Brain Tumor Pathol (2015) 32:49–55
DOI 10.1007/s10014-014-0187-z

CASE REPORT

Primary diffuse leptomeningeal glioneuronal tumors

Hwa Jin Cho · Jae Kyung Myung · Hannah Kim · Chul-Kee Park · Sung-Ki Kim · Chun Kee Chung · Seung-Hong Choi · Sung-Hye Park

Received: 29 January 2014 / Accepted: 6 April 2014 / Published online: 26 April 2014

Abstract Diffuse leptomeningeal disseminated glioneuronal tumor (DL-GNT) is a rare brain tumor that presents as a plaque-like subarachnoid tumor, commonly involving the basal cisterns and interhemispheric fissure of children but lacking intraparenchymal tumor. Histologically, the tumors are composed of sheets of monotonous rounded cells. Here, we report three cases of DL-GNTs, focusing on clinicopathologic features. Two patients were adult male, but one patient was child. The patients presented with seizures ($n = 1$) or headaches ($n = 2$). In all patients, radiography revealed characteristic leptomeningeal thickening and enhancement with minor superficial parenchymal lesions. All three cases were diffusely positive for both GFAP and synaptophysin, and scattered positive for OLIG2 and NeuN, but negative for IDH-1 (H09). Electron microscopic examination showed astrocytic and neuronal differentiation. The patient with the anaplastic tumor died due to aggressive progression of the tumor, but the remaining two patients were stable without tumor recurrence for 23 and 37 months. Thus, these findings suggest that DL-GNT can occur in both children and adult and both supra- and infra-tentorial leptomeninges. It has unique radiological and histopathological features and biological behavior. Further clinicopathological data with molecular genetic study are required for establishing DL-GNT as a unique entity.

Keywords Brain tumor · Glioneuronal tumor · Leptomeninges · Brainstem · Electron microscope

H. J. Cho · J. K. Myung · H. Kim · S.-H. Park (✉)
Department of Pathology, Seoul National University Hospital, College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 110-744, Republic of Korea
e-mail: shparknp@snu.ac.kr

C.-K. Park · C. K. Chung
Department of Neurosurgery, Seoul National University Hospital, College of Medicine, Seoul, Korea

S.-K. Kim
Division of Pediatric Neurosurgery, Seoul National University Hospital, College of Medicine, Seoul, Korea

S.-H. Choi
Division of Neuroradiology, Seoul National University Hospital, College of Medicine, Seoul, Korea

S.-H. Park
Neuroscience Institute and Department of Pathology, Seoul National University, College of Medicine, Seoul, Korea

Introduction

Diffuse leptomeningeal glioneuronal tumors (DL-GNT) were described in a case report by Yamamoto et al. [24] in 1996, following which Psarros et al. [20] reported a case of neurocytoma-like neoplasm of the thoracic spine with diffuse leptomeningeal dissemination. A few years later, Gardiman et al. [7] described these DL-GNTs in greater detail.

In addition to glioneuronal histology, diffuse leptomeningeal oligodendrogliomas or oligodendrogliosis have also been reported [4, 15, 17, 21]. Considering that these studies were published in the era before the concept of glioneuronal tumor emerged and that there is no specific immunomarker for oligodendroglial tumors yet, the tumors in these cases might have actually been neurocytoma-like leptomeningeal GNT [4, 15]. The tumors in the above-mentioned cases were characterized by diffuse leptomeningeal dissemination, neurocytoma-like, bland-looking histology, and aggressive clinical behavior. Gardiman et al. [8] reported 3 cases of DL-GNT with the following 5 distinct characteristics: (1) characteristic involvement of

Table 1 Summary of clinical features

	Case 1	Case 2	Case 3
Age/sex	62/M	22/M	11/M
Initial symptoms	Headache (for 1 month)	Seizures	Headache/vomiting
Prior history	None	Seizures (1 year)	Headache/vomiting (1 year)
Site	Cerebellum, diffuse LM seeding	Temporal lobe, right	Suprasellar to whole brainstem, diffuse LM seeding
Therapy	STR, CSF drainage, CCRT with TMZ	GTR	VP shunt, CT
Outcome	Died 1 month after operation	AWSD for 37 months	AWPD with tomotherapy for 23 months

URI upper respiratory infection, *LM seeding* leptomeningeal seeding, *STR* subtotal resection, *GTR* gross total resection, *CSF* cerebro-spinal fluid, *CCRT* chemoradiation therapy, *CT* chemotherapy, *TMZ* temozolomide, *AWSD* alive with stable disease, *AWPD* alive with progressive disease, *VP shunt* ventriculo-peritoneal shunt

the basal cisterns and interhemispheric fissure; (2) thickened and enhanced leptomeninges (subarachnoid space); (3) wide leptomeningeal dissemination of the tumor, without a well-defined intraparenchymal mass; (4) bland-looking neurocytoma-like monotonous round tumor cells; and (5) glioneuronal differentiation. These characteristics and additional clinicopathological data of DL-GNT appear to be unique and it should be regarded as a novel entity. Here, we have reported three more cases of DL-GNTs, which showed typical clinicopathological features. The Institutional Review Board of Seoul National University Hospital (H-1305-040-485) approved this research. The IRB board waived informed consents.

Case summary

Clinical and radiological findings

All the cases of our DL-GNTs reported below involved male patients and their mean age was 32 years

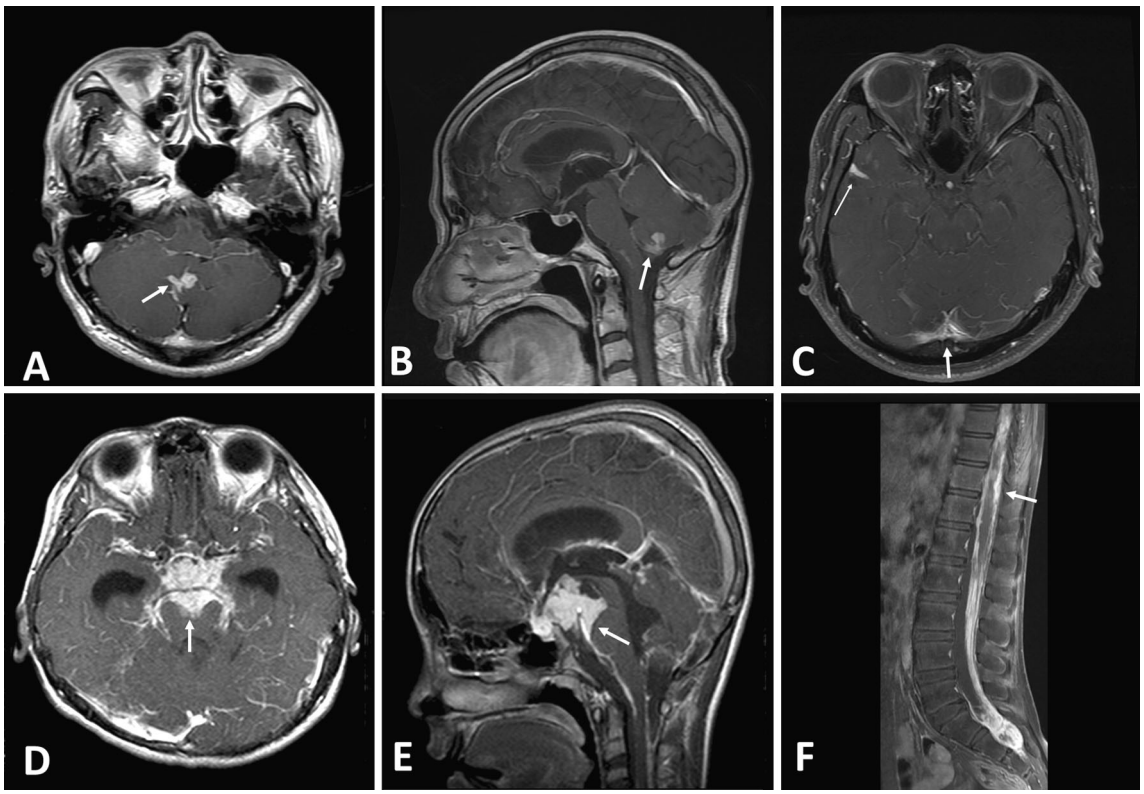

Fig. 1 **a**, **b** Contrast-enhanced T1WIs (case #1) revealed leptomeningeal enhancement at the surface of the brain stem, and nodular enhancement at the inferior cerebellar vermis, which suggested leptomeningeal seeding. **c** Contrast-enhanced T1WI (case #2) showed thick leptomeningeal enhancement at the right temporal lobe, which suggested leptomeningeal involvement. **d**, **e** Contrast-enhanced T1WI (case #3) showed thick leptomeningeal enhancement at the suprasellar and prepontine area, which suggested leptomeningeal involvement. **f** A sagittal contrast-enhanced T1WI (case #3) showed the diffuse thick enhancement along the spinal cord and cauda equina, which suggests the diffuse leptomeningeal involvement

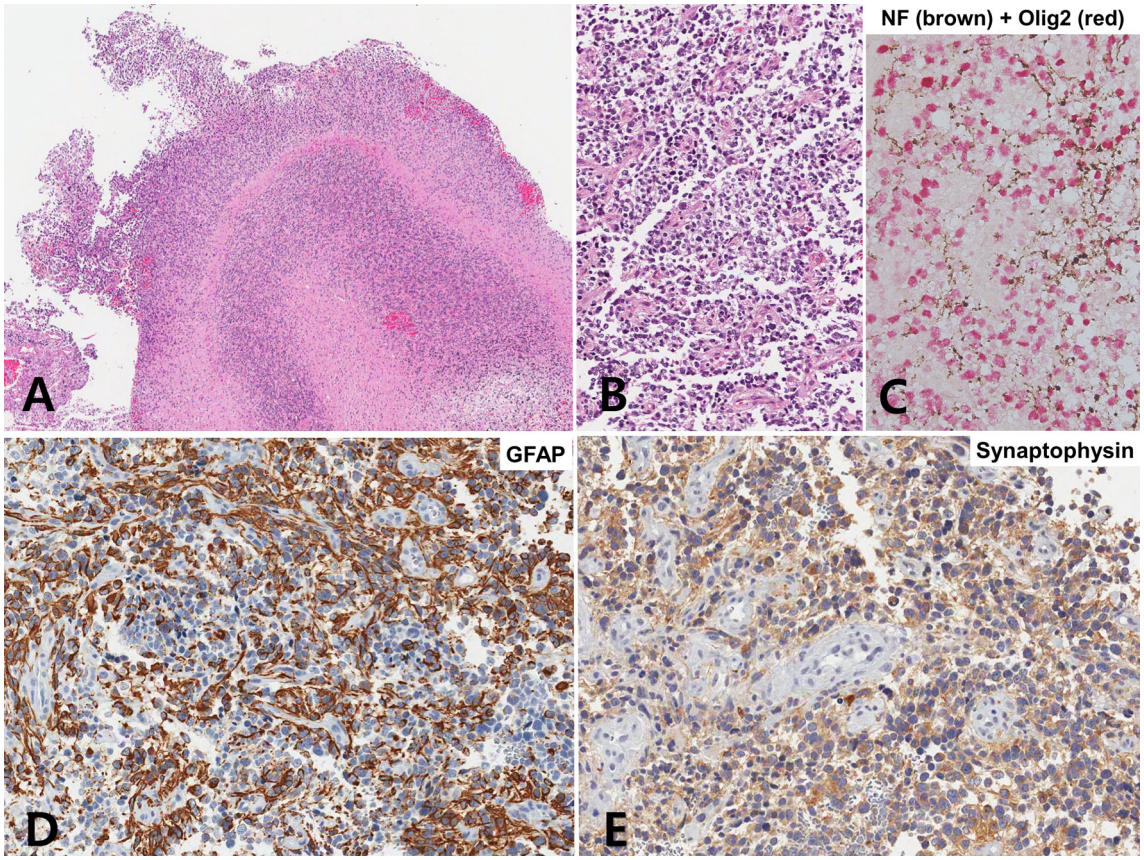

Fig. 2 **a** H&E section in case #1 mainly revealed the leptomeningeal tumor with superficial involvement of the cerebellar molecular layer. **b** High-power view shows sheets of monotonous rounded tumor cells with rounded nuclei and clear cytoplasm. **c**, **d** Double immunostaining of neurofilaments (*brown*) and olig2 (*red*) revealed positivity in the cytoplasmic processes and tumor cell nuclei, respectively, suggesting glioneuronal differentiation. **d**, **e** Tumor cells are robustly positive for GFAP and synaptophysin. (**a** H&E ×20, **b** H&E ×200, **c** GFAP ×400, **c** NF and Olig2 double immunostaining ×400, **d** GFAP ×400, **e** Synaptophysin ×400) (color figure online)

(11–66 years), who were treated in SNU hospital. The patients presented with seizures ($n = 1$) or headaches ($n = 2$) (Table 1). Radiology showed leptomeningeal thickening with enhancement and minor superficial parenchymal lesion on the contrast-enhanced T1-weighted image (T1WI) in all cases (Fig. 1). The tumor in each case located in the cerebellum (case #1), temporal lobe (case #2), and a wide area of the brainstem (from the brainstem to the suprasellar area), spinal cord and cauda equina (case #3). Neurosurgeons carried out subtotal resection (case #1), gross total resection (case #2), or biopsy of tumors and ventriculo-peritoneal shunt (case #3) (Table 1).

Pathological findings

Microscopically, all tumors grew along the leptomeninges. The cases #2 and #3 showed low-grade features but case #1 was high-grade tumor. The high-grade one (case #1) revealed a pseudo-papillary pattern of atypical glial cells with high mitotic rate and necrosis (Fig. 2), while two cases of low-grade ones were composed of bland-looking monotonous round shaped cells with clear cytoplasm (Fig. 3). In low-grade ones, mitotic rate was nearly absent and MIB-1 indices were low (1.3 and 3.9 %), but it was high (38.4 %) in case #1. All three patients were diffusely positive for synaptophysin and scatter positive for OLIG2 and NeuN, but all were negative for IDH-1 (H09) (Fig. 2; Table 2). GFAP was diffusely or partly positive in the tumor cells. Nestin was focal positive in all cases. On electron microscopic examination, all cases showed predominantly neuronal differentiation with synapses and synaptic vesicles, along with astrocytic differentiation with glial filaments. Ultrastructure of case #2 revealed numerous perikaryal and synaptic electron-dense core neurosecretory granules (Fig. 4).

Follow-up

The patient with the anaplastic tumor (case #1) died due to aggressive progression of the tumor despite of one cycle of

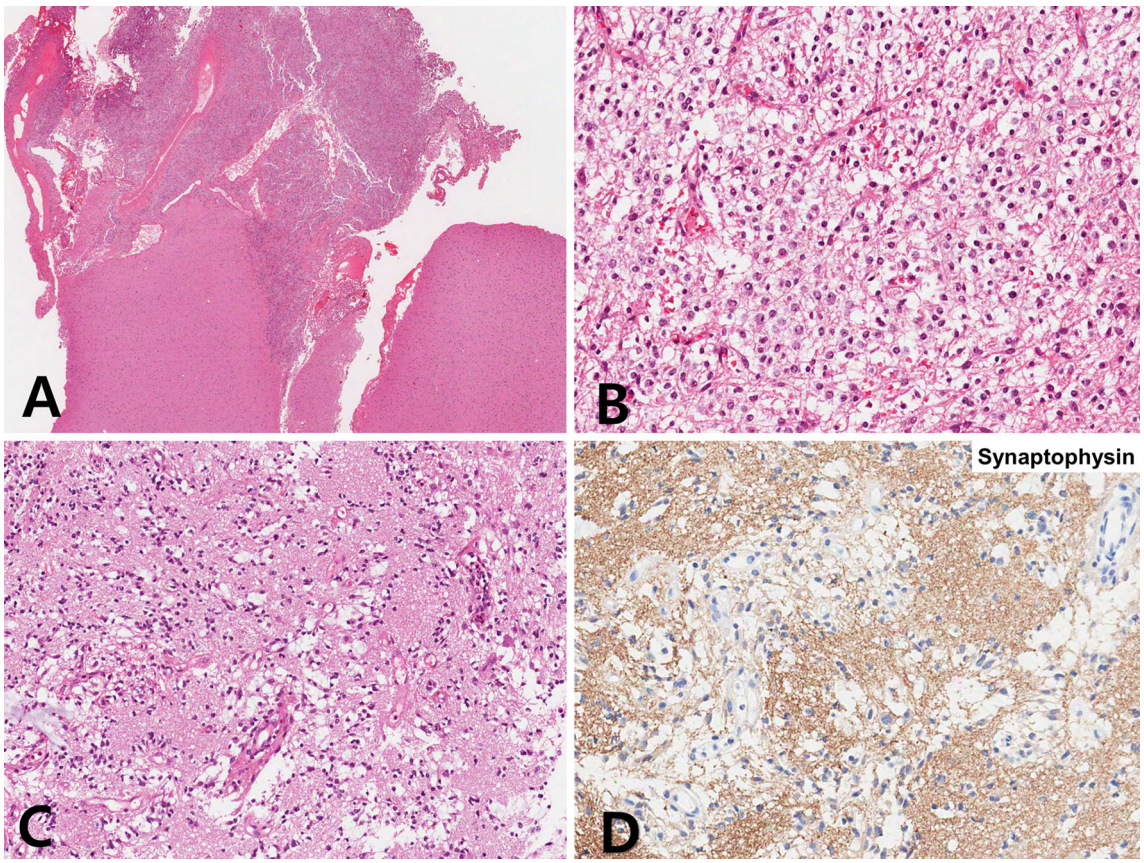

Fig. 3 **a**, **b** Leptomeningeal tumor composed of monotonous neurocyte-like tumor cells was also observed in case #2. **c**, **d** Case #3 showed perivascular accentuated distribution of monotonous neurocyte-like cells with neuropil background. Synaptophysin was diffusely positive in the background of tumor cells that are exclusively located in the leptomeningeal area (**a** H&E ×10, **b** H&E ×400, **c** H&E ×200, **d** synaptophysin ×250)

Table 2 Primary antibodies and results of immunohistochemical stains

Antibody	Company	Retrieval method	Dilution	Case 1	Case 2	Case 3
Synaptophysin	Invitrogen, Camarillo, USA	Microwave	1:200	+	+	+
Neurofilaments	DAKO, Glostrup, Denmark	EDTA microwave	1:2000	fP	fP	fP
NeuN	Millipore, Temecula, USA	EDTA	1:500	fP	−	fP
GFAP	DAKO, Glostrup, Denmark	EDTA microwave	1:300	+	+	+
Nestin	Millipore, Temecula, USA	EDTA microwave	1:200	fP	fP	fP
OLIG2	SantaCruz, CA, USA	9.0 high pH	1:500	fP	fP	fP
IDH-1 R132H	Dianova, Hamburg, Germany	Microwave	1:50	−	−	−
Ki-67	DAKO, Glostrup, Denmark	EDTA microwave	1:1000	38.4 %	1.3 %	3.9 %

GFAP glial fibrillary acidic protein, *NeuN* neuronal nuclear antigen, *EMA* epithelial membrane antigen, *OLIG2* oligodendrocyte lineage transcription factor 2 antibody, *IDH-1* isocitrate dehydrogenase 1, *fP* focal positive

chemoradiation therapy (Table 1). Case #3 had a persistent residual tumor because he underwent biopsy only and he was hopelessly discharged with respirator. The remaining alive patient (case #2) did not have tumor recurrence for 37-month follow-up period.

Discussion

Davila et al. [5] have reported 3 clinical settings for leptomeningeal gliomatosis, which are: concurrent extensive meningeal dissemination with recurrence of intracerebral

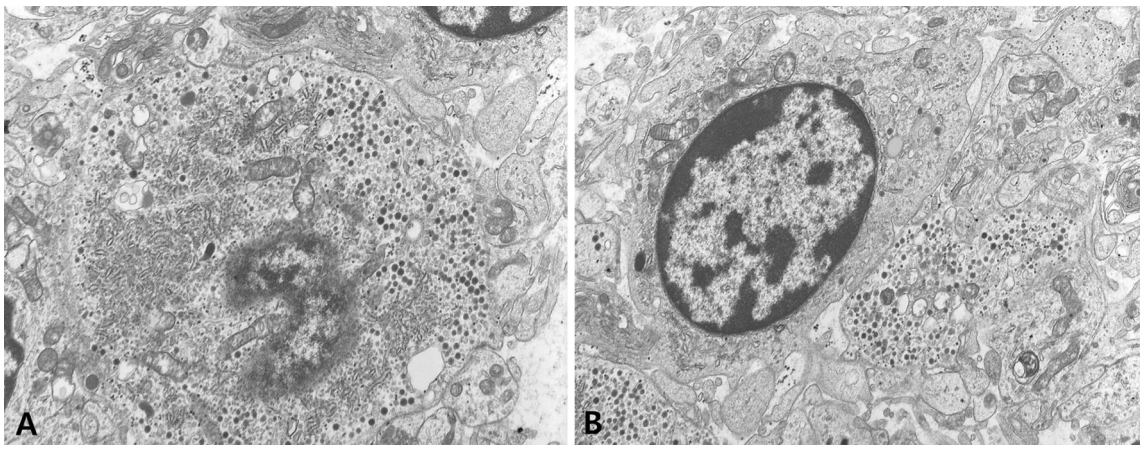

Fig. 4 **a** Ultrastructurally, the tumor cells of case #2 have oval to round nuclei and scanty to moderate amount of perikaryal cytoplasm, which contains numerous electron-dense core neurosecretory granules, abundant RER cisternae and mitochondria. **b** Surrounding the tumor cells, there are rich neuropils. Some of neuropils have many neurosecretory granules (uranyl acetate and lead citrate, **a** ×8,000, **b** ×7,000)

gliomas (20–25 % of gliomas), fatal meningeal dissemination without recurrence of primary gliomas (3 %), and primary leptomeningeal gliomatosis (very rare). The primary leptomeningeal glioma/gliomatosis are well-known entities and histopathologically can be similar to astrocytic, oligodendroglial, or neuronal/glioneuronal tumors (Table 3) [1–3, 5, 6, 9–14, 16, 18, 19, 23]. They predominantly occur in children (mean age 18.45 years; range 3–49 years) (Table 3). Further, 73 % of the patients in the above-mentioned cases were aged less than 20 years, and there was a slight male dominance (M:F, 6:5). They often involve a wide area of the cerebrum or the cerebellum; however, most cases were of low-grade glioneuronal tumors, which had been variously diagnosed as oligodendroglioma, astrocytoma, or glioblastoma (Table 3). The prognosis was poor (average survival, 22 months), and 73 % (8/11) of the patients died. Of note, 63 % (5/8) of the patients died within 9 months after diagnosis. By definition, primary DL-GNT should have diffuse leptomeningeal tumor without significant parenchymal involvement and/or previous parenchymal tumor. However, some cases involved superficial parenchyma or Virchow–Robin spaces [5, 8, 12]. DL-GNT might be a novel brain tumor because it has 5 clinicopathological characteristics: (1) involvement of a wide area of the leptomeninges, particularly the basal cisterns and interhemispheric fissure; (2) bland-looking oligodendroglioma or neurocytoma-like monotonous histology; (3) immunohistochemical glioneuronal differentiation; (4) common occurrence in children; and (5) aggressive behavior (Table 3). Thickened and enhanced meninges on MRI are also characteristic findings.

Yamamoto et al. [24] described a case of multifocal neurocytoma/gangliocytoma with extensive leptomeningeal dissemination in 1996, and Gardiman et al. [8] reported four cases of diffuse leptomeningeal GNTs in children including one case of anaplastic one. The findings of those cases were consistent with our findings, especially the neurocytic histology. Among our cases, the case #3 was the most typical case, which involved the wide basal brain surface of the cerebrum, cerebellum, and spinal cord of the patient.

In our series, two cases revealed bland-looking histology, but one case showed a high-grade feature (case #1). It had a high mitotic rate (20/10HPF) and a high MIB-1 labeling index (38.4 %), suggesting malignant GNT. The differential diagnosis of this case included anaplastic clear cell ependymoma and anaplastic papillary glioneuronal tumor. We were able to rule out the possibility of an ependymoma, because immunohistochemically, this tumor did not show dot-like positivity for EMA and/or CD99. Moreover, electron microscopic examination did not reveal any ependymal features. To our knowledge, only leptomeningeal involvement has not been reported in any ependymoma. In addition, PGNT do not typically show primarily leptomeningeal development and/or leptomeningeal dissemination. Our case of high-grade DL-GNT (case #1) was similar to the Gardiman et al.'s high-grade DL-GNT. The existence of high-grade DL-GNT had been pointed out by Rossi et al. [22].

In contrast to low-grade histopathological features of usual DL-GNTs, they often showed aggressive biology like our case #3. Our case #3 showed wide leptomeningeal involvement of suprasella to brainstem and spinal cord, which could not be surgically removed entirely. The patient showed respiratory difficulty and was discharged to the nursing home with ventilator in a poor recovery state, 1 month after operation.

Table 3 The summary of previously reported diffuse leptomeningeal gliomatosis and DL-GNTs

References	Age	Sex	Symptoms	Involvement	Histological diagnosis	Immunohistochemistry	Treatment	Follow-up
[15]	16	M	Petit mal epilepsy	Temporal subarachnoid	Oligodendroglioma			DOD, 9 months survival
[13]	15	F	Headache	Entire cerebrum and cerebellum, maximum thickness: 1.0 cm	L/G astrocytoma	GFAP (+)	ACNU	DOD, 3.5 years survival
[5]	38	M	Multiple cranial nerve palsy	Cerebrum, cerebellum and spinal cord, involvement of Virchow–Robin spaces	L/G astrocytoma	GFAP (+)	Methotrexate, RT	DOD, 3 months survival
[4]	17	F	Headache, hydrocephalus	Suprasellar cistern and spinal cord	Oligodendroglioma	GFAP (−), vimentin (−), SNP (−), NF (−)		DOD, 2 years survival
[9]	49	F	Generalized epilepsy, hydrocephalus	Diffuse cerebrum and spinal cord	Glioblastoma	GFAP (+) MIB-1: 10.78 %	Methotrexate	DOD, 2 months survival
[24]	17	M	Sudden fever and gait disturbance	Cerebrum, cerebellum and spinal cord	Neurocytoma/gangliocytoma	GFAP (−)	CCRT	DOD, 21 month survival
[12]	28	M	Intracranial hypertension	Cerebellum, pons, and spinal cord	Primary diffuse leptomeningeal gliomatosis, WHO grade III	GFAP (+), SNP (−)		DOD, 5 months
[8]	4	M	Dizziness, hydrocephalus	Cerebrum, brainstem, and spinal cord	DL-GNT	GFAP: patchy (+), MIB-1: <1 %	Temozolomide (6 mo), VP-shunt	AWSD, 2 years
	3	F	Headache, hydrocephalus	Cerebellum, basal temporal and frontal lobes, brainstem and spinal cord	DL-GNT	GFAP: patchy (+), MIB-1: <1 %	VP-shunt	DOD, 6 years survival
	3	F	Walking difficulty, hydrocephalus	Cerebellum, basal frontal and temporal lobes, brainstem and spinal cord	DL-GNT	GFAP: patchy (+), MIB-1: >5 % 1 %	CCRT	AWSD, 6 years survival
	13	M	Confusion, hydrocephalus	Cerebellum, diffuse cerebral and spinal cord	Leptomeningeal glioneuronal tumor	GFAP: patchy (+), MIB-1: <1 %	None	AWSD, 1.5 years survival

CCRT combined chemotherapy and radiotherapy, *DL-GNT* diffuse leptomeningeal glioneuronal tumor, *DOD* death of disease, *AWSD* alive with stable disease

The main differential diagnosis of the DL-GNTs is primary DL-glioma/gliomatosis, which also can be either high- or low-grade glioma [1, 13, 18, 19]. They should be differentiated histomorphologically and/or immunohistochemically and ultrastructurally. DL-GNT should be positive for both neuronal and glial markers, while DL-glioma/gliomatosis is negative for neuronal markers.

Conclusion

Here, we have reported three cases of DL-GNTs, which showed particular clinicopathological and radiological features, specifically, plaque-like dural thickening by the tumor involvement, with minor parenchymal involvement, as well as a neurocytoma-like bland-looking histology with immunohistochemical glioneuronal differentiation. Even though they are histologically benign, they can show aggressive behavior due to tendency of involvement of wide area of leptomeninges and common development around the brainstem, resulting in difficulty in surgical intervention. Further clinicopathological data with molecular genetic study are required for establishing DL-GNT as a unique entity.

Acknowledgments This study was supported by a grant (A112005) of the Korean Health Technology R&D Project, Ministry of Health and Welfare, Republic of Korea and National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2010-0028631).

Conflict of interest There is no conflict of interest to declare.

References

1. Baborie A, Dunn EM, Bridges LR et al (2001) Primary diffuse leptomeningeal gliomatosis predominantly affecting the spinal cord: case report and review of the literature. J Neurol Neurosurg Psychiatry 70:256–258
2. Blumenkopf B, Gutierrez J, Bennett W (1986) Primary leptomeningeal gliomatosis and "numb, clumsy hands": a case report. Neurosurgery 18:363–366
3. Bohner G, Masuhr F, Distl R et al (2005) Pilocytic astrocytoma presenting as primary diffuse leptomeningeal gliomatosis: report of a unique case and review of the literature. Acta Neuropathol 110:306–311
4. Chen R, Macdonald DR, Ramsay DA (1995) Primary diffuse leptomeningeal oligodendroglioma. Case report. J Neurosurg 83:724–728
5. Davila G, Duyckaerts C, Lazareth JP et al (1993) Diffuse primary leptomeningeal gliomatosis. J Neurooncol 15:45–49
6. Debono B, Derrey S, Rabehenoina C et al (2006) Primary diffuse multinodular leptomeningeal gliomatosis: case report and review of the literature. Surg Neurol 65:273–282 discussion 282
7. Gardiman MP, Fassan M, Nozza P et al (2012) Diffuse leptomeningeal glioneuronal tumours: clinico-pathological follow-up. Pathologica 104:428–431
8. Gardiman MP, Fassan M, Orvieto E et al (2010) Diffuse leptomeningeal glioneuronal tumors: a new entity? Brain Pathol 20:361–366
9. Giordana MT, Bradac GB, Pagni CA et al (1995) Primary diffuse leptomeningeal gliomatosis with anaplastic features. Acta Neurochir (Wien) 132:154–159
10. Havlik DM, Becher MW, Nolte KB (2001) Sudden death due to primary diffuse leptomeningeal gliomatosis. J Forensic Sci 46:392–395
11. Ho KL, Hoschner JA, Wolfe DE (1981) Primary leptomeningeal gliomatosis: symptoms suggestive of meningitis. Arch Neurol 38:662–666
12. Kastenbauer S, Danek A, Klein W et al (2000) Primary diffuse leptomeningeal gliomatosis: unusual MRI with non-enhancing nodular lesions on the cerebellar surface and spinal leptomeningeal enhancement. J Neurol Neurosurg Psychiatry 69:385–388
13. Kitahara M, Katakura R, Wada T et al (1985) Diffuse form of primary leptomeningeal gliomatosis. Case report. J Neurosurg 63:283–287
14. Ko MW, Turkeltaub PE, Lee EB et al (2009) Primary diffuse leptomeningeal gliomatosis mimicking a chronic inflammatory meningitis. J Neurol Sci 278:127–131
15. Korein J, Feigin I, Shapiro MF (1957) Oligodendrogliomatosis with intracranial hypertension. Neurology 7:589–594
16. Nakagawa K, Sasaki S, Hatakeyama T et al (1990) A clinicopathological study of the spinal leptomeningeal dissemination from cerebral malignant gliomas without a recurrence of the primary lesions. Gan No Rinsho 36:57–65
17. Ozkul A, Meteoglu I, Tataroglu C et al (2007) Primary diffuse leptomeningeal oligodendrogliomatosis causing sudden death. J Neurooncol 81:75–79
18. Park JS, Van Den Noort S, Kim RC et al (1996) Primary diffuse leptomeningeal gliomatosis with signs of increased intracranial pressure and progressive meningeal enhancement on MRI. J Neuroimaging 6:250–254
19. Pingi A, Trasimeni G, Di Biasi C et al (1995) Diffuse leptomeningeal gliomatosis with osteoblastic metastases and no evidence of intraaxial lesions. AJNR Am J Neuroradiol 16:1018–1020
20. Psarros TG, Swift D, Mulne AF et al (2005) Neurocytoma-like neoplasm of the thoracic spine in a 15-month-old child presenting with diffuse leptomeningeal dissemination and communicating hydrocephalus. Case report. J Neurosurg 103:184–190
21. Rodriguez FJ, Perry A, Rosenblum MK et al (2012) Disseminated oligodendroglial-like leptomeningeal tumor of childhood: a distinctive clinicopathologic entity. Acta Neuropathol 124:627–641
22. Rossi S, Rodriguez F, Dei Tos A et al (2009) Re: Diffuse leptomeningeal glioneuronal tumors: a new entity? Brain Pathol 19:745 author reply 746
23. Singh M, Corboy JR, Stears JC et al (1998) Diffuse leptomeningeal gliomatosis associated with multifocal CNS infarcts. Surg Neurol 50:356–362 discussion 362
24. Yamamoto T, Komori T, Shibata N et al (1996) Multifocal neurocytoma/gangliocytoma with extensive leptomeningeal dissemination in the brain and spinal cord. Am J Surg Pathol 20:363–370