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Pediatric Diffuse Leptomeningeal Glioneuronal Tumors: Diagnosis, Follow-up, and Treatment Options

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ABSTRACT

AIM: To highlight the diagnosis, follow-up, and treatment options for diffuse leptomeningeal glioneuronal tumor (DLGNT) by examining pediatric patients diagnosed with DLGNT by molecular pathological evaluation and next generation sequencing at our center.

MATERIAL and METHODS: In this retrospective analysis, patients diagnosed with DLGNT between January 2017 and December 2022 are outlined according to their demographic data, radiological data, pathology results, treatments, and follow-up data.

RESULTS: Four patients were diagnosed with DLGNT. All the patients were male. The mean age was 6.5 years. All but one patient had symptoms of increased intracranial pressure. An open biopsy was obtained from all patients for diagnosis. Three patients received radiotherapy and chemotherapy after the diagnosis. Two patients died during their follow-up, one of them in the early postoperative period. Two patients were clinically and radiologically stable in their follow-up after treatment.

CONCLUSION: Further work with larger cohorts is required to determine a common algorithm for DLGNT treatment and follow-up. This analysis may keep this entity in mind in patients with pediatric communicating hydrocephalus and may present insight into diagnosis, follow-up, and treatment options.

KEYWORDS: Glioneuronal tumor, Leptomeningeal, Next - generation sequencing, BRAF-KIAA1549

ABBREVIATIONS: DLGNT: Diffuse leptomeningeal glioneuronal tumor, **WHO:** World Health Organization, **CT:** Computed tomography, **V-P:** Ventriculo-peritoneal, **MRI:** Magnetic resonance imaging, **NGS:** Next generation sequencing, **RT:** Radiation treatment, **Chx:** Chemotherapy, **ICP:** Intracranial pressure

INTRODUCTION

Diffuse leptomeningeal glioneuronal tumors (DLGNT) are tumors outlined in the World Health Organization (WHO) classification of central nervous system tumors in 2021 (19). DLGNT is more commonly found in children and in adolescents. They are mixed tumors that comprise both glial and neuronal components. They emerge as multiple subarachnoidal seedings with diffuse contrast enhancement, and plaque-like spread, and are characterized by subpial nodules. They are mostly observed in the spinal cord and basal cisterns (5). Patients may notice signs of hydrocephalus and/or signs of spinal cord involvement with back pain or motor deficits.

MATERIAL and METHODS

This retrospective study highlights pediatric cases diagnosed with DLGNT between January 2017 and December 2022. Four pediatric cases whose immunohistochemical, molecular pathological evaluations, and next generation sequencing (NGS) results conformed to DLGNT are presented. The patient demographics, their major complaints, and symptoms at the time of presentation, imaging findings, surgical reports,

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pathology reports, hospital progress notes, treatment outcomes, and follow-up visits were assessed, and all surgical interventions were conducted at a single center by the senior author (MMO) [Acibadem University Ethic Committee (ATADEK), Decision No: 2024-4/153; Date: 14.03.2024].

RESULTS

Clinical presentations and interventions of the cases are summarized in Table I and pathological findings are summarized in Table II.

Case 1

A five-year-old boy was admitted to the emergency department with the symptoms of vomiting and sleepiness. A cranial Computed Tomography (CT) scan discovered acute hydrocephalus. The patient underwent an emergency Ventriculo-Peritoneal (V-P) shunt operation. Elective cranial Magnetic Resonance Imaging (MRI) indicated multiple leptomeningeal contrast enhancements that designate tumor seedings. The patient also had a whole spinal MRI with contrast, which also highlighted multiple spinal pial seedings (Figure 1). The leptomeningeal biopsy acquired from the thoracal 3 spinal cord level indicated histopathologic and molecular findings in consistent with DLGNT. The tumor comprised glial and neuronal cells, showing synaptophysin (Figure 2C) and Olig-2 (Figure 2D) positivity. BRAF-KIAA1549 fusion (Figure 2I) and 1p/19q codeletion (Figure 2G, H) were observed by targeted NGS using the Acibadem Molecular Pathology Brain Tumors Panel, Miniseq Sequencing System, Illumina, and Archer Analysis Ver 6.0.3.2 platforms. Radiation treatment (RT) and chemotherapy (Chx) were recommended for the patient. Since the family refused to conduct RT, the patient received only Chx. The patient was put on Chx with low-grade glial tumor protocol. (Vincristine and Carboplatin). During his hospital stay in the oncology department, the patient consulted a pediatric neurosurgery clinic with CT outcomes of acute cerebellar hemorrhage (Figure 1B). The patient was operated on with emergency. The cerebellar hematoma was evacuated, along with the resection of an intraparenchymal hemorrhagic mass lesion. Pathology was also coherent with DLGNT (Figure 2F). The latest biopsy was much more cellular than the first biopsy with increased mitotic activity (Figure 2E). The postoperative period was uneventful. Due to the radiological progression of the lesions, the patient's chemotherapy was switched to a high-grade glial tumor chemotherapy protocol (Bevacizumab, Temozolomide, and Irinotecan). Since the patient's clinical condition kept worsening, the family agreed, and the patient had RT (36 Gy/20 Frc IMRT) 18 months after the initial diagnosis. The patient died in the second year of follow-up due to the advancement of the disease (Figure 1C, D) and aggravation of the general condition despite the treatment.

Table I: Summary of Clinical Presentation and Interventions About 4 DLGNT Cases

Patient	Sex	Age	Presentation	Neuroimaging	Treatment	Survival
1	M	5	Vomiting, sleepiness, headache	Diffuse leptomeningeal enhancement and thoracal intramedullary mass and hydrocephalus	Biopsy from thoracal intramedullary lesion Chx+RT	Died at 2nd year follow up
2	M	4	Headache	Diffuse leptomeningeal enhancement and cervical intramedullary mass	Biopsy from cervical intramedullary lesion Chx+RT	Alive at 9th follow-up
3	M	6	Headache	Diffuse leptomeningeal enhancement	Biopsy from right temporal lobe Chx+RT	Alive at 1st year follow-up
4	M	11	Low back pain	Diffuse leptomeningeal enhancement, thoracal intramedullary cystic lesion, and mild hydrocephalus	Biopsy from thoracal intramedullary lesion	Died due to extensive cerebral vasospasm

DLGNT: *Diffuse leptomeningeal glioneuronal tumor,* ***Chx:*** *Chemotherapy,* ***RT:*** *Radiation treatment.*

Table II: Summary of Pathological Findings in Four DLGNT Patients

Patient	Olig-2 Staining	Synaptophysin Staining	1p Status	19q Status	Ki67 Index	BRAF Status	IDH Mutation
1	+	+	Deleted	Deleted	15-20 %	+ (BRAF-KIAA1549)	-
2	+	+	Deleted	Deleted	1 %	+ (BRAF-KIAA1549)	-
3	+	+	Deleted	Deleted	2 %	+ (BRAF-KIAA1549)	-
4	+	+	Deleted	Deleted	4 %	+ (BRAF-KIAA1549)	-

DLGNT: *Diffuse leptomeningeal glioneuronal tumor.*

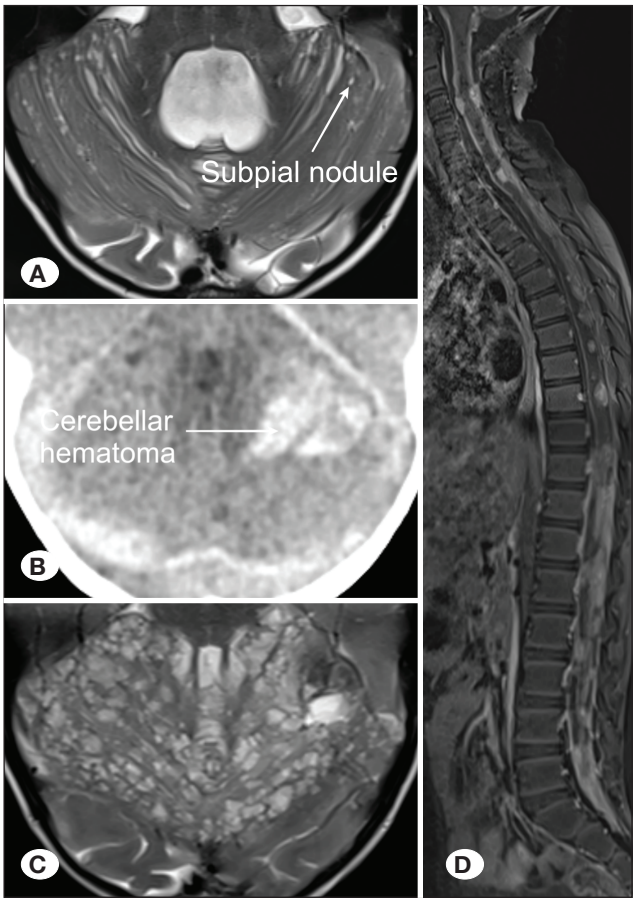

Figure 1: MRI of Case-1. **A)** T2W sequence axial cranial MRI showing cerebellar subpial hyperintense nodules; **B)** Cranial CT showing cerebellar hemorrhagic mass lesion; **C, D)** T1W contrast enhanced axial cranial MRI and sagittal whole spinal MRI showing the progression of the leptomeningeal lesions respectively.

Case 2

A four-year-old boy who was shunted in his hometown 2 years ago with the diagnosis of communicating hydrocephalus, was admitted to our hospital with symptoms of intractable headache. Cranial MRI detected T2 hyperintense diffuse leptomeningeal nodular cystic lesions (Figure 3A). The whole spinal MRI indicated diffuse leptomeningeal contrast enhancement and a cervical intramedullary cystic mass lesion (Figure 3C). V-P shunt was functional. A biopsy was acquired from a cervical lesion. The pathology result was constant with DLGNT, identified with the BRAF-KIAA1549 fusion and 1p/19q codeletion. The patient had RT (5040 cGy/28 Frc IMRT) and Chx (Vincristine and Carboplatin). The patient's general condition and lesions are still stable after three years.

Case 3

A six-year-old boy who had a history of V-P shunt surgery at another center, due to hydrocephalus, was admitted to our hospital. The physical examination discovered macrocephaly, and the neurological examination was normal. Craniospinal MRI presented diffuse leptomeningeal contrast enhancement. It was found that the lesions demonstrated more progression than the previous MRI. Infectious markers and serological tests were normal. Tuberculosis tests were normal. Pial and cortical biopsies were retrieved from the right temporal lobe. The tumor comprised glial and neuronal cells, showing synaptophysin and Olig-2 positivity. No IDH mutation was observed. BRAF-KIAA1549 fusion and 1p/19q codeletion were observed in NGS analyses. Histopathologic and molecular outcomes were coherent with DLGNT. The patient had an RT (5040 cGy/28 Frc IMRT) and Chx (Temozolomide, Trametinib, intrathecal Methotrexate, Cytosine Arabinoside, Dexamethasone) schedule. The patient's general condition and lesions improved during the second year of follow-up.

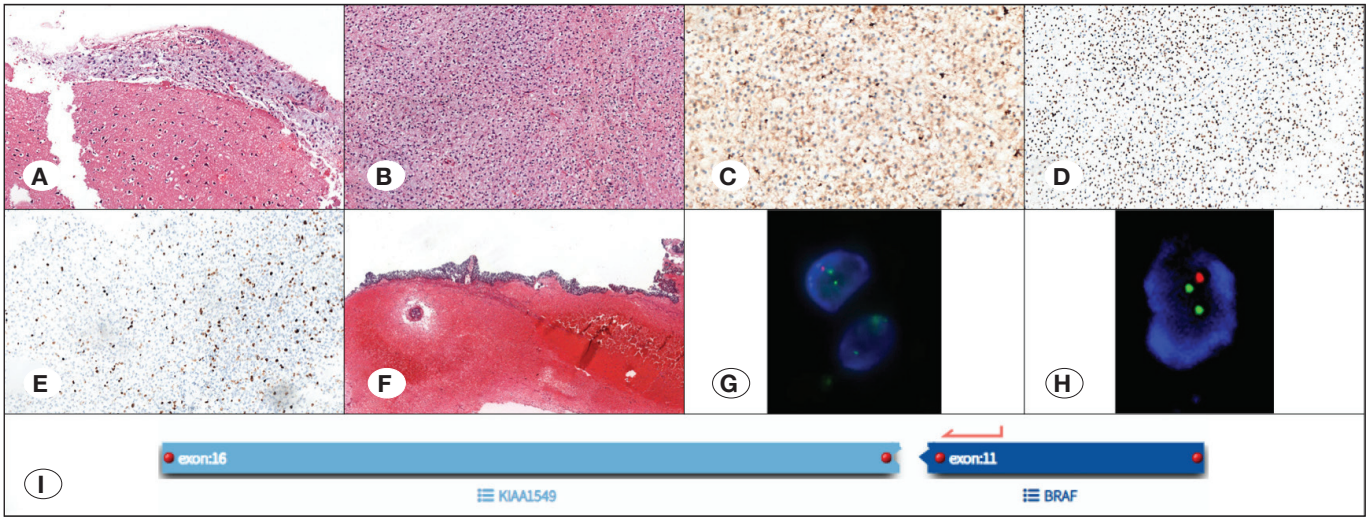

Figure 2: Photomicrographs of cases. **A)** The tumor typically infiltrates leptomeninges usually without parenchymal involvement, as seen in Case-3 (H&E, 200X); **B)** the cellularity may be low, moderate, or high. Moderate cellularity is observed in Case-1 (H&E, 200X); the neoplastic cells are typically immunopositive with **C)** synaptophysin as neuronal (Anti-Synaptophysin, 400X) and **D)** Olig-2 as the glial marker (Anti-Olig-2, 100X); **E)** the Ki67 proliferation index is high in Case-1 (Anti-MIB1, 100X); **F)** in Case-1 hematoma is surrounded by hypercellular tumor infiltrate (H&E, 40X); the neoplastic cells both show **G)** 1p and **H)**19q deletion by FISH analysis (Zytolight® Glioma 1p/19q Probe Set); (I) BRAF-KIAA1549 translocation is shown by NGS analysis.

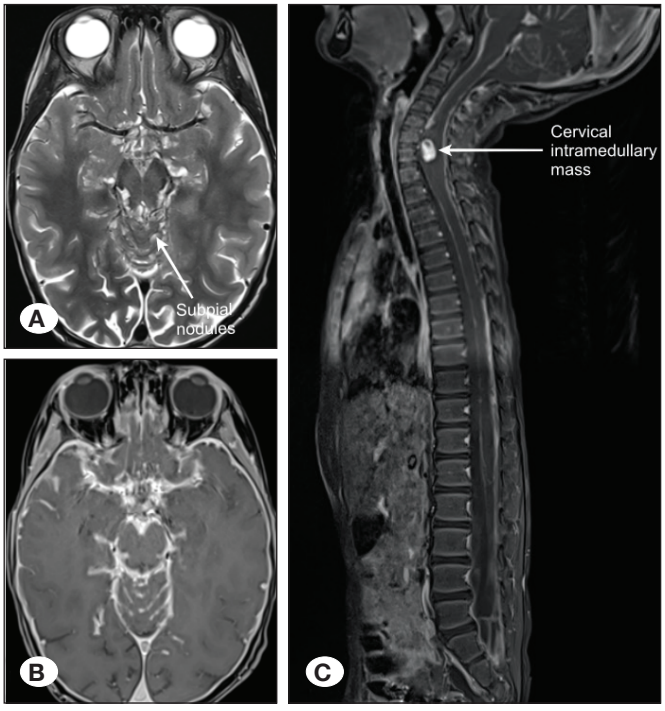

Figure 3: MRI of Case-2. **A)** T2W axial MRI shows the subpial nodules that extend basal cisterns and Willis's polygon; **B)** T1W contrast enhanced axial MRI shows leptomeningeal and cisternal diffuse contrast enhancement; **C)** T1W contrast enhanced whole sagittal MRI shows the cervical intramedullary mass lesion and leptomeningeal contrast enhancement.

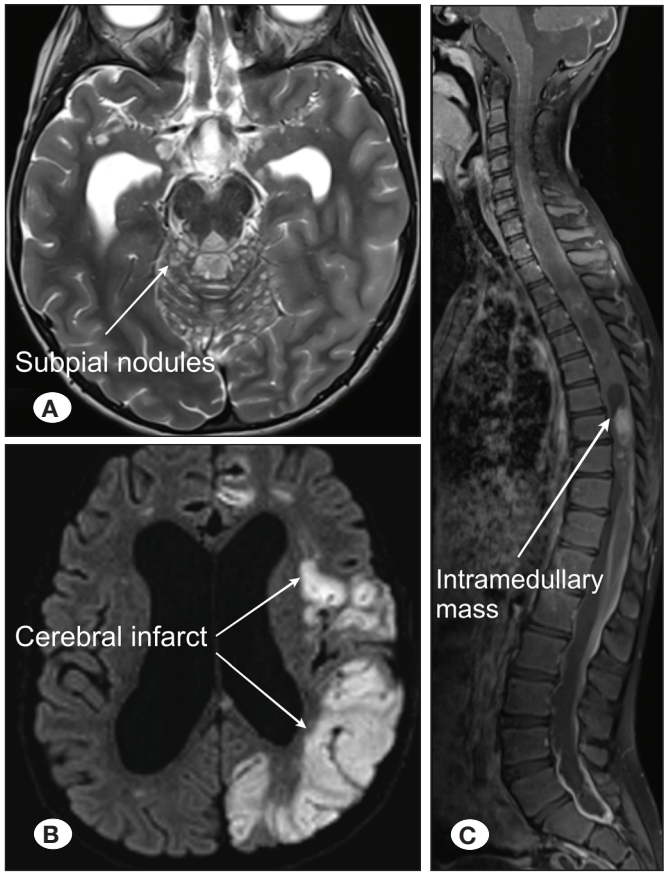

Figure 4: MRI of Case-4. **A)** Subpial nodules that extend basal cisterns are observed in T2W axial MRI; **B)** left cerebral infarction is seen in diffusion MRI **C)** thoracal intramedullary cystic tumor and leptomeningeal contrast enhancement is detected in T1W contrast enhanced whole spinal MRI.

Case 4

An eleven-year-old boy was admitted to our hospital because of low back pain. His neurological examination was normal. Thoracolumbar MRI indicated diffuse leptomeningeal contrast enhancement and a thoracal intramedullary cystic mass lesion (Figure 4C). The patient also had a cranial MRI, which indicated diffuse leptomeningeal nodular contrast-enhancing lesions and mild hydrocephalus. We acquired an excisional biopsy from a thoracal intramedullary lesion for pathological examination and NGS. Histopathological features (Synaptophysin and Olig-2 positivity) and NGS analyses (BRAF-KIAA1549 fusion and 1p/19q codeletion) are constant with DLGNT. On a postoperative day 3, the patient had progressive right hemiparesis, slurred speech, and sleepiness. Cranial MRI found left-sided temporal and parietal lobe watershed infarcts (Figure 4 B). Serial MRI scans discovered gradually increasing infarcts involving both the cerebral hemispheres. Transcranial Doppler ultrasound was coherent with cerebral vasospasm involving the circle of Willis and major cerebral arteries. Postoperative day 7, the patient lost light reflex, and both pupils became mydriatic. Neurological examination, brainstem reflex tests, and cranial CT angiography determined brain death.

DISCUSSION

DLGNT shows a different presentation with diffuse leptomeningeal involvement and cytologically indicating glial and neuronal differentiation. Before being included in the WHO classification, DLGNTs were regarded as diffuse leptomeningeal spreads of oligodendrogliomas or extraventricular neurocytomas (12). DLGNTs were listed as neuronal or mixed neuroglial tumors because they comprise oligodendroglial-like cells with variable neuronal components. Gardiman et al. called this entity DLGNT in 2010 for the first time (9).

Most studies on DLGNT in the literature consisted of retrospective analyses of patients who were diagnosed before the diagnostic criteria declared first in the WHO 2016 tumor classification system (12). The latest WHO classification CNS5 highlights that the clinical courses are comparable to those of CNS WHO Grade 2 entities for cases of conventional DLGNT and DLGNT MC-1 and to those of CNS WHO Grade 3 entities for tumors with anaplastic features, 1q gain, and/or the DLGNT MC-2 profile (19). The current research is important regarding its appliance of contemporary diagnostic criteria which had been complemented by molecular findings.

DLGNTs seem to be found mostly in pediatric patients, but there are also a growing number of adult case reports (7). Male gender dominance (1.6 / 1) is observed in meta-analyzes

containing case reports (6). Our report supports this outcome with all four cases being male. Although most DLGNTs are slow-progressing tumors, cases with anaplastic transformation have been observed (18,22). One of our cases also exhibited malignant features with hemorrhagic transformation during his follow-up period (Case-1).

MRI findings of DLGNT in the literature were prevalent leptomeningeal enhancement within the basal cisterns and spinal cord. On T2-weighted images, hyperintense cystic lesions (subpial cysts) are observed in the cerebellar folia, subarachnoid, and subpial space along the basal cisterns. Generally, no solid lesion is detected in the cerebral parenchyma. The spinal intramedullary mass appearance is not unusual and may be linked to hydromyelia (13,20). The MRI outcomes of our cases were coherent with the literature. Three of the cases had an intramedullary mass lesion from which biopsy samples were acquired (Figure 1, 3, 4).

Histologically, DLGNTs have oligodendroglial-like cytology. They express OLIG-2, S100, and synaptophysin. Unlike oligodendrogliomas, DLGNTs do not reveal IDH mutations (11,12). Most DLGNTs have low-grade histology and low mitotic index (mean value 1.5%). It has been found that few cases with cellular anaplasia and microvascular proliferation in addition to a high mitotic index have a more aggressive clinical course. DLGNTs were discovered to be substantially associated and linked to KIAA1549-BRAF fusion and 1p deletion. BRAFV600E mutation was not observed in most DLGNTs (16). In our report, the mitotic index in Case-1 (Figure 2E) and Case-4 were greater than in the literature (15–20 / 4). Clinically, two cases had a poor prognosis, Case-1 died in the second-year follow-up, and Case-4 died in the early post-op period. This may support that there may be a connection between the mitotic index and prognosis. All cases had 1p and 19q deletions (Figure 2G, H). BRAF-KIAA1549 mutation was positive in all cases (Figure 2I). Table II presents the pathological and molecular outcomes of the patients.

Before DLGNTs were included in the WHO classification, case reports with comparable clinical presentations and histopathological findings were outlined (3,8,9,14). Schniederjan et al. indicated nine pediatric cases that had increased intracranial pressure (ICP) symptoms and revealed prevalent leptomeningeal enhancement on MRI (17). In their literature review, Chen et al. discovered the rate of hydrocephalus in patients with DLGNT to be 82% (4). Garibotto et al. highlighted that revision was conducted due to dysfunction in two DLGNT patients with V-P shunt. They related this to cerebrospinal fluid biochemical properties (high protein level) (10). Constant with the literature, all our cases except Case-4 were diagnosed with elevated ICP findings. In Case-2 and Case-3, who were operated for hydrocephalus in different centers, contrast-enhanced MRI was not executed as an additional investigation, despite detecting subpial nodules in the T2 MRI sequence. We propose that; patients with obstructive hydrocephalus in the pediatric age group should be analyzed comprehensively, particularly in T2 sequence cranial MRI, and if there is an irregular pathology, MRI with contrast should be executed. No shunt dysfunction was experienced during the follow-up period. Case-1, presented with hemorrhage of cerebellar DLGNT lesions during the Chx and had been operated on for hemorrhagic tumor evacuation. In the analysis, we did not observe any other case with a diagnosis of DLGNT who had hemorrhagic tumor formation. This is the first case of hemorrhagic DLGNT in the literature. Case-4 died in the early post-op period due to advanced cerebral vasospasm. This is the first case of vasospasm in DLGNTs in the literature. We presumed that the spread of the tumor in the basal cisterns and the Willis polygon may influence this by affecting the feeding arteries here with the impact of compression and/or through chemical mediators.

Rodriguez et al. retrospectively evaluated low-grade glial, oligodendroglial, and glioneuronal tumors with leptomeningeal dissemination. They presented 36 pediatric patients whose pathological investigations were compliant with DLGNT. Immunohistochemically OLIG2 staining was positive in all tested patients with an absent IDH mutation. Chromosome 1p loss was commonly encountered. They stated that the number of mitoses on the first biopsy was linked to poor overall survival (OS). Age, gender cellularity, and 1p19q status were not correlated with OS (16).

Deng et al. undertook a study including DNA methylation, copy number variation, and a new gene sequencing analysis in 30 DLGNT cases. When they contrasted these findings with clinical neuropathological and radiological findings, they derived two groups with different molecular and clinical features. They named these groups DLGNT methylation class (MC) 1 and MC 2. The DLGNT MC 2 group was clinically more aggressive. They hypothesized that the DLGNT MC 1 group best corresponded with WHO Grade 1 and DLGNT MC 2 Group corresponded with WHO Grade 2-3 tumors. They finally suggested that the recurrent 1p deletion could be employed as a diagnostic biomarker and stimulation of the MAPK / ERK pathway could be used as a therapeutic biomarker (6).

There are few other prognostic studies on DLGNT in the literature. The longest follow-up period was 164 months (15). Xu et al. assessed 54 DLGNT patients from 19 studies in the literature concerning prognostic factors. They segmented the patients into two groups: poor prognosis and stable condition. Patients in the poor prognosis group were older and had extensive disease with an increased incidence of hydrocephalus. They proposed that DLGNT patients with 1p / 19q codeletion and BRAF fusions could stay stable for longer (21). In our series, unlike this study, two patients (Case-1 and Case-4) with 1p / 19q codeletion exhibited a poor prognosis and died during their follow-up.

Despite developments in clinical manifestations, radiological imaging findings, and diagnostic criteria for DLGNT, there is no prevalent algorithm in the literature regarding its treatment yet. In most reports published in the literature, it was mentioned that the disease demonstrated a partial response or remained stable to RT and/or low-grade glial tumor Chx (2,8,9,15). However, these patients may need to receive different Chx regimens in their follow-up, depending on the clinical course and the course of the disease (1). Targeted therapy regimens should be designed. In our series, Case-2

and Case-3 received RT treatment. RT was initialized in the late phase of the disease because of the patient rejection and could not be completed due to the worsening of the general condition of Case-1 during the treatment process. More than one chemotherapy regimen was employed during the treatment in Case-1, who had a poor prognosis. Case-2 was stable with RT and low-grade glioma chemotherapy. Patient-3 is stable after RT, temozolomide, trametinib, and intrathecal chemotherapy treatments.

CONCLUSION

DLGNT is an uncommon entity. We should consider it during the differential diagnosis of patients who had communicating hydrocephalus and diffuse leptomeningeal lesions. In the diagnosis of the disease, a molecular analysis should be executed with histological parameters. NGS technology is crucial for a better understanding of tumor genetics and to determine possible targeted therapy agents. There remains no common approach in the literature about the treatment of DLGNT. More studies are required to improve therapy and better comprehend tumor biology.

AUTHORSHIP CONTRIBUTION

Study conception and design: AO
Data collection: AO, BT
Analysis and interpretation of results: AO, BT, AED, MMO
Draft manuscript preparation: AO, BT, AED, MMO
Critical revision of the article: MMO
Other (study supervision, fundings, materials, etc...): MMO
All authors (AO, BT, AED, MMO) reviewed the results and approved the final version of the manuscript.

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