Case Report

Diffuse Leptomeningeal Glioneuronal Tumor in Adults: Case Report and Literature Review

Nova Kristine de los Reyes-Nabhan[a, b]   Stefanie Scheil-Bertram[c, d]
Sangamitra Boppudi[c]   Barbara Carl[a]   Daniel Jussen[b]

[a]Department of Neurosurgery, HELIOS Dr. Horst Schmidt Kliniken, Wiesbaden, Germany;
[b]Department of Neurosurgery, Klinikum der Goethe Universität Frankfurt, Frankfurt, Germany;
[c]Department of Pathology and Cytology, HELIOS Dr. Horst Schmidt Kliniken, Wiesbaden, Germany;
[d]Pathology Institute, Klinikum Region Hannover am Nordstadtklinikum, Hannover, Germany

Abstract

Introduction: Diffuse leptomeningeal glioneuronal tumor (DLGNT), a new addition to the 2016 World Health Organization (WHO) classification, is a rare childhood neoplasm presenting with disseminated leptomeningeal enhancement and an occasional intraparenchymal mass. Diagnosis is often impeded by infectious/immunological differentials, necessitating a biopsy to confirm the diagnosis. We report an adult male with DLGNT without hydrocephalus, which is rare in patients with cerebellar masses. ***Case Presentation:*** A 56-year-old man presented with headaches, vertigo, diplopia, impaired hearing, and gait imbalance over 6 months. Magnetic resonance imaging showed a cystic right cerebellar mass with its leptomeningeal dissemination but without hydrocephalus. Cerebrospinal fluid analysis revealed elevated proteins with CD56-positive tumor cells. Cerebellar lesion biopsy verified the diagnosis of DLGNT (WHO Grade 3) with *KIAA1549::BRAF* fusion and 1p deletion. Radiotherapy was prematurely aborted due to clinical deterioration. The patient was subsequently discharged to palliative home care and lost to follow-up. ***Conclusion:*** We conducted the first review of all 34 adult DLGNT cases, including ours (one of the oldest), hitherto published in the literature. The majority presented with signs and symptoms of increased intracranial pressure. 52.0% of adult DLGNT patients were alive at follow-up. DLGNT should be considered in the differential diagnoses of diffuse leptomeningeal enhancement in imaging. Further studies comparing pediatric and adult subgroups of DLGNT are needed to evaluate histopathological prognosticators and standardize therapy for both subpopulations.

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Correspondence to:
Nova Kristine de los Reyes-Nabhan, nkm.delosreyes @ gmail.com

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Introduction

Diffuse leptomeningeal glioneuronal tumor (DLGNT) was a new addition to the 2016 World Health Organization Classification of Tumors of the Central Nervous System (2016 WHO CNS). DLGNT is considered a rare neoplasm of childhood with a median age of 5 years [1] and male preponderance [2]. However, this novel entity was probably already previously identified in the literature as diffuse leptomeningeal oligodendroglioma, diffuse leptomeningeal neuroepithelial tumor, or disseminated oligodendroglial-like leptomeningeal tumor of childhood, among various terminologies. Expedient diagnosis is further confounded by imaging and exam that may mimic neurosarcoidosis, human herpes virus 6, tuberculosis [3], Whipple's disease, even subarachnoid hemorrhage, and hemiplegic migraine. Patients commonly present with hydrocephalus and associated symptoms [4]. Cerebrospinal fluid (CSF) analysis is often unrevealing with unspecific protein elevation and normal cytology [5]. Imaging reveals diffuse leptomeningeal enhancement involving the whole neuraxis [4], albeit with exceptions [6], with associated cystic lesions and occasional intraparenchymal masses [1], which may be calcified [2].

We report a rare male adult DLGNT patient with a cystic cerebellar mass and its leptomeningeal dissemination (LMD) without hydrocephalus, a relative rarity among the plethora of pediatric cases. To our knowledge, only 34 adult cases exist in the literature. Information on DLGNT is based mainly on sporadic case series, the largest with 36 patients [1]. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536400).

Case Report

Our 56-year-old patient presented to neurology in mid-November 2020 with a 6-month history of recurrent headaches, vertigo, diplopia, impaired hearing, and gait imbalance. Despite these symptoms, no neurologic deficits were found on examination. History is significant only for controlled Graves' disease. Initial cranial computer tomography scans ruled out acute pathology, including hydrocephalus. Magnetic resonance imaging of the neuraxis (shown in Fig. 1) revealed a small cystic lesion of the right cerebellar hemisphere, diffuse leptomeningeal enhancement of the cerebellum, brainstem, and cervical cord, especially ubiquitous nodular thickening of the spinal cord, including caudal fibers, and multiple punctuate subcortical lesions of cerebellar hemispheres. Electrophysiologic studies demonstrated correlates to demyelinization of optic and sensory pathways of the right arm and lower extremities.

An inflammatory etiology or leptomeningeal carcinomatosis was initially suspected. Antibiotics were started empirically. Extensive laboratory work-up for infectious diseases, including human immunodeficiency virus, tuberculosis, Epstein-Barr virus, syphilis, and echinococcal parasites, was negative. CSF findings revealed elevated proteins (3,032 mg/dL) and CD56-positive cells in cytology, which were negative for S100, Melan A, and CD138. Genetic analysis revealed BRAF wild-type status for single nucleotide variants/Indels. Repeat CSF was negative in tests for Listeria and Whipple's disease. Complete body scans showed hepatic focal nodular hyperplasia and small hemangioma with no signs of malignancy. A dermatology consult found no cutaneous neoplasms.

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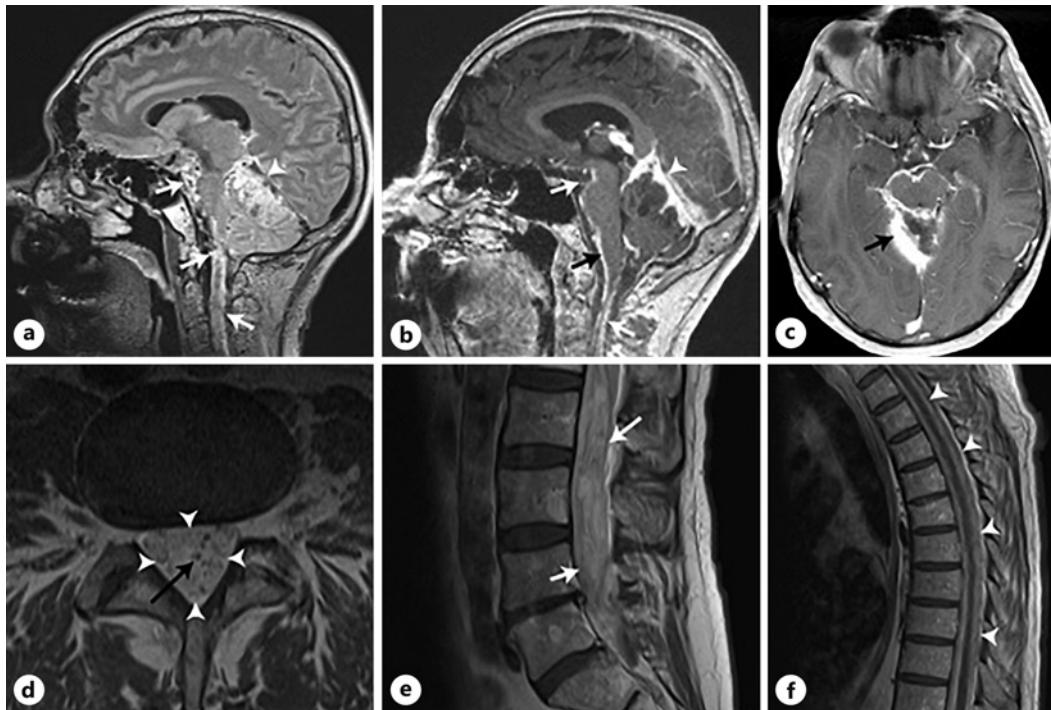
Fig. 1. Magnetic resonance images (MRIs) of a 56-year-old adult male with DLGNT WHO grade 3 (case 34). **a**, **b** Cranial MRI sagittal image in T2 FLAIR (**a**) and T1 with contrast (**b**) sequences, demonstrating a contrast-enhancing right cerebellar lesion with cystic changes (*arrowheads*, **a**, **b**), as well as diffuse leptomeningeal enhancement sugarcoating the entire surface of the brainstem and cervical medulla (*arrows*, **a**, **b**). **c** Cranial MRI axial image in T1 sequence with contrast showing bright contrast enhancement of the same cystic, right cerebellar lesion (*black arrow*). Biopsy of this lesion revealed DLGNT (WHO grade 3) with *KIAA1549::BRAF* fusion and 1p deletion. **d** Spinal MRI axial image in T1 sequence with contrast at the disk level between the third and fourth lumbar vertebrae, illustrating the sugarcoating effect (*arrowheads*) of the leptomeningeal dissemination (LMD) along the caudal fibers (*black arrow*). **e**, **f** Spinal MRI sagittal image of the lumbar spine (**e**) below the conus medullaris and of the thoracic spine (**f**) in T1 sequence with contrast, displaying the entire spinal cord sugarcoated by DLGNT dissemination with nodular leptomeningeal thickening. LMD was treated with local irradiation of the neuraxis, which was halted due to the clinical deterioration of the patient.

The patient was subsequently referred to neurosurgery for a surgical biopsy for a definitive histopathological diagnosis. After obtaining consent, a tentorium and cystic cerebellar lesion biopsy was performed via suboccipital craniotomy. The patient was started on high-dose dexamethasone after frozen section analysis ruled out leptomeningeal carcinomatosis or lymphoma.

Immunoreactivity for periodic acid-Schiff, vimentin, epithelial membrane antigen, CD10, CD68, and CD45 was negative, as were tests against herpes viruses and mycobacteriosis. Microscopy revealed tumor cells strongly positive for synaptophysin (Fig. 2d) and negative for chromogranin A and beta-catenin. Further tests showed immunonegativity for D2–40 (podoplanin), placental alkaline phosphatase (PLAP), alpha-fetoprotein (AFP), CD30, CD117, human chorionic gonadotropin (beta-HCG), inhibin, Oct3/4, glypican 3, and pancytokeratin, thus ruling out germinoma as a differential. Biopsy specimens were harvested from tentorial dura, cerebellum, and cystic lesion. Biopsy of the tentorium revealed no tumor cells. Biopsy of the cerebellar lesion

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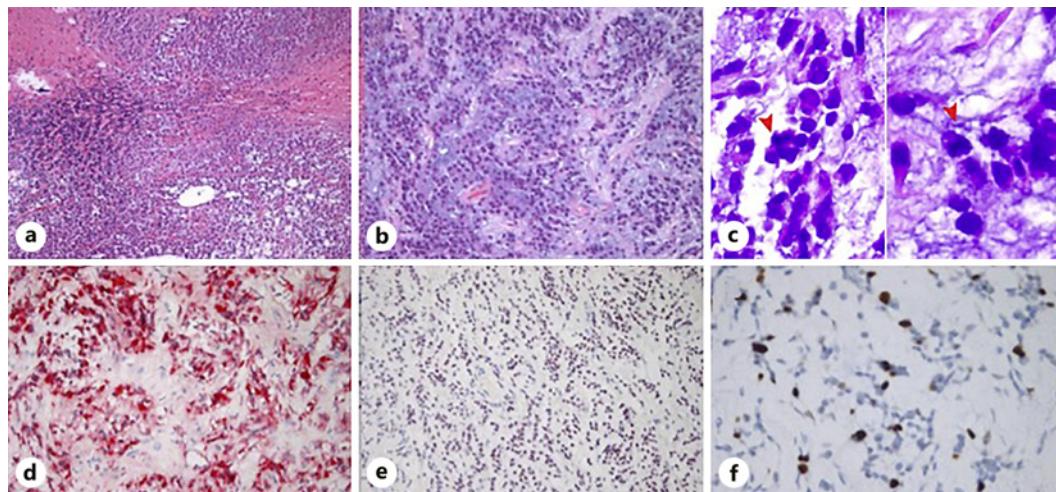
Fig. 2. a, **b** Hematoxylin and eosin (H&E) showing monomorphic, oligodendroglioma-like cells in the myxoid matrix without vascular proliferates or necrosis in low (**a**) and high (**b**) magnification. **c** H&E showing up to 4 mitotic figures/10 HPF (2 examples indicated by *red arrowheads*), conferring our patient (*case 34*) a WHO grade 3. **d–f** Immunochemistry staining positive for synaptophysin (**d**), Olig2 (**e**), and MIB1/Ki67 (**f**).

demonstrated monomorphic, oligodendroglioma-like cells in the myxoid matrix without vascular proliferates or necrosis within the subarachnoid space, partially infiltrating parenchymal tissue (Fig. 2a, b). Analysis of the cystic lesion also showed a myxoid tumor with monomorphic, mononuclear tumor cells with up to 4 mitotic figures/10 HPF (Fig. 2c). Neoplastic cells were strongly immunoreactive for CD56, MAP2, Olig2 (Fig. 2e), and alpha thalassemia/mental retardation syndrome X-linked (ATRX) protein. GFAP and neurofilament were focally expressed in the tumor. The neoplastic cells were immunonegative for mutated isocitrate dehydrogenase-1 (IDH1) protein (p.R132H), epithelial membrane antigen, vimentin, CD68, CD45, CD3, CD20, S100, Melan A, and CD138. MIB1/Ki67 labeling index was ca. 15–20% (Fig. 2f). The p53 was expressed in <5% nuclei. IDH1 or IDH2 mutations were negative. Fluorescence in situ hybridization analysis demonstrated a 1p deletion but no 1q/19q codeletion. No mutations in the TERT promoter region (C228T, C250T) were found, thus ruling out oligodendroglioma. Reverse transcription polymerase chain reaction testing showed a *KIAA1549::BRAF* fusion. DNA-methylation profiling using EPIC-Array revealed the methylation class of DLGNT with a calibration classifier score of 0.77. Copy number profile indicated 1p, 4p, 4q, and 6q deletion and gains of chromosomes 1q, 3q, 6q, 8p, 8q, 9p, and 18q. Next-generation sequencing analysis detected wild-type status for AKT1, BRAF, EGFR, ERBB2, FOXL2, GNA11, GNAQ, KIT, KRAS, MET, NRAS, PDGFRA, PIK3CA, RET, and TP53. Mutations in H3F3A gene coding for histone H3.3 (H3K27M) were not detected by sequencing. No methylation of O6-MGMT was detected by tumor-DNA isolation. Since all the essential criteria according to the 2021 WHO CNS were present, the histopathological diagnosis of DLGNT (WHO grade 3) was established.

The postoperative course was uneventful; the patient was referred for total neuraxial irradiation. Two days into radiotherapy, treatment was halted after 3.6 Gy radiation dose due to intractable seizures and clinical deterioration. The patient was eventually discharged from the palliative ward into palliative home care and lost to follow-up.

Discussion

Thirty-four adult cases have been published in the literature since 1995 (shown in online suppl. Table 1). Our case (case 34) is the antithesis of the DLGNT prototype of a male hydrocephalic child and contributes to the current dearth of information on adult DLGNT. Our patient is one of the oldest cases of DLGNT (56 years), with only two other cases being older (both 62 years) [3, 7]. Reviewed cases had a mean age of 35.6 years (19–62 years). Similar to the general DLGNT population, adult cases displayed a male preponderance (M: F = 1.43:1). Elevated intracranial pressure signs predominate with headaches (32.4%), vomiting (8.8%), and seizures (20.6%). 68.8% presented with an intraparenchymal mass and 77.8% with LMD. 29.4% had hydrocephalus. Pediatric patients are usually treated with carboplatin and vincristine per Children's Oncology Group (COG) protocols and temozolomide as second-line therapy [8]. In contrast, adult patients often received temozolomide chemotherapy (33.3%) and radiotherapy (47.6%). At a mean follow-up of 40.25 months (follow-up not provided in 26.5%), 52.0% were alive, 28.0% were alive with stable disease, 8.0% were alive in remission, and 8.0% were alive with progressive disease; 48.0% were deceased. 70.6% were diagnosed as DLGNT, 29.4% with other diagnoses before the 2016 WHO CNS. Among adult cases, only one case (2.9%) was classified as DLGNT-MC-1 [9] and another as DLGNT-MC-2 [5].

DLGNT remains a rare CNS neoplasm of childhood, presenting as hydrocephalus. Rodriguez et al. [1] and Deng et al. [10] published the largest case series to date. The latter found that DLGNT-MC-2 tends to present older with a more aggressive clinical outcome. DLGNT is extremely rare in adults [11]. Here, we reported a rare adult case of DLGNT without the classic manifestation of hydrocephalus, despite exhibiting a cystic cerebellar mass with diffuse LMD in both T1- and T2-weighted magnetic resonance imaging and concomitant *KIAA1549::BRAF* fusion and 1p deletion. We also present here the first review of 34 published adult DLGNT cases.

Histopathological diagnosis of DLGNT is usually obtained through biopsy of the leptomeninges or resected tumor specimens [11]. Immunohistochemistry stains variably for neuronal and glial markers such as oligodendrocyte transcription factor (Olig2), synaptophysin, glial fibrillary acidic protein (GFAP), and S100. In addition, studies also investigated neuronal nuclear protein (NeuN), neurofilament (neuronal markers), and microtubule-associated protein 2 (MAP2) [1], which is expressed in oligodendroglial-like tumor cells [11]. Fluorescence in situ hybridization analysis demonstrated recurrent genetic alterations in the MAPK/ERK pathway, most notably rearrangements leading to a *KIAA1549::BRAF* fusion, alterations in the B-Raf murine sarcoma viral oncogene homolog B leading to BRAF V600E mutations, a chromosomal 1p deletion [10], occasionally a 1p/19q codeletion, and H3K27M mutations [12]. DLGNT may be classified into methylation class MC-1 and MC-2 subgroups according to DNA-methylation profiling, with molecular distinctions and prognostic relevance [10]. 1q gain, which is highly associated with DLGNT-MC-2 profile, portends a poor prognosis [9].

Long-term data on survival and outcomes are limited. As a rare neoplasm, an international treatment protocol for DLGNT has yet to be established [11], especially for adults. Differences in pediatric and adult subpopulations of DLGNT have not been previously analyzed [13]. Recent reviews identified higher age and Ki67 index, signs of increased intracranial pressure, presence of an intraparenchymal mass [14], and hydrocephalus as poor prognosticators [15]. 1q gain has already been established as an unfavorable prognostic factor in DLGNT [9], which was more frequent in the DLGNT-MC-2 subclass [9, 10]. According to a recent pediatric review [8], most pediatric DLGNT patients make it to adulthood, with chemotherapy conferring longer survival times. A review analyzing pediatric and adult cases

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found that radiotherapy did not improve survival [15]. The relative rarity of adult DLGNT complicates the assessment of survival outcomes and prognosis in this subgroup. In our literature review, 52.0% of adult DLGNT cases were alive at follow-up. As the first analysis of all adult DLGNT cases in the literature, limitations of this review arise from the heterogeneity of the incorporated case reports and series, with a substantial number of cases omitting critical information on histopathological parameters and methylation class, thus limiting their analysis. Future multicentric studies should perform standardized panels of histopathological parameters, especially that of *KIAA1549::BRAF* fusion, 1p deletion, and DNA methylation profiling (MC-1 and MC-2), to identify prognostic markers.

In conclusion, DLGNT is a rare diagnosis in adults. The male hydrocephalic child remains the prototype DLGNT patient. We presented a rare adult case with a cerebellar mass and LMD of DLGNT without hydrocephalus. We conducted the first review of all published adult cases in the literature, thus counteracting the current paucity of research on adult DLGNT. Prognosis and survival in this subgroup remain unclear, which is reflected in the current lack of standardized treatment protocols and guidelines for adult DLGNT. DLGNT should be considered in the differential diagnoses of diffuse leptomeningeal enhancement in imaging. Prompt diagnosis relies heavily on invasive biopsy of intraparenchymal masses or leptomeninges. Histopathological parameters should be further investigated in larger studies for their prognostic significance.

Statement of Ethics

The article does not contain data to identify patients. The authors have no ethical conflicts to disclose. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed to the study's conception and design, commented on previous versions of the manuscript, and read and approved the final manuscript. The case report was conceptualized by Barbara Carl, while the literature review was conceptualized by Daniel Jussen. Information on histopathology was provided by Sangamitra Boppudi and Stefanie Scheil-Bertram, while histopathology slides were prepared by Stefanie Scheil-Bertram. Literature review, case report, and data analysis were performed by Nova Kristine de los Reyes-Nabhan. The first draft of the manuscript was written by Nova Kristine de los Reyes-Nabhan.

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Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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