurocytomas: non-classical sites and mixed elements. J Neuropathol Exp Neurol 51: 364, 1992
19. Soylemezoglu F, Scheithauer BW, Esteve J, Kleihues P: Atypical central neurocytoma. J Neuropathol Exp Neurol 56: 551–556, 1997
20. Rades D, Fehlauer F, Schild SE: Treatment of atypical neurocytomas. Cancer 100: 814–817, 2004

21. Brat DJ, Scheithauer BW, Eberhart CG, Burger PC: Extraventricular neurocytomas: pathologic features and clinical outcome. Am J Surg Pathol 25: 1252–1260, 2001
22. Sharma MC, Rathore A, Karak AK, Sarkar C: A study of proliferative markers in central neurocytoma. Pathology 30: 355–359, 1998
23. Takao H, Nakagawa K, Ohtomo K: Central neurocytoma with craniospinal dissemination. J Neurooncol 61(3): 255–259, 2003
24. Mackenzie IR: Central neurocytoma: histologic atypia, proliferation potential and clinical outcome. Cancer 85: 1606–1610, 1999
25. Yasargil MG, von Ammon K, von Deimling A, et al.: Central neurocytoma: histopathological variants and therapeutic approaches. J Neurosurg 76: 32–37, 1992
26. Rades D, Schild SE, Fehlauer F: Prognostic value of the MIB-1 labeling index for central neurocytomas. Neurology 62: 987–989, 2004
27. Sharma MC, Sarkar C, Karak AK, Gaikwad S, Mahapatra AK, Mehta VS: Intraventricular neurocytoma: a clinicopathological study of 20 cases with review of the literature. J Clin Neurosci 6: 319–323, 1999
28. Tsuchida T, Matsumoto M, Shirayama Y, Imahori T, Kasai H, Kawamoto K: Neuronal and glial characteristics of central neurocytoma: electron microscopical analysis of two cases. Acta Neuropathol 91: 573–577, 1996
29. Harris BT, Horoupian DS. Spinal cord glioneuronal tumor with 'rosetted' neuropil islands and meningeal dissemination: a case report. Acta Neuropathol 100: 575–579, 2000
30. Schmidt MH, Gottfried ON, von Koch CS, Chang SM, McDermott MW: Central neurocytoma: a review. J Neurooncol 66: 377–384, 2004

Address for offprints: Dr Mehar C. Sharma, Department of Pathology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India; Tel.: 91-11-26593371; Fax: 91-11-26588663; E-mail: meharsharma@hotmail.com