Rapidly progressive diffuse leptomeningeal glioneuronal tumor in an adult female: illustrative case

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BACKGROUND Diffuse leptomeningeal glioneuronal tumor (DLGNT) is a rare brain tumor only recently classified by the World Health Organization in 2016 and has few reports on its incidence in adults.

OBSERVATIONS The authors describe a case of DLGNT presenting in a 47-year-old female with seizures, cranial neuropathies, and communicating hydrocephalus with rapid clinical progression. Workup demonstrated progressive leptomeningeal enhancement of the skull base, cranial nerves, and spine, and communicating hydrocephalus. Elevated serum rheumatological markers and early response to systemic corticosteroids and immunosuppressant therapy complicated the diagnosis. Multiple biopsy attempts were required to obtain diagnostic tissue. Pathology demonstrated hypercellularity surrounding leptomeningeal vessels with nuclear atypia, staining positive for GFAP, Olig2, S100, and synaptophysin. Molecular pathology demonstrated loss of chromosome 1p, BRAF overexpression but no rearrangement, and H3K27 mutation. Repeat cerebrospinal fluid (CSF) diversion procedures were required for hydrocephalus management due to high CSF protein content.

LESSONS This report describes a rare, aggressive, adult presentation of DLGNT. Leptomeningeal enhancement and communicating hydrocephalus should raise suspicion for this disease process. Biopsy at early stages of disease progression is essential for early diagnosis and prompt treatment. Further study into the variable clinical presentation, histological and molecular pathology, and optimal means of diagnosis and management is needed.

https://thejns.org/doi/abs/10.3171/CASE22502

KEYWORDS diffuse leptomeningeal glioneuronal tumor; histopathology; imaging; case report

Diffuse leptomeningeal glioneuronal tumor (DLGNT) is a rare disease first identified in 1996 and only recently classified by the World Health Organization in 2016.1,2 It has most commonly been reported affecting pediatric patients with a male to female ratio of 2:1.3 A variety of presentations have been described including gadolinium contrast enhancement of the brain and/or spinal cord leptomeninges and cranial nerves with T1-weighted magnetic resonance imaging (MRI), communicating hydrocephalus, and isolated intraparenchymal masses within the brain and/or spinal cord.3–7 Diagnosis is based on tissue biopsy for histological and molecular pathology analysis.8

Because of its new identification and low incidence, additional reports and case series are needed to better understand the variations in clinical presentation, diagnosis, and management of DLGNT.9 Here we present a case of a 47-year-old female with rapidly progressive DLGNT. The clinical presentation, imaging findings, histological and molecular pathology, and challenges in diagnosis and management are described.

Illustrative Case

A 47-year-old female with no significant medical history presented with new generalized tonic-clonic seizures, diplopia from a left abducens nerve palsy, confusion, and worsening headaches. Brain MRI with and without contrast demonstrated communicating hydrocephalus, a 4-mm gadolinium enhancing mass within the left internal auditory canal, and leptomeningeal enhancement throughout the skull base, along the ventral midbrain, surrounding the pons, and along the cranial
nerves (Fig. 1). She underwent a lumbar puncture demonstrating elevated opening pressure of 49 mm Hg. Cerebrospinal fluid (CSF) cytology and flow cytometry were unrevealing.

Due to worsening neurological symptoms, an external ventricular drain was placed, with subsequent symptomatic improvement. She underwent extracranial imaging studies identifying only a small thyroid nodule, which underwent biopsy with a benign result. Rheumatological testing demonstrated elevated immunoglobulin (Ig) G (IgG) antibodies, anticardiolipin antibodies, and beta-2 glycoprotein IgM antibodies. Right frontal dura biopsy, corresponding to an area of nodular contrast enhancement on MRI, was nondiagnostic. Methylprednisolone, hydroxychloroquine, rituximab, and cyclophosphamide were administered throughout the initial several months of therapy with resulting symptomatic improvement suggestive of a rheumatological process.

A ventriculoperitoneal shunt was placed for permanent CSF diversion. The patient underwent 4 shunt revision operations, with recurrent shunt failure from valve dysfunction caused by markedly elevated CSF protein consistently greater than 1000 mg/dL. Ultimately, a valveless shunt system was placed with no further failure events.

After initial improvement, 2 months later the patient began to rapidly neurologically decline with worsening quadriplegia and confusion. Repeat MRI of the brain and spine with gadolinium contrast demonstrated worsening leptomeningeal disease involving the skull base, cranial nerves (Fig. 2), pan-spinal cord, and spinal nerve roots (Figs. 3 and 4). Intramedullary T2 hyperintensity with hydromyelitis was noted throughout the spine, most prominently in the cervical spine (Fig. 3).

Biopsy was again pursued, this time via lumbar laminectomy with sampling of multiple areas of lumbar dural thickening. Hematoxylin and eosin (H&E) staining demonstrated atypical neuroepithelial cells with hyperproliferation involving the leptomeninges (Fig. 5). Cells were ovoid or slightly spindle shaped with hyperchromatic nuclei, inconspicuous nucleoli, and eosinophilic or pale cytoplasm. Cellular staining was positive for glial fibrillary acid protein (GFAP), oligodendrocyte transcription factor 2 (Olig2), S100, and synaptophysin. Staining for EMA, CAM5.2, CD45, CD1a, CD68, and neurofilament

![FIG. 1. Initial brain MRI with and without gadolinium contrast demonstrating leptomeningeal enhancement and communicating hydrocephalus at the level of the lateral and third ventricles (A), midbrain and basal cisterns (B), and pontomedullary junction (C).](image1)

![FIG. 2. Repeat brain MRI with and without gadolinium contrast 2 months later demonstrating significantly increased leptomeningeal enhancement at the level of the lateral and third ventricles (A), midbrain and basal cisterns (B), and pontomedullary junction (C).](image2)
was negative. The Ki-67 proliferation index was 2%–5%. Fluorescence in situ hybridization (FISH) demonstrated chromosome 1p deletion, BRAF overexpression from amplification or duplication of chromosome 7, and an H3K27 gene mutation. A diagnosis of DLGNT was made.

The patient was started on chemotherapy with temozolomide and palliative craniospinal irradiation. Unfortunately, the patient experienced a massive pulmonary embolism and died after completing approximately half of her planned radiation treatments.

Discussion

Observations

Clinical Presentation

This case of an adult female with rapidly progressive DLGNT highlights the difficulties associated with diagnosis and treatment of this disease. DLGNT most commonly affects children in a child-to-adult ratio of 6.1:1 and affects males twice as often as females. Cases of adult DLGNT cases, especially in females, have been sparsely reported in the literature. The clinical presentation of DLGNT is often nonspecific, with symptoms of hydrocephalus, seizures, and spinal cord compression syndromes. Imaging may demonstrate leptomeningeal enhancement, discrete intramedullary spinal masses, communicating hydrocephalus, or combinations of these findings. Symptomatology varies, depending on the rate of tumor growth and specific neural structures involved. Due to its extremely low incidence, variable clinical presentation, nonspecific imaging findings, and variable symptomatology, DLGNT may be misdiagnosed, most often as infectious or inflammatory pathologies.

Diagnosis

Obtaining the correct tissue to obtain a pathological diagnosis of DLGNT is essential but may be challenging. The optimal place to biopsy is currently unclear, but a consensus appears to exist regarding targeting tissue with leptomeningeal enhancement or intraparenchymal lesions when present in a safe location. CSF cytology may be unrevealing; however, some authors do report obtaining diagnostic samples. In this case, initial intracranial leptomeningeal biopsy and CSF cytology yielded nondiagnostic tissue, but biopsy of the lumbar leptomeninges after further disease progression yielded the diagnosis. Future study is needed to better understand disease pathogenesis to provide insight into the optimal biopsy strategy to reduce the likelihood of unsuccessful biopsy and diagnostic delay.

Histological and Molecular Pathology

Case reports and small case series of DLGNT report moderate to hyper-cellularity and nuclear atypia without necrosis or mitotic figures. Specimens demonstrate positive staining for synaptophysin, S100, neuronal nuclei protein (NeuN), Olig2, and GFAP. The Ki-67 index is typically low, and an index greater than 7% is associated with a poorer prognosis. Previously reported molecular
pathology has included gain or loss of chromosome 1p, 15, 16 BRAF gene rearrangement, 18 and rarely, H2K27 mutations. 19 Cells are negative for isocitrate dehydrogenase-1 (IDH-1). 16, 20

The reported case displays many similar pathological features. H&E staining similarly demonstrated hyperproliferation involving the leptomeninges without mitotic figures or necrosis. Cellular staining was positive for GFAP, Olig2, S100, and synaptophysin. The Ki-67 proliferation index was 2%–5%, lower than the cutoff of 7% thought to be associated with a poorer prognosis. 17 FISH demonstrated chromosome 1p deletion, BRAF overexpression from amplification or duplication of chromosome 7, and a H3K27 gene mutation.

As reported by Xu et al., 15 patients with 1p/19q co-deletions, 1p or 19q deletions, or BRAF gene abnormalities may have a more aggressive course. This report supports this observation. Additionally, this case demonstrates a rare H3K27 mutation, which has only been reported in 2 case reports of DLGNT. 19, 21 H3K27 mutations more commonly occur in high-grade, aggressive midline glial tumors and are only rarely associated with low-grade tumors like DLGNT. 16, 21 These pathological findings may help explain the rapid disease progression in this patient.

Management Challenges

Communicating hydrocephalus is the most frequently reported clinical finding and may be a direct result of leptomeningeal membrane thickening and impaired CSF circulation and reabsorption. 22 CSF diversion procedures are often required for treatment of hydrocephalus in these cases. In DLGNT, the CSF may incur elevated protein levels, high cell counts, and alterations of CSF viscosity. These factors contribute to increasing resistance to CSF flow and CSF sedimentation and subsequent valve malfunction. 7 In this report, the patient required multiple ventriculoperitoneal shunt revision surgeries due to valve failure. All instances presented with symptoms of elevated intracranial pressure and symptomatic hydrocephalus. This finding is consistent with reports in the literature and demonstrates the challenges associated with CSF diversion in this patient population. 8, 23 In our report, no further shunt failures were noted after the placement of a valveless shunt system. This may represent a useful clinical observation for neurosurgeons facing a similar clinical dilemma.

In our case, chemotherapy with temozolomide and palliative craniospinal irradiation therapy were initiated but not completed due to a fatal thromboembolic event. Various treatment regimens have been proposed in the literature, including craniospinal irradiation and the use of chemotherapeutic or biological agents such as carboplatin, bevacizumab, and temozolomide. 8, 24–26 Craniospinal irradiation provides more targeted treatment and has been documented to improve clinical outcomes and slow disease progression. 4, 5 In addition, multiple groups found that carboplatin and vincristine were able to improve survival and halt disease progression. 8, 24, 26 Combined treatment regimens may be more promising as complete resection of the disease was achieved using both craniospinal irradiation and temozolomide in 1 case report of a teenager. 27 No consensus has been achieved on optimal treatment protocols because of limited reports of this disease in the literature.

Lessons

Our case highlights the diagnostic and therapeutic difficulties associated with DLGNT. The current epidemiology, pathophysiology, clinical presentation, imaging findings, and diagnosis of DLGNT are poorly understood. A high index of suspicion should exist in cases of leptomeningeal enhancement with communicating hydrocephalus in both adult and pediatric patients. Leptomeningeal biopsy early in the disease course may help prevent misdiagnosis and treatment delay; however, multiple biopsies may be needed. CSF shunting may be complicated by changes in CSF characteristics and patients should be monitored closely for evidence of shunt failure throughout their treatment. Valveless shunt systems may prove useful in patients with shunt failure due to high CSF protein. Further study is needed to better understand this complex disease entity to optimize patient outcomes.

References


**Disclosures**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author Contributions**

Conception and design: Heller, Bao, Sweeney. Acquisition of data: Bao, Sweeney, Liu, Genovese. Analysis and interpretation of data: Heller, Bao, Genovese, Adamo. Drafting of the article: Heller, Bao, Sweeney. Critically revising the article: Heller, Bao, Sweeney. Reviewed submitted version of the manuscript: Heller, Bao, Sweeney, Adamo. Approved the final version of the manuscript on behalf of all authors: Heller.


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