A case of diffuse leptomeningeal glioneuronal tumor in a 10-year-old boy: First report from Iran

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Abstract
A 10-year-old boy who was referred due to acute hydrocephalus symptoms was diagnosed as the first case of pediatric DLGNT in Iran. The results suggested that using shunting for hydrocephaly and anti-seizure medicines, as well as chemotherapeutic agents, can be an effective treatment strategy for DLGNT. Although the patient was stable without a tumor recurrence for a limited follow-up period of 22 months, further studies are expected.

KEYWORDS
brain tumor, children, Diffuse leptomeningeal glioneuronal tumor (DLGNT), hydrocephalus

1 | INTRODUCTION

Diffuse leptomeningeal glioneuronal tumor (DLGNT) is a rare neoplasm, which was previously known as a disseminated oligodendroglia-like leptomeningeal tumor of childhood. DLGNT has been defined as a neuronal/glioneuronal tumor in the 2016 World Health Organization (WHO) classification of brain tumors.1 However, DLGNT has not yet been graded by WHO because of a limited number of case reports.2,3 Most of these tumors have a slowly progressive course, but in a few cases, an anaplastic transformation has been reported.4,5 Predominant diffuse abnormal nodular leptomeningeal enhancement without a definite intraparenchymal mass associated with subpial
Cyst formation that almost coats the brain surface is the most common imaging feature. However, some DLGNT cases without diffuse growth and leptomeningeal dissemination have been reported. There is still no specific treatment for patients with DLGNT.

According to the previous reports, clinical presentations are dominated by hydrocephalus due to the pronounced development of the tumor within the subarachnoid space. Appay et al. reported two unexpected adult cases of DLGNTs, characterized by a unique supratentorial circumscribed intraparenchymal tumor without leptomeningeal involvement during long-term follow-up. Chen et al. presented a case-based review summarizing the clinical characteristics and potential treatments of DLGNT. To the best of our knowledge, no case of DLGNT was reported from Iran, so far, and also, a limited number of studies have been reported about managing pediatric DLGNT in the English literature. Therefore, a further pathological investigation is still needed for better understanding toward appropriate treatment. In this case report, we performed radiological, histological, and immunohistochemical assessments of a 10-year-old boy with DLGNT. The suggested treatment approach has been conducted as well.

2 | CASE REPORT

A 10-year-old boy was admitted to the pediatric neurology department of the Mofid Children’s Hospital, Tehran, Iran. He was referred with headaches and vomiting prolonged for 20 days. It should be noted that 6 months prior to admission, the patient was suffering from occasional headaches and vomiting. Neurological examination at that time showed the following: consciousness, tone of all extremities being normal without gait disturbance, and bilateral normal deep tendon reflexes (DTR++). Bilateral papillary edema was evident on ophthalmoscopy examination. In the CSF specimen, protein levels increased slightly (41 mg/dl) and glucose levels and white blood cell (WBC) counts were normal. Moreover, the cytological study of CSF revealed no tumor cell. The initial MRI performed at another institution 3 days after the first clinical events, revealed no significant findings except for non-obstructive four ventricular hydrocephalus and faint leptomeningeal enhancement in cerebral fluid and the basal cistern. A ventriculoperitoneal shunt was embedded, and the patient was discharged in good general condition without vomiting. After three months of follow-up, the patient complained of occasional headaches and daily vomiting. Due to headache and vomiting accompanied by one seizure attack with sudden hemiparesis of the right side of the body, unintelligible speech, lateral gaze, and drowsiness, the patient was hospitalized again.

In the new neurological examination, there was no particular problem, except for the weakness of the right limb. Consciousness, cognition, cranial nerves, motor function, speech, cerebellar tests, and sensory examination were normal. Moreover, there was no gait disorder, the plantar reflex was flexor, and the skin examination did not show hypopigmented or Café-au-lait spots. EEG was performed, and no significant abnormality was observed. The glucose and protein levels of the CSF specimen were 70 mg/dl and 45 mg/dl, respectively, and the WBC count was zero. Sodium valproate was started for seizure attacks. The new MRI performed right after hospitalization at the Mofid Children’s Hospital indicated cystic lesions in the frontal lobe and lateral ventricle near the temporal horn and enlarged ventricles. The latest MRI, which is illustrated in Figure 1, showed aggravation of diffuse nodular leptomeningeal enhancement, especially in the basal cistern and posterior fossa along with small subpial cystic lesions in basal frontal lobes, mesial temporal regions, and prominent Virchow-Robin space around basal ganglia. T2 and fluid-attenuated inversion recovery (FLAIR) images showed added Virchow-Robin space and small subpial cysts in the bilateral frontal lobe surface. Post-contrast T1W axial and sagittal images showed thick nodular enhancement of leptomeninges in the brain and in the anterior surface of the cord. Pachymeningeal enhancement as an additional finding in follow-up MRI after shunt insertion is justified by a ventriculoperitoneal shunt.

A leptomeningeal and brain biopsy of the right medial frontal lobe was performed. Histological and immunohistochemical studies revealed a marked expansion of leptomeninges with mixed infiltration of relatively monomorphic spindle myofibroblastic-like and nests of round oligo-like or epithelioid cells with clear or scant eosinophilic cytoplasm (Figure 2A). The desmoplastic background was noted in a more superficial layer accompanied by the only infiltration of rare small lymphocytes. These tumor cells were diffusely and strongly positive for oligodenoglioma 2 (OLIG2) (Figure 2B) and S100 protein (Figure 2C) and negative for glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA), and cytokeratin. Synaptophysin was weakly positive. There was no evidence of anaplasia, and Ki-67 proliferative index activity was low (Figure 2D). Based on the above-mentioned histological and MRI findings, a DLGNT diagnosis was made. Consequently, the patient was referred to chemotherapy treatments.

However, because of some personal reasons, the patient did not start chemotherapy treatment right after. One month later, the patient again experienced a right focal seizure with eye blinking. Therefore, the patient was treated with phenytoin (100 mg/day), depakene (1000 mg/day), and acetazolamide (250 mg/day). After recovering
from the seizure, the patient was treated with temozolomide daily for five days, carboplatin, and vincristine (one dose weekly). As a result, the patient’s headache and vomiting were greatly improved clinically.

3 | DISCUSSION

Most of the existing studies on DLGNT have been presented in the general pathology and oncology literatures. So many tumors may have been previously misdiagnosed by clinicians, especially pediatric neurologists; however, considering DLGNT’s somehow distinctive imaging presentation, rapid biopsy, and correct diagnosis with a suitable treatment of patients could improve the symptoms. It is important to confirm MRI findings by histological and immunohistological assessments; however, sampling error should be considered in a small piece of tissue.12

Generally, patients with DLGNT show almost similar MRI manifestations.13,14 The initial MRI of our case revealed no significant findings except for non-obstructive four ventricular hydrocephalus and faint leptomeningeal enhancement in cerebellar folia and basal cistern. Therefore, shunt insertion was applied for our patient who was suffering from a recurrence of symptoms of headache and vomiting. The follow-up MRI (6 months after shunting) revealed multiple small hyperintense cysts on T2 images and isohypointense cysts on T1 and FLAIR images scattered across the surfaces of the central nervous system (CNS). According to the literatures, case reports of the spinal cord DLGNT are limited in number and have described variable presentations and management.12 In our case, thick nodular enhancement of leptomeninges in the brain and also in the anterior surface of the cord was observed.

According to Chen et al., 2015, a discrete intraparenchymal lesion (usually in the spine) has also been observed.14 On the contrary, our case showed non-obstructive four ventricular hydrocephalus in the initial MRI imaging. However, the follow-up MRI (after 6 months) showed the aggravation of diffuse nodular
leptomeningeal enhancement, especially in the basal cistern and posterior fossa along with small subpial cystic lesions in basal frontal lobes, mesial temporal regions, and prominent Virchow-Robin space around basal ganglia. T2 and FLAIR images showed added Virchow-Robin space and small subpial cysts in bilateral frontal lobe surface, and intracranial lesions were also found. Similarly, Cho et al. (2015) and Gardiman et al. (2010) observed superficial parenchyma or Virchow-Robin space involvement.6,15

It has been previously reported that DLGNTs are low-to-moderate cellularity lesions consisting of relatively monomorphous oligodendrocyte-like cells with a “glioneuronal commitment,” embedded in a desmoplastic or myxoid leptomeningeal stroma.1,6 Similarly, the present case showed the expansion of leptomeninges with mixed infiltration of relatively monomorphic spindle myofibroblastic-like and nests of round oligo-like or epithelioid cells with clear or scant eosinophilic cytoplasm. Consequently, the tumor cells from our case were diffusely and strongly positive for OLIG2 and S100 protein; also, they were negative for GFAP, EMA, and cytokeratin. Synaptophysin was weakly positive. The results showed that there was no evidence of anaplasia and Ki-67 proliferative index activity was low. Similar results have been observed previously.1,11,14,15

In the treatment process of DLGNT, symptomatic treatment of hydrocephalus is quite important. For example, ventriculoperitoneal shunts and mannitol are effective for patients with hydrocephalus. Therefore, a ventriculoperitoneal shunt was embedded for the present case because of severe hydrocephalus during the initial phase of the disease. For DLGNT treatment, we have used multiple combination therapy of chemotherapy besides the oral temozolomide or vincristine and carboplatin to improve clinical symptoms. As a result, the chemotherapy started for our patient with temozolomide, carboplatin and vincristine. Consequently, the patient showed no seizure any longer, and additionally, headache and vomiting were greatly improved clinically.

4 | CONCLUSION

Here, we reported a case of DLGNT in a 10-year-old boy for the first time from Iran. Most of the symptoms of DLGNT were not specific; so when a patient presents with persistent vomiting, headache, and hydrocephalus in CT scan or MRI imaging, in the absence of clinical and laboratory signs of chronic infections, such as meningitis or tuberculosis, there should be a suspicion of DLGNT, especially in young male children as a result of this case study. When the diagnosis is suspected, a prompt biopsy should be performed to reduce the time to definitive diagnosis and treatment. We suggest that using temozolomide, carboplatin, and vincristine can be an effective treatment strategy for DLGNT.

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CONFLICT OF INTEREST

On behalf of all of the authors, the corresponding author states that there is no conflict of interest.
AUTHOR CONTRIBUTIONS
Parvaneh Karimzadeh: supervised and drafted the work. Yalda Nilipour: contributed to pathological finding and conceptualized the study. Mitra Khalili: involved in radiological interpretations. Ali Nikkhah: analyzed, interpreted, and validated the study. Mehdi Taghavijelodar: contributed to methodology, wrote the original draft, and edited the manuscript. Ehsan Moradi: performed biopsy and shunting for hydrocephalus.

CONSENT
Written informed consent was obtained from the patient.

DATA AVAILABILITY STATEMENT
The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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