Neuroendocrinology Letters Volume 40 No. 4 2019
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

Diffuse Leptomeningeal Glioneuronal Tumor Presented with Language Developmental Delay

Qian Lu[2], Li-Ping Zou[1,2], Qiu-Ping Gui[3], Xiu-Yu Shi[1], Xuan Zhai[4], Guang Yang[1], Jian Chen[1], Yang-Yang Wang[1]

1 Department of Pediatrics, the First Medical Center of PLA General Hospital, Beijing 100853, China.
2 Center for Brain Disorders Research,Capital Medical University, Beijing Institute for Brain Disorders, Beijing 100069, China.
3 Department of Pathology, the First Medical Center of PLA General Hospital, Beijing 100853, China.
4 Children's hospital of Chongqing Medical University, Chongqing 400012, China.

Correspondence to: Li-Ping Zou
Department of Pediatrics, the First Medical Center of PLA General Hospital, Beijing China,100853.
Center for Brain Disorders Research, Capital Medical University, Beijing Institute for Brain Disorders, Beijing China, 100069
TEL.: +86-010-55499016; FAX: +86-10-66939770; E-MAIL: zouliping21@sina.com

Submitted: 2019-03-29 Accepted: 2019-07-30 Published online: 2019-08-28

Key words: **diffuse leptomeningeal glioneuronal tumor; development delay; imagingpathology; magnetic resonance imaging**

Neuroendocrinol Lett 2019; **40**(4):161–165 **PMID:** 32087090 NEL400419A01 • **www.nel.edu**

Abstract

Diffuse leptomeningeal glioneuronal tumor (DLGNT) is a new central nervous system tumor defined by the WHO in 2016 characterized mainly by hydrocephalus, headache, and epilepsy. We reported the case of a patient diagnosed with DLGNT who presented with language developmental delay and positive but subtle changes in imaging two years before the emergence of typical clinical symptoms. Few studies were conducted on early tumor symptoms due to the limited number of cases. We hypothesized that with the existence of pre-tumor symptoms, language developmental delay may be related to tumor.

Abbreviations:

DLGNT	- diffuse leptomeningeal glioneuronal tumor;
MRI	- magnetic resonance imaging
CSF	- cerebrospinal fluid
CT	- computed tomography
Olig-2	- oligodendrocyte transcription factor 2
ATRX	- alpha thalassemia/mental retardation syndrome X-linked;
GFAP	- glial fibrillary acidic protein
NeuN	- neuron-specific nuclear protein
NSE	- neuron-specific enolase
EMA	- epithelial membrane antigen
PR	- progesterone receptor
IDH-1	- isocitrate dehydrogenase 1
FISH	- fluorescence in situ hybridization studies.

INTRODUCTION

Diffuse leptomeningeal glioneuronal tumor (DLGNT) is a new central nervous system tumor defined by the WHO in 2016(Louis *et al.* 2016). The patients affected are mainly children and adolescents manifested with hydrocephalus, headache and epilepsy. Head magnetic resonance imaging (MRI) of patients with DLGNT shows diffuse leptomeningeal thickening and contrast enhancement over the brain surface on T1-weighted images; cystic lesions diffusely scattered throughout the surface of the cerebellum, brain stem and basal ganglia on T2-weighted images (Dodgshun *et al.* 2016; Gardiman *et al.* 2012; Gardiman *et al.* 2010). Oligodendrocytes-like cells were found in some cases (Rodriguez *et*

CASE REPORT

al. 2012; Schniederjan *et al.* 2013; Schwetye *et al.* 2017a). All routine tests on cerebrospinal fluid (CSF) including cell count and cytologic analysis show negative results except for the increased protein level(Karlowee *et al.* 2017; Lyle, Dolia, Fratkin, Nichols, & Herrington, 2015). We report a patient diagnosed with DLGNT who presented with language developmental delay and positive but subtle changes in imaging two years before the emergence of typical clinical symptoms.

CASE REPORT

The first visit to the hospital of the patient resulted from language developmental delay at 2 years old in May 2013. A MRI scan was performed and we revealed subtle but suspected signals on the T2 images. The abnormal signals are lesions around the midbrain aqueduct and near the anterior horn of the lateral ventricle with slight mass effect of local brain parenchyma (Fig.1B, 1C). Two years later, in October 2015 the patient suffered convulsions during sleep without clear cause. Head computed tomography (CT) examination showed that the bilateral lateral ventricles and third ventricle were significantly enlarged. Patient was admitted to hospital for examination and treatment. Head MRI (Fig.1D, 1E) examination showed communicating hydrocephalus, and numerous T2-hyperintense lesions coating the basilar cistern, cerebellum and brain stem regions. Arachnoid cyst in left temporal lobe was observed. Spinal cord MRI (Fig.1F) showed abnormal signals located at C5-C7 level of the spinal cord; Leptomeninges located at the brain stem, bilateral cerebellar hemisphere and spinal meninges at the whole spinal cord membrane were enhanced. CSF showed slightly elevated protein level (4680 mg/L). Ommaya sac was implanted into the left ventricle to relieve the symptoms of hydrocephalus and phenobarbital was administered to the patient to prevent seizures 11 days after the first convulsion. One week later, the patient experienced seizure again and repeated vomiting due to intracranial hypertension. The symptoms were slightly alleviated after the CSF was drained.

The patient finally underwent the operation to resect the thoracic vertebral lesion 18 days after the second convulsion attack. During the operation, a translucent and jelly-like abnormal tissue was observed located between the spinal cord dorsal arachnoid and soft spinal membrane. Histological HE staining (Fig.2A, 2B) showed small round tumor cells with

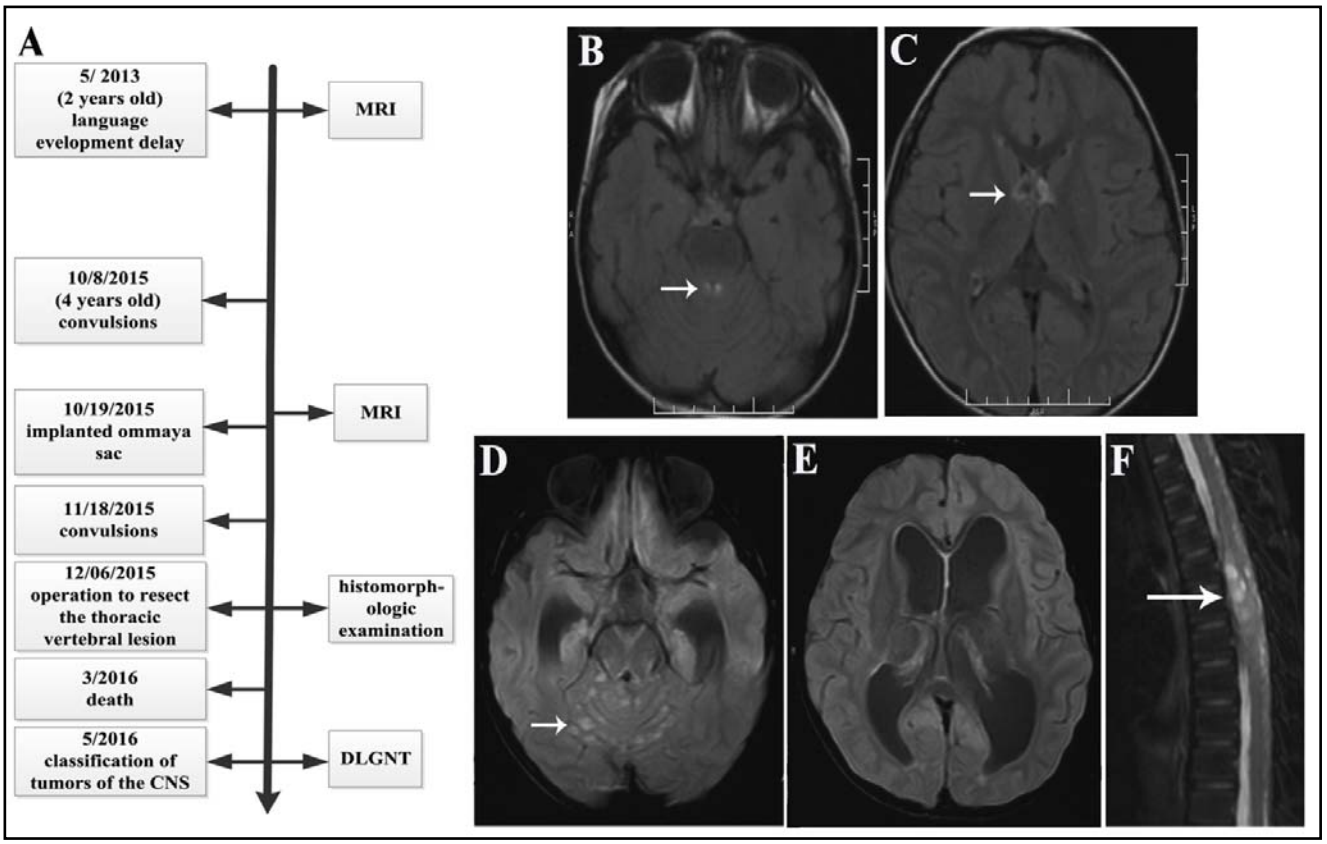

Fig. 1. Fig A is the timeline for patient's condition changes. Fig. B and C show the MRI results of the patient at 2 years old (T2-Flair), respectively. (B) A T2-hyperintense lesion around the midbrain aqueduct (arrow). (C) A T2-hyperintense lesion near the anterior horn of the lateral ventricle which lead to the deformation of anterior horn (arrow). Fig. D, E and F are the initial head and spinal cord MRI after seizure attack. Fig. D shows numerous T2-hyperintense lesions coating bilateral cerebellum (arrow). Arachnoid cyst in left temporal lobe was observed. Fig. E shows obvious broadening of the cerebral ventricles. Fig. F shows spinal cord thickening and abnormal signals located at the C5-C7 level spine cord (arrow).

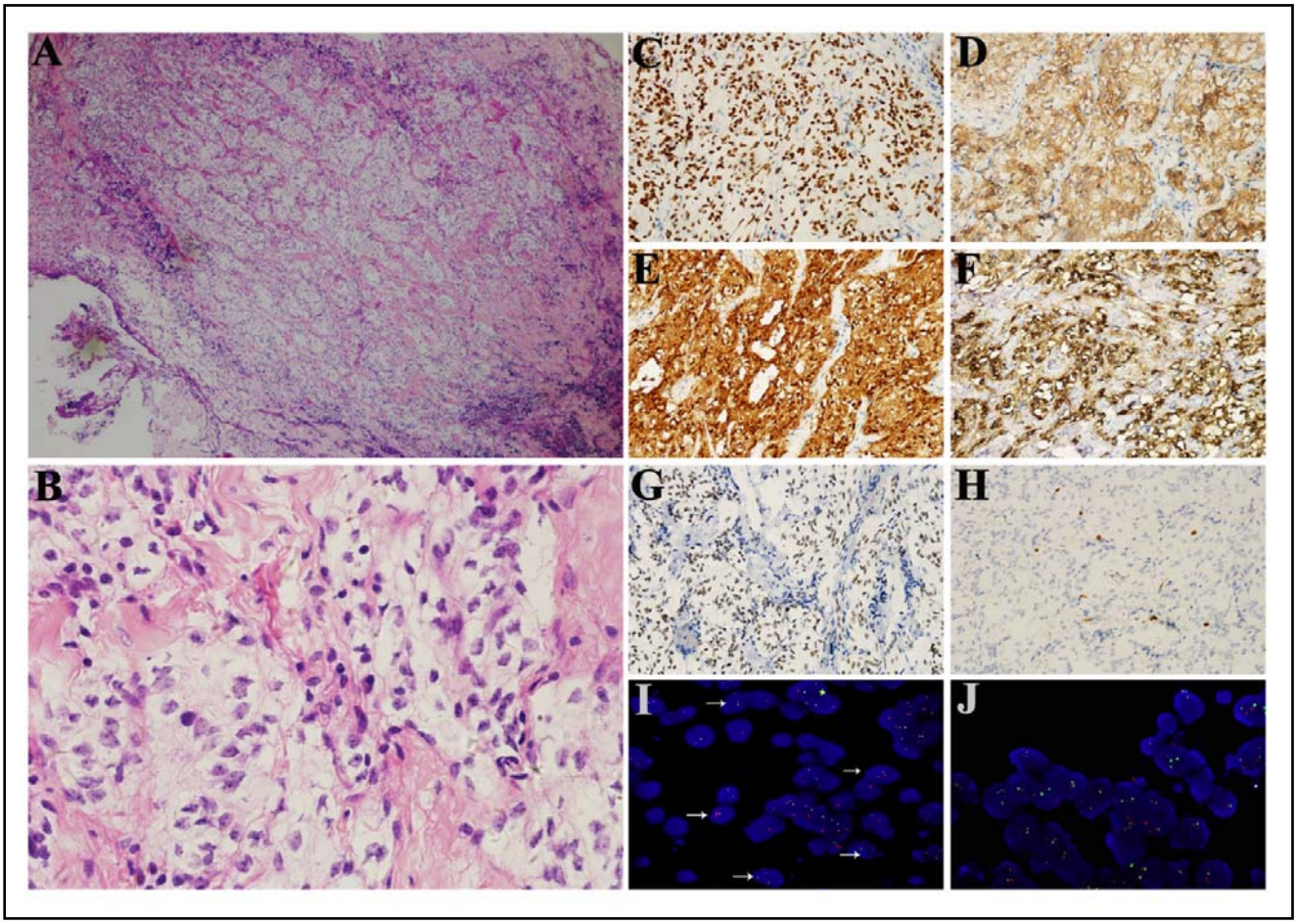

Fig. 2. Histomorphologic examination. Fig. A (HEx100) and B (HEx400) shows small round tumor cells with translucent cytoplasm in hyperplastic fibrous tissue. Fig. C-H show immunostainings results (x400) that are positive for Olig-2 (C), synaptophysin (D), S-100 (E), the Map-2 (F), and ATRX (G). The Ki-67 proliferation index is <4% (H). FISH analysis of 1p/19q shows only 1p deletion (arrows) (I) without 19q deletion (J).

translucent cytoplasm and without nuclear fission, vascular endothelial cell proliferation or necrosis in hyperplastic fibrous tissue. Immunostaining revealed positive for oligodendrocyte transcription factor 2 (Olig-2) and weak positive for synaptophysin, S-100, Map-2, alpha thalassemia/mental retardation syndrome X-linked (ATRX) (Fig. 2C-G), and glial fibrillary acidic protein (GFAP). However, neuron-specific nuclear protein (NeuN), neuron-specific enolase (NSE), vimentin, p53, epithelial membrane antigen (EMA) and progesterone receptor (PR) were negative. The Ki-67 (Fig. 2H) proliferation index was less than 4%. Immunostaining for isocitrate dehydrogenase 1 (IDH-1) and BRAF V600E were negative. Fluorescence in situ hybridization studies (FISH) analysis of 1p/19q revealed only 1p deletion without deletion of 19q (Fig. 2I, 2J). FISH analysis of BRAF-KIAA1549 fusion was negative.

The patient still suffered severe vomiting after surgery and died three months later. He was finally diagnosed with DLGNT based on clinical symptoms, imaging data and pathology report.

DISCUSSION

DLGNT was first proposed by Gardiman (Gardiman *et al.* 2010)reporting four patients with similar clinical manifestations and imaging characteristics in 2010. In 2016, this disease was officially named by WHO as a new central nervous system tumor and there was no effective treatment (Louis *et al.* 2016). Most of patients diagnosed with DLGNT are male (51/78). The most common manifestations of DLGNT include headache and vomiting, accounting for about 47% (32/67), hydrocephalus accounting about 44% (27/61), movement disorder 23%(16/67), and seizures accounting for 13% (9/67).(Agamanolis *et al.* 2012; Aguilera *et al.* 2018; Cho *et al.* 2015; Gardiman *et al.* 2010; Preuss *et al.* 2015; Rodriguez *et al.* 2012; Schniederjan *et al.* 2013; Schwetye *et al.* 2017b) (Table 1) Although the symptoms of our patients after the onset of the seizure were consistent with those in previous reports, the child exhibited language developmental delay before the typical clinical symptoms appeared. To date, the pathogenesis of DLGNT is unclear, and early development and imaging of patients are rarely reported.

Tab. 1. The Characteristics of diffuse leptomeningeal glioneuronal tumor patients

References	Number of cases	Gender (male)	Age range (years)	Main Manifestations				Olig-2	S100	GFAP	synaptophysin	NeuN	IDH-1
				hydrocephalus	Headache/vomiting	seizures	movement disorder						
Gardiman *et al.*[2]	4	2/4	3-13	3/4	2/4	0/4	3/4	NA	4/4	4/4	4/4	1/4	NA
Agamanolis *et al.*[10]	3	2/3	4-9	3/3	2/3	1/3	3/3	NA	3/3	NA	0/3	NA	NA
Rodriguez *et al.*[5]	36	24/36	0.5-46	8/36	14/36	5/36	6/36	7/9	11/12	12/31	19/27	0/36	0/36
Schniederjan *et al.*[6]	9	4/9	1.5-6	7/9	5/9	1/9	3/9	NA	9/9	4/9	8/9	0/6	0/8
Cho *et al.*[11]	3	3/3	11-62	0/3	2/3	1/3	0/3	3/3	NA	3/3	3/3	2/3	0/3
Preuss *et al.*[12]	4	4/4	1.9-8.7	4/4	NA	NA	NA	4/4	4/4	2/4	1/4	0/4	0/4
Dodgshun *et al.*[3]	10	6/10	1.5-14	NA	5/10	1/10	1/10	10/10	NA	10/10	10/10	NA	NA
Aguilera *et al.*[13]	7	4/7	2-7	NA	NA	NA	NA	NA	7/7	7/7	7/7	NA	0/7
Schwetye *et al.*[14]	2	2/2	7-9	2/2	2/2	0/2	0/2	1/1	1/2	1/2	1/1	0/2	0/1
Total	78	51/78	0.5-62	27/61	32/67	9/67	16/67	25/27	39/41	43/70	53/68	3/55	0/59

Olig-2: oligodendrocyte transcription factor 2; GFAP: glial fibrillary acidic protein; NeuN: neuron-specific nuclear protein; IDH-1: isocitrate dehydrogenase 1

We believe that poor language development may be related to the presence of the tumor, and we do not rule out the prodrome of tumor.

Given that head MRIs in DLGNT patients showed areas of diffuse leptomeningeal enhancement with T2-hyperintense, this disease often needs to be differentiated from tuberculosis infection(Karlowee *et al.* 2017). The T2-weighted images of our patient showed numerous hyperintense lesions similar to those found in literature, but his CSF and blood tuberculosis infection indicators were negative, and CSF examination showed only elevated protein, but did not support tuberculosis infection.

DLGNT tumor cells are singular oligodendrocyte-like cells with medium-sized round nuclei (nucleoli are not evident) (Gardiman *et al.* 2010). Immunohistochemical staining of tumor cells reported the expression of Olig-2(92%), S100(95%), Map-2, and synaptophysin(77%). Approximately 61% of the cases expressed GFAP, but lacked NeuN, which are different from oligodendrocytes tumors. None of the cases expressed IDH-1. (Table 1)

The mutation of the BARF gene activates the MAP/ERK signaling pathway and leads to the generation of tumors, which is highly common in BRAF V600E and BRAF KIAA1549 mutations(Gierke *et al.* 2016).Dodgshun studied 33 patients with DLGNT and showed that the most common mutation is BRAF KIAA1549, which accounts for approximately 48.5%; 3% of the patients had BRAF V600E mutation, and 18% did not show the mutated BRAF gene changes(Dodgshun *et al.* 2016).

In conclusion, the study of DLGNT remains relatively rare. The accuracy of diagnosis depends on MRI and pathology. Patients with atypical clinical and radiographic changes shall be subjected to long-term follow-up for early recognition. We hypothesized that with the existence of pre-tumor symptoms, language developmental delay may be related to tumor. Further studies with increased samples are needed to support this finding.

ACKNOWLEDGEMENTS

We thank Dr. Lin-Yan Hu (Department of Pediatrics, the Fisrt Medical Center of PLA General Hospital) and Xin Lou (Department of Radiology, the Fisrt Medical Center of PLA General Hospital) for much helpful advice in analysis of data. The authors declare that they have no competing interests.

FUND PROGRAM

This work is supported by the National Nature Fund (81471329) and the National Key R&D Program of China (2016YFC1000707).

REFERENCES

1 Agamanolis DP, Katsetos CD, Klonk CJ, Bartkowski HM, Ganapathy S, Staugaitis SM et al. (2012). An unusual form of superficially disseminated glioma in children: report of 3 cases. J Child Neurol. **27**(6): 727–733. doi: 10.1177/0883073811426500

2 Aguilera D, Castellino RC, Janss A, Schniederjan M, McNall R, MacDonald T, Mazewski C (2018). Clinical responses of patients with diffuse leptomeningeal glioneuronal tumors to chemotherapy. Childs Nerv Syst. **34**(2): 329–334. doi: 10.1007/s00381-017-3584-x

3 Cho HJ, Myung JK, Kim H, Park CK, Kim SK, Chung CK, et al. (2015). Primary diffuse leptomeningeal glioneuronal tumors. Brain Tumor Pathol. **32**(1): 49–55. doi: 10.1007/s10014-014-0187-z

4 Dodgshun AJ, SantaCruz N, Hwang J, Ramkissoon SH, Malkin H, Bergthold G et al. (2016). Disseminated glioneuronal tumors occurring in childhood: treatment outcomes and BRAF alterations including V600E mutation. J Neurooncol, **128**(2): 293–302. doi: 10.1007/s11060-016-2109-x

5 Gardiman MP, Fassan M, Nozza P, Orvieto E, Garre ML, Milanaccio, C et al. (2012). Diffuse leptomeningeal glioneuronal tumours: clinico-pathological follow-up. Pathologica. **104**(6): 428–431.

6 Gardiman MP, Fassan M, Orvieto E, D'Avella D, Denaro L, Calderone M, et al. (2010). Diffuse leptomeningeal glioneuronal tumors: a new entity? Brain Pathol. **20**(2): 361–366. doi: 10.1111/j.1750-3639.2009.00285.x

7 Gierke M, Sperveslage J, Schwab D, Beschorner R, Ebinger M, Schuhmann MU, Schittenhelm J. (2016). Analysis of IDH1-R132 mutation, BRAF V600 mutation and KIAA1549-BRAF fusion transcript status in central nervous system tumors supports pediatric tumor classification. J Cancer Res Clin Oncol, **142**(1): 89–100. doi: 10.1007/s00432-015-2006-2

8 Karlowee V, Kolakshyapati M, Amatya VJ, Takayasu T, Nosaka R, Sugiyama, K et al. (2017). Diffuse leptomeningeal glioneuronal tumor (DLGNT) mimicking Whipple's disease: a case report and literature review. Childs Nerv Syst. **33**(8): 1411–1414. doi: 10.1007/s00381-017-3405-2

9 Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK et al. (2016). The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol, **131**(6): 803–820. doi: 10.1007/s00401-016-1545-1

10 Lyle MR, Dolia JN, Fratkin J, Nichols TA, Herrington, B. L. (2015). Newly Identified Characteristics and Suggestions for Diagnosis and Treatment of Diffuse Leptomeningeal Glioneuronal/ Neuroepithelial Tumors: A Case Report and Review of the Literature. Child Neurol Open. **2**(1): 2329048x14567531. doi: 10.1177/2329048x14567531

11 Preuss M, Christiansen H, Merkenschlager A, Hirsch FW, Kiess W, Muller W et al. (2015). Disseminated oligodendroglial-like leptomeningeal tumors: preliminary diagnostic and therapeutic results for a novel tumor entity [corrected]. J Neurooncol. **124**(1): 65–74. doi: 10.1007/s11060-015-1735-z

12 Rodriguez FJ, Perry A, Rosenblum MK, Krawitz S, Cohen KJ, Lin D et al. (2012). Disseminated oligodendroglial-like leptomeningeal tumor of childhood: a distinctive clinicopathologic entity. Acta Neuropathol, **124**(5): 627–641. doi: 10.1007/s00401-012-1037-x

13 Schniederjan MJ, Alghamdi S, Castellano-Sanchez A, Mazewski C, Brahma B, Brat DJ et al. (2013). Diffuse leptomeningeal neuroepithelial tumor: 9 pediatric cases with chromosome 1p/19q deletion status and IDH1 (R132H) immunohistochemistry. Am J Surg Pathol, **37**(5): 763–771. doi: 10.1097/PAS.0b013e31827bf4cc

14 Schwetye KE, Kansagra AP, McEachern J, Schmidt RE, Gauvain K, Dahiya S (2017a). Unusual high-grade features in pediatric diffuse leptomeningeal glioneuronal tumor: comparison with a typical low-grade example. Hum Pathol. doi: 10.1016/j.humpath.2017.06.004

15 Schwetye KE, Kansagra AP, McEachern J, Schmidt RE, Gauvain K, Dahiya S (2017b). Unusual high-grade features in pediatric diffuse leptomeningeal glioneuronal tumor: comparison with a typical low-grade example. Hum Pathol. **70**: 105–112. doi: 10.1016/j.humpath.2017.06.004