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Case Report

Atypical and aggressive diffuse leptomeningeal glioneuronal tumor in a young adult: A case report and review of the literature

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ABSTRACT

Background: DLGNT is a rare tumor, commonly diagnosed in pediatric age; in most cases, the pathology presents a slow and indolent evolution. We present a case report of a young adult affected by DLGNT characterized by aggressive and atypical behavior.

Case Description: A 21-year-old male presented with mild paraparesis and hypoesthesia with a D2 level. MRI scan of the brain and spine showed a dorsal intramedullary lesion; a diffuse craniospinal leptomeningeal thickening was also present. After a week, the neurological status deteriorated rapidly with paraparesis worsening and onset of acute hydrocephalus. The patient underwent external ventricular drain positioning; a C7-D4 laminectomy was subsequently performed with partial tumor resection. Histological examination revealed a DLGNT with aggressive aspects (Ki67 30%). Postoperatively, the patient showed an immediate mild worsening of the lower limbs deficit. After a few days, severe further neurological deterioration occurred with progressive motor deficit to the upper limbs and ultimately respiratory failure. Mechanical ventilation was necessary and the patient was transferred to the ICU; during the following weeks, he developed tetraplegia and underwent ventriculoperitoneal shunt positioning. By the time, the histological diagnosis was available, the clinical status would not allow radiotherapy or chemotherapy. The patient deceased approximately 90 days after hospitalization due to respiratory complications.

Conclusion: DLGNT is a rare tumor; diagnosis requires a high index of suspicion and confirmation with biopsy. Although most cases have an indolent course, some patients may have aggressive forms. High proliferation index, hydrocephalus occurrence, and massive craniospinal leptomeningeal spread appear to be associated with worse prognosis.

Keywords: Brain tumor, Central nervous system tumor, Diffuse leptomeningeal glioneuronal tumor, DLGNT, Spine tumor

INTRODUCTION

The diffuse leptomeningeal glioneuronal tumor (DLGNT) is a rare neoplasm. Described as a distinguished entity in the 2016 WHO classification of tumors of the central nervous system (CNS),[17] it was initially referred to with this term by Gardiman *et al.*[9] in 2010. Other authors

used names such as disseminated oligodendroglial-like leptomeningeal tumor,[13,27] diffuse leptomeningeal neuroepithelial tumor,[31] and superficially disseminated glioma.[2] Based on the morphological description and immunohistochemical profile, it appears that these previous reports have all been describing the same entity. It is a rare tumor, commonly diagnosed in pediatric age although adult patients have been reported. Radiologically, they are characterized by a diffuse leptomeningeal enhancement (DLE) on magnetic resonance imaging (MRI), usually involving the spinal cord and basal cisterns. Cystic T2 hyperintense lesions without contrast-enhancement are frequently found.[6,7,27] DLE is peculiar but some cases show concomitant single or multiple solid encephalic or spinal lesions. Occasionally, these lesions are isolated, with no leptomeningeal involvement. In most cases, the pathology presents a slow and indolent evolution, but cases with very aggressive behavior and poor prognosis have been described.[6,7,27]

The WHO has not yet assigned a grade to this neoplasm due to the limited number of cases described and clinical, treatment, and outcome heterogenicity. Moreover, the literature data are insufficient to formulate guidelines or suggest a standard management[16] and there are no clear prognostic factors.

A young adult affected by DLGNT characterized by aggressive and atypical behavior was recently treated in our center, with rapidly evolving poor prognosis. We describe the case and report a review of the literature.[15]

MATERIALS AND METHODS

Case description

In June 2020, a 21-year-old male was admitted to our department after 2 weeks onset of headache, mild paraparesis (right side worse than left side), tactile, and thermic hypoesthesia with a D2 level. A contrast-enhanced MRI scan of the brain and spine showed an intramedullary lesion extending from D1 to D5. The cranial portion of the tumor presented an apparently exophytic extramedullary component which extended on the right posterolateral side up to C7 [Figure 1]. A diffuse craniospinal leptomeningeal thickening was also present [Figure 2]. A total-body CT scan ruled out lesions outside the CNS and cerebrospinal fluid (CSF) analysis excluded infection. Corticosteroid therapy was administered with no clinical improvement. After a week, the neurological status deteriorated rapidly with paraparesis worsening and onset of hydrocephalus with headache, emesis, and lethargy. The patient, therefore, underwent external ventricular drain positioning, once again, cultural and cytologic CSF analysis was not diagnostic. A C7-D4 laminectomy was subsequently performed. Intraoperatively, the spinal cord appeared swollen and distorted, with difficult to identify the apparent exophitic nodule. The tumor was then approached with intraoperative ultrasound and functional mapping with direct electrical stimulation with a monopolar probe.[22,23] The procedure was interrupted due to sudden deterioration of the motor evoked potentials; then, to decompress the spinal cord, a duraplasty was completed using a dural patch and a pedicled multifidus muscle flap was performed to decrease the risk of CSF leakage.[21,29]

Postoperatively, the patient showed an immediate mild worsening of the lower limbs deficit. After a few days, severe further neurological deterioration occurred with progressive motor deficit to the upper limbs and ultimately respiratory failure. Mechanical ventilation was necessary and the patient was, therefore, transferred to the Intensive Care Unit. During the following weeks, he developed tetraplegia and underwent surgery for ventriculoperitoneal shunt positioning. By the time, the histological diagnosis was available; the clinical status would not allow radiotherapy (RT) or chemotherapy

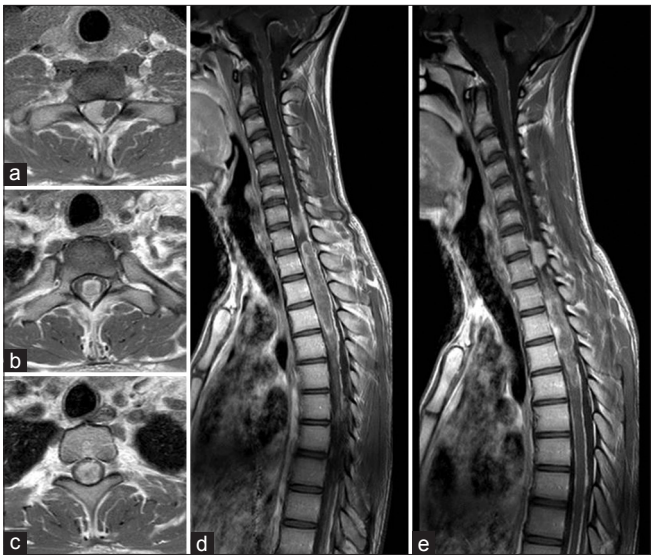

Figure 1: Preoperative spine MRI with gadolinium showing cervicothoracic intramedullary tumor; panel (a-c) axial scans, respectively, at level C7-T1 (a), T2-T3 (b), and T4 (c). Panel (d and e) sagittal scans.

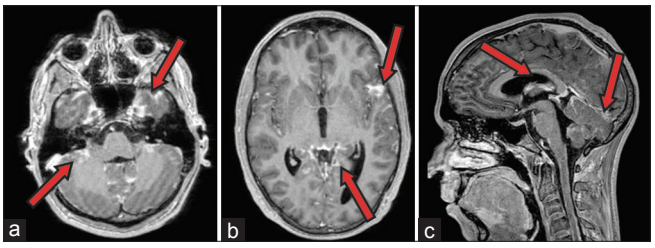

Figure 2: Panel a: Axial scan at level of the posterior cranial fossa (infratentorial). Panel b: Axial scan at level of supratentorial space. Panel c: Sagittal scan showing supra- and infratentorial spaces. Red arrows indicate multiple areas of leptomeningeal thickening.

(ChT). The patient deceased approximately 90 days after hospitalization due to respiratory complications.

Histopathological findings

At histological examination, the lesion showed sections of solid neoplasm consisting of small cells proliferation with scarce cytoplasm and round nucleus and larger cells with light cytoplasm, small nucleus, and chromatin granules. The cells were arranged in perivascular aggregates and showed oligodendroglial-like aspects. Immunohistochemistry showed positivity for CD65, GFAP, S100 protein, synaptophysin, olig2 and negativity for EMA, CD45, IDH1 and BRAF V600E mutation, negative BRAF fusion, absence of 1p deletion, or 1p/19q codeletion. Ki-67 was 30%. Diagnosis was consistent with DLGNT.

We conducted a literature review of prior reported case report and case series dealing with DLGNT to identify potential prognostic factors and treatment strategies.

The search was limited to papers in English language published between 2009 and 2020. The only papers considered eligible were those containing a clear description of the clinical, radiological, and pathological features as well as the type of treatment, the outcome, and a minimum 6-month follow-up (FU) (except for cases with lower survival).

Data regarding the patients' demographic characteristics, symptoms at clinical onset, neuroimaging, presence/absence of hydrocephalus, presence/absence of intraparenchymal lesions, molecular features, type of treatment (surgery, ChT, and RT), outcome, and FU length were collected from the selected papers.

We analyzed the potential prognostic significance of age, radiological appearance (leptomeningeal thickening/intraparenchymal nodules), hydrocephalus, proliferation index (PI) (Ki67), molecular features (BRAF status, 1p deletion, and 1p/19q codeletion), and type of treatment.

RESULTS

The literature search yielded 26 articles dealing with DLGNT that clearly met our inclusion criteria:[1-5,7-9,11-14,18-20,24,27,28,30-35,37,38] 14 case report e 12 case series for a total of 100 treated patients. Our case was added to the total number.

All data regarding the patients are represented in [Table 1]. Based on the outcome, the patients were divided in two groups; the first group includes deceased patients (poor-outcome group), and the second group includes patients with stable disease or in slow progression at the time of FU (better outcome group) including a patient with slowly progressive disease who died 20 years after diagnosis. [Table 2] summarizes and compares the main characteristics between the two groups. [Table 3] summarizes average mortality and overall survival (average and range) regarding to age, hydrocephalus, ki-67, ChT, RT, and surgery.

The case histories comprehend 100 patients, 61 males and 39 females.

Average FU of the whole group was 53 months, range 1–240 months. In 22 cases, the patients died because of the disease, average OS 43 months (range 1–240); a patient who die after 20 years was included in the group of patients with better prognosis [Table 2]. At last FU among the 78 living patients, 17 cases of disease progression, 26 cases of stable disease, and 35 undefined cases were described (average FU 56 months, range 1–240).

Age at diagnosis

Average age at diagnosis was 10.5 years, median 5 years, and mode 3 years. Minimum age at clinical onset was 0.5 years and maximum age was 62 years. Overall eight patients were older than 30 (adults), seven were between 18 and 30 (young adults), 17 were between 11 and 17 (teenagers), and 68 were between 0 and 10 (children). In the children group, 51 patients were between 0 and 5 and 17 patients were over 5.

Average age at diagnosis resulted higher in the poor-outcome group (14 years vs. 9 years). Mortality 16% (10pt/62) in patients aged 0–8 years versus mortality 32% (12pt/38) in patients older than 8 years.

Clinical onset

Signs and symptoms at clinical onset were heterogeneous and appeared to correlate with the location and extension of the tumor. Signs and symptoms related to hydrocephalus were the most common. Headache is reported as the initial symptom in 45% of cases, both isolated or associated with nausea/vomiting and decreased level of consciousness. Seizures occurred in 15% of cases. Spinal cord or radicular compression syndromes (paraparesis, tetraparesis, ataxia, and radiculopathy) were described in 14% of patients. Meningismus (rigor nucalis, radicular irritation, and photophobia) was present in 10% of cases. Cerebellar syndromes, visual disturbances, aphasia, hemiparesis, scoliosis, pain, behavior disorders, and cranial nerves deficits were also described with the lower incidence.

Based on clinical presentation, no substantial differences were appreciated between the two outcome groups.

Neuroimaging

The typical brain and spine DLE features on MRI were reported in 72 patients. In 15 cases, meningeal involvement was present only at the cerebral level while in seven cases, it was limited to the spine. Altogether 46 solid intraparenchymal

Table 1: Summary of the included study with relevant patients' characteristics.

S. No.	Author	Patients	Male/ Female	Age (years)	Leptomeningeal thickening	Intraparenchymal solid mass		Hydrocephalus	Shunt	Pathological findings/ Immunohistochemistry	Ki-67	Surgery	Chemotherapy	Radiotherapy	Follow-up (months)	Deaths
					Single/multiple/brain/spine	Brain	Spine									
1.	Aguilera *et al.* 2017	7	M	2	Multiple DLE - Spine	0	0	0	0	S100, GFAP, synaptophysin, BRAF V600E mutation negative	2–15%	Biopsy	CV - Temozolomide	No	15	0
			M	2	Multiple DLE - Brain/Spine	0	0	0	0			Biopsy	CV	No	122	0
			F	7	Multiple DLE - Brain/Spine	0	0	0	0			Biopsy	CV - Temozolomide	No	24	0
			M	3	Multiple DLE - Brain/Spine	0	0	0	0			Biopsy	Temozolomide	No	144	0
			M	3	Multiple DLE - Brain/Spine	0	0	0	0			Biopsy	Temozolomide - CV	No	94	0
			F	4	Multiple DLE - Brain/Spine	0	0	0	0			Biopsy	Temozolomide	Cranio-Spinal RT	164	0
			F	3	Multiple DLE - Brain/Spine	0	0	0	0			Biopsy	Temozolomide - CV	No	28	0
2.	Xu *et al.* 2019	1	M	25	Single Parietal solid mass	1	0	0	0	S100, GFAP, synaptofisin, olig2, BRAF mutation, 1p deletion	4%	Resection	No	Yes	12	0
3.	Fiaschi *et al.* 2018	1	F	35	Multiple DLE - Brain	1	0	0	0	S100, GFAP, synaptofisin, olig2, BRAF V600E negative	25%	Resection	No	No	6	1
4.	Lyle *et al.* 2015	1	F	14	Multiple DLE - Brain/Spine	0	0	1	1	GFAP, synaptophysin, olig-2	Nd	Biopsy	Temozolomide	Cranio-Spinal RT	26	0
5.	Abongwa *et al.* 2020	3	M	6	Multiple DLE - Brain/Spine	0	0	1	1	GFAP, Synaptophysin, NSE	2%	Biopsy, Surgical decompression	CV - Temozolomide	No	156	0
			F	4	Multiple DLE - Brain/Spine	0	0	1	1	GFAP, S100, synaptophysin	2%	Biopsy	Temozolomide - CV	Yes	204	0
			M	2.5	Multiple DLE - Brain	0	0	1	0	Synaptophysin, S100, GFAP	2%	Biopsy	CV - Temozolomide	No	12	1
6.	Agamanolis *et al.* 2012	3	M	4	Multiple DLE - Brain/Spine	0	1	1	1	1p deletion	5%	Biopsy - resection spinal nodule	CV	no	48	0
			M	5	Multiple DLE - Brain/Spine	0	0	0	0	1p deletion	1%	Biopsy	No	no	36	0
			F	9	Multiple DLE - Brain/Spine	0	0	1	1	S100, beta III-tubulin	20%	Biopsy	V, cyclophosphamide, Temozolamide	Cranio-Spinal RT	24	1
7.	Gardiman *et al.* 2009	4	M	4	Multiple DLE - Brain/Spine	0	0	1	1	Synaptophysin, S100, GFAP	1%	Biospy	Temozolamide	No	24	0
			F	3	Multiple DLE - Brain/Spine	0	1	1	1	Synaptophysin, S100, GFAP	1%	Biopsy - resection spinal nodule	Yes	No	72	1
			F	3	Multiple DLE - Brain/Spine	0	1	1	0	Synaptophysin, S100, GFAP, 1p deletion	0%	Biopsy - resection spinal nodule	Yes	Yes	72	0
			M	13	Multiple DLE - Brain/Spine	0	0	1	0	Synaptophysin, S100, GFAP	1%	Biopsy	No	No	18	0
8.	Kang *et al.* 2018	1	F	28	Single spinal nodule	0	1	0	0	Synaptophysin, S100, 1p/19q codeletion, BRAF fusion	10%	Resection (subtotal)	No	Yes	72	0
9.	Karlowee *et al.* 2017	1	M	17	Multiple DLE - Brain	0	0	1	1	GFAP, Olig2, synaptophysin, S100, ATRX and MGMT, 1p deletion	40%	Biopsy	No	Yes	10	0
10.	Kessler *et al.* 2014	1	F	12	Multiple DLE - Brain/Spine	0	0	1	1	Synaptophysin, olig-2	Nd	Biopsy	CV, tacrolimus	Cranio-Spinal RT	13	1
11.	Lee *et al.* 2018	1	M	62	Multiple DLE - Brain/Spine	0	0	1	1	Synaptophysin, olig-2, MGMT	5%	Biopsy	Procarbazine, CCNU	Cranio-Spinal RT	60	0
12.	Tiwari *et al.* 2020	1	F	3	Multiple DLE - Brain/Spine	0	1	1	1	Olig-2, BRAF V600E negative	1%	Biopsy	CV	No	12	0

(Contd...)

Table 1: *(Continued).*

S. No.	Author	Patients	Male/ Female	Age (years)	Leptomeningeal thickening	Intraparenchymal solid mass		Hydrocephalus	Shunt	Pathological findings/ Immunohistochemistry	Ki-67	Surgery	Chemotherapy	Radiotherapy	Follow-up (months)	Deaths
					Single/multiple/brain/spine	Brain	Spine									
13.	Yamasaki *et al.* 2018	1	M	22	Multiple DLE - Brain/Spine	0	0	1	1	Synaptophysin, S100, GFAP, 1p deletion	5%	Biopsy	Temozolomide, Bevacizumab	Cranio-Spinal RT	54	1
14.	Appay *et al.* 2020	2	F	35	Single Parietal solid mass	1	0	0	0	Synaptophysin, olig-2, BRAF V600E, 1p/19q codeletion	10%	Resection	No	No	240	0
			F	31	Single Parietal solid mass	1	0	0	0	Synaptophysin, olig-2, BRAF fusion, 1p/19q codeletion	3%	Resection	No	No	120	0
15.	Tiwari *et al.* 2019	1	F	13	Single spinal nodule	0	1	0	0	GFAP, Olig-2, 1p/19q codeletion, BRAF fusion	2%	Resection	No	No	18	0
16.	Schwetye *et al.* 2017	2	M	9	Multiple DLE - Brain/Spine	0	0	1	1	Synaptophysin, olig-2, GFAP	53%	Biopsy	Temozolomide, BCV	Cranio-Spinal RT	12	1
			M	7	Multiple DLE - Brain/Spine	1	0	1	1	Synaptophysin, vimentin	1%	Biopsy	CV, irinotecan	No	36	0
17.	Valiakhmetova *et al.* 2020	2	M	8	Multiple DLE - Brain/Spine	0	0	1	1	BRAF V600E	Nd	Biopsy	CV, vermufenib	No	24	0
			M	2	Multiple DLE - Brain/Spine	0	0	1	1	BRAF fusion	Nd	Biopsy	Trametinib	No	25	0
18.	Cho *et al.* 2014	3	M	62	Multiple DLE - Brain/Spine	1	0	1	1	Synaptophysin, olig-2, GFAP	38%	Resection (subtotal)	Temozolomide	Cranio-Spinal RT	1	1
			M	22	Multiple DLE - Brain/Spine	1	0	0	0	Synaptophysin, olig-2, GFAP	1%	Resection	No	No	35	0
			M	11	Multiple DLE - Brain/Spine	0	0	1	1	Synaptophysin, olig-2, GFAP	4%	Biopsy	Chemoterapy	No	23	0
19.	Peerboccus *et al.* 2017	1	M	4	Multiple DLE - Brain/Spine	0	1	1	1	Olig-2, GFAP	3%	Biopsy	CV	No	48	0
20.	Schniederjan *et al.* 2013	9	M	2.5	Multiple DLE - Spine	0	0	1	1	Synaptophysin, S100, 1p deletion	10%	Biopsy	Temozolomide	No	68	0
			M	3	Multiple DLE - Brain/Spine	0	1	0	0	Synaptophysin, S100, 1p deletion	3%	Biopsy	Temozolamide	No	120	0
			F	1.5	Multiple DLE - Brain/Spine	0	0	1	1	Synaptophysin, S100, 1p deletion	15%	Biopsy	VCR/CBP	No	96	0
			F	4	Multiple DLE - Brain/Spine	0	1	0	0	Synaptophysin, S100, 1p deletion	10%	Biopsy	Chemotherapy	Cranio-Spinal RT	137	0
			F	2	Multiple DLE - Brain	0	0	1	1	Synaptophysin, S100, GFAP, 1p deletion	3%	Biopsy	TMZ, VCR/CBP	No	84	0
			F	5	Multiple DLE - Brain	1	0	0	0	S100, GFAP, 1p deletion	2%	Biopsy	No	Cranio-Spinal RT	Nd	0
			F	7	Multiple DLE - Brain/Spine	0	0	0	0	Synaptophysin, S100	10%	Biopsy	No	No	1	0
			F	4	Multiple DLE - Brain/Spine	0	0	1	1	Synaptophysin, S100, GFAP	12%	Biopsy	No	No	1	0
			M	6	Multiple DLE - Brain/Spine	0	0	1	1	Synaptophysin, S100, GFAP	4%	Biopsy	Temozolamide	No	24	0
21.	Preuss *et al.* 2015	4	M	2	Multiple DLE - Brain/Spine	0	0	1	1	MAP2, S100, olig-2	5–10%	Biopsy	CV	No	40	0
			M	9	Multiple DLE - Brain/Spine	0	0	1	1	MAP2, S100, olig-2	5–10%	Biopsy	CV	Yes	60	0
			M	4	Multiple DLE - Brain/Spine	0	0	1	1	MAP2, S100, olig-2	0%	Biopsy	CV	No	96	0
			M	4	Multiple DLE - Brain/Spine	0	0	1	1	MAP2, S100, olig-2, GFAP	5–10%	Biopsy	CV	No	19	1

(Contd...)

Table 1: *(Continued).*

S. No.	Author	Patients	Male/ Female	Age (years)	Leptomeningeal thickening	Intraparenchymal solid mass		Hydrocephalus	Shunt	Pathological findings/ Immunohistochemistry	Ki-67	Surgery	Chemotherapy	Radiotherapy	Follow-up (months)	Deaths
					Single/multiple/brain/spine	Brain	Spine									
22.	Ruppert *et al*. 2011	1	F	54	Multiple DLE - Spine	0	1	0	0	GFAP	7%	Resection (subtotal)	No	Cranio-Spinal RT	12	0
23.	Nambirajan *et al*. 2019	1	F	13	Multiple DLE - Brain/Spine	0	1	0	0	GFAP, synaptophysin, Neu-N, MAP2, 1p/19q codeletion	12%	Biopsy	No	No	4	0
24.	Sasaki *et al* 2019	1	M	42	Multiple DLE - Brain/Spine	0	0	1	1	GFAP, Olig2, synaptophysin, H3 K27M mutation and a gain of 1q	8%	Biopsy	No	No	7	1
25.	Rodriguez *et al* 2012	36	M	2	Multiple DLE - Brain/Spine	0	1	1	1	1p/19q codeletion three patients	The median MIB-1 labeling index was 1.5% (range 1–30%)		Temozolamide			0
			M	6	Multiple DLE - Brain/Spine	0	1	1	1	1p deletion eight patients			Nd			0
			F	4	Multiple DLE - Brain	0	1			S100 positive 11 patients			Nd			0
			F	10	Multiple DLE - Spine	0	0			GFAP positive 12 patients			CV	Cranio-Spinal RT		0
			M	5	Multiple DLE - Brain/Spine	0	1	1	1	Synaptophysin positive 19 patients			CV			0
			F	5	Multiple DLE - Brain/Spine	0	1						CCNU, PCV			0
			M	16	Multiple DLE - Brain/Spine	0	0						Nd			1
			M	3	Multiple DLE - Brain/Spine	0	0						Cisplatin, cyclophosphamide, etoposide, methotrexate			0
			M	3	Multiple DLE - Brain/Spine	0	0						Nd			1
			M	5	Multiple DLE - Brain/Spine	0	0						Nd			0
			M	6	Multiple DLE - Spine	0	0						IFO+CBDCA+VP16			0
			M	0.5	Multiple DLE - Brain	1	0						Nd			1
			M	7	Multiple DLE - Brain/Spine	0	1						CV			0
			F	4	Multiple DLE - Brain	1	0						Avastin	Cranio-Spinal RT		0
			F	46	Multiple DLE - Brain/Spine	1	0						Nd			0
			M	5	Multiple DLE - Brain	1	0						Nd			0
			M	2	Multiple DLE - Brain/Spine	0	0						Nd			0
			M	25	Multiple DLE - Brain/Spine	0	0						CV	Cranio-Spinal RT		0
			M	26	Multiple DLE - Brain/Spine	0	1					Resection	CV, Temozolomide		240	1

(Contd...)

Table 1: *(Continued).*

S. No.	Author	Patients	Male/ Female	Age (years)	Leptomeningeal thickening	Intraparenchymal solid mass		Hydrocephalus	Shunt	Pathological findings/ Immunohistochemistry	Ki-67	Surgery	Chemotherapy	Radiotherapy	Follow-up (months)	Deaths
					Single/multiple/brain/spine	Brain	Spine									
			F	11	Multiple DLE - Brain	1	0						After second surgery "baby POG" for 18 months; Avastin later			0
			M	2	Multiple DLE - Spine	0	0						Avastin			0
			M	16	Multiple DLE - Brain/Spine	0	0						Nd			0
			M	1	Multiple DLE - Brain/Spine	0	0						Nd		48	1
			M	3	Multiple DLE - Brain	0	0						Nd		72	1
			F	5	Multiple DLE - Brain	0	0	1	1				Chemotherapy	Yes	24	1
			F	5	Multiple DLE - Brain/Spine	1	1						Nd			0
			F	11	Multiple DLE - Brain/Spine	0	0						CV			0
			M	3	Multiple DLE - Brain	0	0	1	1				Nd			0
			F	5	Multiple DLE - Brain	1	1						Temozolamide	Cranio-Spinal RT		0
			M	15	Multiple DLE - Brain/Spine	1	0						CV, Temozolomide			0
			M	3	Multiple DLE - Spine	0	1						CV, lomustine			0
			M	8	Multiple DLE - Brain	1	0						Nd		24	1
			F	2	Multiple DLE - Brain/Spine	0	0						CV			0
			M	11	Multiple DLE - Brain/Spine	0	1						Temozolomide			0
			M	10	Multiple DLE - Brain/Spine	0	0						Nd		60	1
			F	12	Multiple DLE - Brain/Spine	0	0						Nd			0
26.	Dodgshun *et al.* 2016	10	M	3	Multiple DLE - Brain/Spine	1	0	3	3	GFAP, Olig2, synaptophysin	MIB-1 labeling range 1–7%	Biopsy	CV		29	0
			M	1.5	Multiple DLE - Brain/Spine	0	1			BRAF duplication		Biopsy	CV		46	0
			M	7	Single temporal solid mass	1	0			BRAF V600E		Biopsy	Thioguanine/ procarbazine/ lomustine/vincristine		19	0
			M	3	Multiple DLE - Brain/Spine	0	0			BRAF duplication		Biopsy	Thioguanine/ procarbazine/ lomustine/vincristine		69	1
			F	11	Multiple DLE - Brain/Spine	0	0					Biopsy	No	Yes	16	0
			F	14	Multiple DLE - Brain/Spine	0	1			BRAF duplication		Biopsy	Temozolomide		60	1
			M	3	Multiple DLE - Brain/Spine	0	1			BRAF duplication		Biopsy	CV		29	0
			F	5	Multiple DLE - Brain/Spine	0	1					Biopsy	Cisplatino, etoposide		17	0
			F	14	Multiple DLE - Brain/Spine	0	0					Biopsy	Vincristine, carboplatin, bevacizumab		18	0
			M	9	Multiple DLE - Brain/Spine	0	0					Biopsy	CV	Yes	6	0
27.	Present case	1	M	21	Multiple DLE - Brain/Spine	0	1	1	1	GFAP, Olig2, synaptophysin, S100, BRAF V600E negative	30%	Resection (subtotal)	No	No	3	1

DLE: Diffuse leptomeningeal enhancement

lesions were found, 19 brain nodules and 27 spinal nodules. Forty solid lesions were seen in conjunction with the DLE. A single intraparenchymal lesion without DLE was present in six cases (four encephalic and two spinal nodules).

DLE was described in all cases of poor outcome and in 73 of the living patients. Solid intraparenchymal lesions were slightly predominant between the cases with favorable outcome [Table 2]. It is notable that the six patients with a single solid lesion and no DLE all had favorable outcome, with stable disease at FU and long average FU (80 months, range 12–240 months).

Hydrocephalus

Hydrocephalus was observed in 41 patients and a ventriculoperitoneal shunt (VPS) was necessary in 38 cases. Hydrocephalus was more frequent in the poor-outcome group (52% vs. 38%). Mortality rate resulted higher in cases with hydrocephalus (27%, OS 21.9 months range 1–72) respect to cases without hydrocephalus (17%; OS 72 months, range 6–240).

PI

Ki-67 PI ranged from 0% to 53% with an average 9% and a median 4%. In three case series[3,7,15] [Table 1], the authors specified the range and average value of Ki-67 proliferation, while in the other papers (43 patients), the value per each patient was reported; among these we observed mortality 12.5% (3/24pt) with average OS 46 months in case of Ki-67 0–5%; mortality 36% (7/19 pt) with average OS 8.8 months in case of Ki-67 more than 5% [Table 3]. Overall PI was higher among deceased patients: average Ki67 was 19% (range 2–53%) versus average Ki67 6% (range 1–40%) in patients with better outcome [Table 2].

Molecular analysis

The molecular features appeared very heterogeneous since not all the papers included in the review report the same type of molecular study. Immunohistochemistry showed positivity for Synaptophysin (36%), Olig-2 (22%), GFAP (29%), and S100 (27%). BRAF V600E mutation in four patients, KIAA1549 BRAF fusion in four patients, BRAF duplication in four patients; BRAF V600E mutations were negative in nine patients and BRAF status was not specified in the remaining 78 patients. 1p deletion was found in 20 cases and 1p/19q codeletion in eight cases while it was not specified in 72 cases. A proper comparison of the molecular analysis (with regard to outcome) was not possible due to the heterogeneity of the molecular profiles in the different studies.

Treatment

Surgical treatment of solid lesions was described in 14 cases. Subtotal (4) or gross total (10) resection of eight spinal and six cerebral nodules was performed. The remaining 86 patients underwent brain or spinal cord biopsy. Mortality 35% (5/14pt) in patients submitted to resective surgery (OS 64.5 months, range 1–240); and mortality 10% (9/86pt) in patients submitted to biopsy (OS 30 months, range 7–69).

ChT was administered to 65 patients. Temozolomide (24), carboplatin (31), and vincristine (31) were the most used medications, although no standard protocol exists [Table 1]. Less frequently bevacizumab, irinotecan, cisplatin, lomustine, and thioguanine were used. Diverse treatments were noted between different authors and between different patients in the same case series. ChT was not administered in 18 cases and in 17 cases, it was not specified if it was ever used.

The 65 patients who have undergone ChT had an average FU at last visit of 59 months, range 1–240 months. Twelve patients (18%) in this group died, average OS 50 months (range 1–240). Average FU in patients not treated with ChT (18) was 36 months (range 1–240 months), 3 of them (16%) deceased, average OS 5 months (range 3–7). It was not possible to identify outcome differences based on the different ChT protocols.

Twenty-four patients underwent RT (15 cerebrospinal RT and nine not specified). In six cases, RT was performed alone while in 18 cases, it was associated with ChT. Among the patients treated with RT (24), average FU was 51 months (range 1–204 months); 6 patients (25%) deceased in this group (average OS 21.3 months, range 1–54). Average FU in patients not treated with RT (18) was 53 months (range 3–240 months); 6 patients (8%) died, average OS 19.3 months (range 3–72). Comparing poor-outcome group with better-outcome group, we observed that surgery and ChT were slightly more frequent in the better-outcome group while RT was slightly prevalent among the poor-outcome group [Table 2].

DISCUSSION

The DLGNT was introduced in the 2016 WHO classification of tumors of the CNS as "a rare glioneuronal neoplasm characterized by predominant and widespread leptomeningeal growth, an oligodendroglial-like cytology, evidence of neuronal differentiation in a subset of cases, and a high rate of concurrent KIAA1549BRAF gene fusions and either solitary 1p deletion or 1p/19q codeletion in the absence of IDH mutation."[25]

Most of these tumors show low-grade histological features and indolent clinical behavior. However, cases presenting anaplasia with increased mitotic activity and aggressive clinical behavior have been described. The clinical picture depends on the location and extension of the neoplasm. Overall signs and symptoms are heterogeneous. DLE is a peculiar aspect on MRI, usually involving the spinal cord and basal cisterns. Non-enhancing multifocal cystic lesions

Table 2: Summarizes and compares the main characteristics between the two groups: Poor prognosis group and better prognosis group.

	Patients	Male/ Female	Age at diagnosis (years)	Leptomeningeal thickening	Intraparenchymal solid mass			Hydrocephalus	V-P Shunt	Ki-67	Surgery	Chemotherapy	Radiotherapy	Follow up (months)
					Brain	Spine	Total							
Poor-prognosis	21	15 M/6 F	Average 14 y (range 0.5–62)	21/21 pt (100%)	4 pt (18%)	3 pt (18%)	7 pt (33%)	11 pt (52%)	10 pt (47%)	19% (range 2–53)	4 resection (19%)/17 biopsy (81%)	12 pt/21 (57%)	6pt/21 (28%)	OS 32 months (range 1–2)
Better-prognosis	79	46 M/33 F	Average 9 y (range 1.5–62)	73/79 pt (92%)	15 pt (19%)	24 pt (29.5%)	39 pt (49%)	30 pt (38%)	28 pt (36%)	6% (range 1–40)	10 resection (12%)/69 biopsy (88%)	53 pt/79 (67%)	18pt/79 (22%)	FU 56 months (range 1–240)

in both the brain and spinal cord are also common. These findings are frequent and may be present in conjunction with intraparenchymal solid lesions. Nevertheless, DLGNT does not always show the typical appearance on neuroimaging.

Diagnosis is often complicated since the pathology is rare and presents heterogeneous clinical patterns.[6] Karlowee *et al*., Lee *et al*., and Rodriguez *et al*.[12,14,27] reported that the clinical onset may wrongly suggest an infectious/inflammatory disease, delaying the diagnosis. The case we described presented several atypical aspects: the patient's age, the histological features, negative BRAF fusion, absence of 1p or 1p/19q deletion, and aggressive clinical behavior with poor outcome in a few weeks.

At the moment, there are no guide-lines or standard of care available, nor the prognostic factors are known. In most cases, the disease behaves as a low-grade tumor with a long overall survival. However, a definitive grading has not been released by the WHO and numerous cases with aggressive clinical course have been described.

A recent study reported that DLGNTs comprise two methylation classes (MCs), DLGNT MC-1 and MC-2, based on genomic DNA methylation profiles.[6] Patients with DLGNT MC-2 showed worse progression-free survival and overall survival. Interestingly, gain of chromosome arm 1q was seen in all tumors of DLGNT MC-2 and less frequently (35%) in those of DLGNT MC-1.

Age and clinical presentation

The literature analysis confirmed predilection for pediatric age as 64% of patients were children and the most affected subgroup was 0–5-years-old. Mean age at diagnosis is higher in the poor-outcome group (14 years vs. 9 years), mortality rate resulted higher in patients older than 8 years (32%) respect to younger patients (16%). These findings suggest that an older age at diagnosis appears to correlate with a worse outcome; however, these data are insufficient to establish age at clinical onset as a certain prognostic factor and need further validation.

Clinical presentation is highly variable, depending on disease extension and location. There is not a pathognomonic set of signs and symptoms, which in most cases are related to hydrocephalus and leptomeningeal involvement. A clinical onset with atypical headache, spinal symptoms, and neuropathy is often observed. Clinical pictures did not show definite differences between the two outcome groups.

Radiological features

The typical radiological picture is characterized by DLE which may be misdiagnosed simulating meningoencephalitis, inflammatory diseases, or other disseminated malignant tumors. Non-invasive investigations (neuroimaging,

serology, microbiological, and cytochemical CSF analysis) are insufficient for diagnosis. Cytological CSF testing is rarely diagnostic as well, resulting insufficient for cellular typing.[3,8] However, CSF cytology is necessary to exclude all potential differential diagnoses like inflammatory conditions. Histological examination is always necessary. In all case reports and case series in our review, a diagnosis was obtained only after biopsy examination. All the patients with poor outcome showed the typical radiological picture with DLE, while 8% of the patients with better-outcome did not. On the opposite, solid intraparenchymal lesions were more frequent in the better-outcome group (49% vs. 33%). The six patients presenting a single-solid lesion with no DLE were all alive at last visit with an average long FU (average FU 80 months vs. average FU 53 months of the whole group).

Although data are insufficient to provide adequate statistics, qualitative analysis suggests that massive leptomeningeal spread at clinical onset may be associated with a worse prognosis. On the other hand, the presence of intraparenchymal lesions seems associated with better prognosis, particularly if in the absence of DLE. These considerations need further verifications and insights.

Hydrocephalus

Patients in the poor-outcome group presented hydrocephalus more frequently (52% vs. 38%) and consequently, a higher number of VPS was performed in this group [Table 2]; we also observed a higher mortality rate in patients affected with hydrocephalus (27%) respect to DLGNT patients without hydrocephalus (17%); OS resulted shorter in patients suffering hydrocephalus (21.9 vs. 72 months), [Table 3]. It is not possible to determine if hydrocephalus occurs more frequently in aggressive form of DLGNTs or if hydrocephalus itself negatively affects the prognosis. In fact, it is well known that VPS in patients with brain tumors is more susceptible to malfunction (and complications) due of valve failure because of the high concentration of proteins in the CSF.[26] Garibotto *et al.* analyzed the CSF in four patients affected by DLGNT. All samples showed important hyperproteinorrachia, while presence of malignant cells was variable. Two out of four patients underwent VPS positioning due to communicating hydrocephalus and subsequently VPS revision for valve malfunction.[10] Dodgshun *et al.* reported ten cases of DLGNT: all three patients treated with VPS insertion needed revision due to shunt malfunction.[7] The incidence of shunt disorders in these patients seems related with the higher CSF viscosity, as well as with the consequences of ChT and RT.

Altogether diagnosis of hydrocephalus, and consequently the need of VPS positioning, in patients affected by DLGNT is associated with worse prognosis.

PI

Preliminary analysis of the literature showed contrasting results about the prognostic role of the PI. Rodriguez *et al.* presented the results of the largest series in the literature (36 patients).[27] They noted that MIB-1 labeling index of 4% or more was associated with worse prognosis. However, the authors themselves state that these results should be interpreted with caution given the small number of patients and limited clinical FU. Aguilera *et al.* as well suggest caution when considering the PI as a certain negative prognostic factor.[3] In this series, all the patients (seven) were long survivors and no correlation between prognosis and MIB index was observed (MIB-1 range 2–15%, FU 15–164 months). Our results, however, seem to confirm that a high PI is associated with an unfavorable outcome. The mean PI in the poor-outcome group was 19% (range 1–53%) compared to 6% observed in the better-outcome group (range 1–40%). Moreover, only two patients in the poor-outcome group had an MIB index lower than 5%, confirming the observations of Rodriguez *et al.*[27] We also observed higher mortality rate (36%) with shorter average OS (8.8 months) in case of PI of 5% or more respect to patients with the lower PI (mortality 12.5%, average OS 46 months), [Tables 2 and 3]. The patient treated in our center presented a 30% MIB-1 labeling and highly aggressive clinical behavior. A similar experience was described by Sasaki *et al.*[30] who report a case with anaplastic elements and 45% PI. The patient presented a malignant 7-month clinical course with poor prognosis.

Table 3: Average mortality and overall survival (average and range) regarding to age, hydrocephalus, ki-67, chemotherapy, radiotherapy, and surgery.

		Mortality	OS		Mortality	OS
Age	0–8 years	16% (10/62)	42.5 (12–69)	>8 years	31% (12 /38)	43.6 (1–240)
Hydrocephalus	No	17% (10/59)	72 (6–240)	Yes	27% (11/41)	21.9 (1–72)
Ki-67	0–5%	12,5% (3/24)	46 (12–54)	>5%	36%(7/19)	8.8 (1–24)
Chemotherapy	Yes	18% (12/65)	50 (1–240)	No	16% (3/18)	5 (3–7)
Radiotherapy	Yes	25% (6/24)	21.3 (1–54)	No	8% (6/76)	19.3 (3–72)
Surgery	Resection	35% (5/14)	64.4 (1–240)	Biopsy	10% (9/86)	30 (7–69)

Overall, the literature analysis suggests that a high PI is associated with an unfavorable prognosis.

Histological and molecular features (BRAF status, 1p deletion, and 1p/19q codeletion)

The previous literature reports tried to assign a prognostic role to several histopathologic and molecular aspects. Rodriguez *et al*. suggested that the presence of glomeruloid microvasculature changes have an unfavorable prognostic role.[27] The 2016 WHO classification definition of DLGNT[25] suggests a high rate of concurrent KIAA1549BRAF gene fusions and either solitary 1p deletion or 1p/19q codeletion in the absence of IDH mutation. These features are considered useful but not indispensable for the diagnosis and it is not clear if they have a prognostic impact. The review of the literature shows how the collected data are currently not sufficient to confirm nor deny a prognostic correlation. The prognostic importance of the glomeruloid aspects, the BRAF status, and 1p deletion or 1p/19q codeletion has not been endorsed by the literature review [Table 1]. Furthermore, histological and molecular analyses have been performed with heterogeneous techniques and timing.

It is, therefore, mandatory to collect further data with standardized molecular diagnostic techniques from larger case series.

Treatment

Assessing a prognostic importance to the different therapeutic options has proved a complex task. The reviewed studies reported highly heterogeneous therapeutic protocols and outcomes. Furthermore, we point out 12 cases which did not undergo any adjuvant treatment following surgery (6) or biopsy (6). These patients had an average FU of 40 months (range 1–240) and 25% mortality, similarly to patients treated with postoperative ChT and RT.

Surgery

In the cases with typical diffuse leptomeningeal involvement, the surgical options are limited to brain or spinal cord biopsy. Surgical resection is indicated in case of solid lesions causing mass effect and focal symptoms. The case we described presented DLE and a spinal nodule causing progressive paraparesis for which surgical resection was performed. Unfortunately, the neoplasm showed infiltrating behavior and malignant biology causing poor outcome.

Surgical resection has been performed on 14 of the 100 patients considered in the present review. In eight cases, both DLE and a solid lesion were present while in six cases, no leptomeningeal involvement occurred. The latter underwent surgical resection followed by ChT in two patients and RT in one. Good outcome was observed in all cases, but it must be taken into consideration that this could be related to less aggressive pathologies rather than treatment efficiency.

Even though we observed higher average mortality in patients submitted to resective surgery (39%) respect to only biopsy (10%), we should point out that the two groups have different number of patients (14 vs. 86) making proper comparison unreliable.

Based on these results, it appears that surgical resection has a therapeutic role when treating mass effect solid lesions. Resective surgery should be, therefore, considered part of a combined therapeutic plan which aims at managing the DLGNT as a disseminated organ pathology rather than a focal lesion. Surgery has, therefore, a positive impact on the prognosis quoad valetudinem but does not seem to influence OS.

ChT

Theoretically, ChT should be a valid therapeutic option, since it has a wide effect on the CNS rather than local action. Based on clinical experience and preliminary literature data, several authors have asserted that ChT is an effective treatment for DLGNT.[3,7,37] Some papers suggest that ChT protocols in use for low-grade gliomas (LGG) may slow down progression and stabilize the disease.[38] No standard of care or guidelines are available for DLGNTs; therefore, the authors use therapeutic protocols validated for other glial neoplasms.[36]

Aguilera *et al*.[3] treated seven patients affected with DLGNT using upfront ChT [Table 1]. The authors reported a symptomatic improvement but no clear radiographic response (stable disease without progression). Similar considerations were proposed by Dodgshun *et al*.[7] and by Xu *et al*.[37]

In the present review, ChT was administered in 67% of cases with better outcome and in 57% of cases with poor outcome.

Mortality was reported in 16% of cases which did not undergo ChT and 18% of cases after ChT. This might as well suggest that patients with slowly progressive diseases were not treated while ChT was administered to patients with more aggressive forms.

Patients treated with ChT had a 59-month mean FU compared to 39-month mean FU in the other cases. The data seem to confirm the effectiveness of ChT in stabilizing the disease and improving length of survival. However, these results are not sufficient to assess the validity of ChT due to the limited number of cases and the treatment heterogeneity which prevent an appropriate statistical analysis. Still, many authors recur to ChT for its diffuse effect on the CNS and suggest that clinical trials are necessary to identify a standard of care.

RT

While ChT is widely accepted by most authors even in the absence of standardized protocols, RT's role remains

uncertain. Reports in the literature present partly contrasting results and considerations. Dodgshun *et al*.[7] and Lyle *et al*.[18] observed clinical benefit and radiological stabilization of the disease from combined RT and ChT treatment. Other authors doubt the utility of RT as first choice treatment because of its uncertain effectiveness and side effects.[3,7,37]

Data analysis showed that the mean OS was very similar between radiotreated and not radiotreated patients (51 months vs. 53 months). Radiotreated patients had poor prognosis in 25% of cases versus 8% in untreated patients. It is impossible, however, to distinguish if this difference is related to a negative prognostic impact of RT or if RT was administered more frequently in patients with more aggressive diseases. RT should not be recommended as initial treatment considering the absence of sufficient data, the potential side effects, and the evidence of prolonged disease control in untreated patients. Irradiation could be considered as salvage therapy after further tumor progression.

CONCLUSION

The DLGNT is a rare entity and no guidelines or management standard are available nowadays. Clinical and radiological presentation, such as the outcome, can be highly variable. While most cases show slow progression, aggressive clinical behavior is not rare. However, the grading has not yet been assigned to this pathology in the WHO classification.

Analysis of the literature suggests that high PI, hydrocephalus occurrence, massive leptomeningeal spread, and older age at diagnosis have been more frequently associated with poor outcome. The presence of solid intraparenchymal lesions with absent or limited leptomeningeal involvement at clinical onset can be considered a positive prognostic factor.

Literature data are still not sufficient to assign a certain prognostic or diagnostic role to BRAF status, 1p deletion, and 1p/19q codeletion. Biopsy is mandatory for diagnosis which cannot be obtained with noninvasive examinations.

A combined therapeutic approach is recommended consisting in biopsy followed by chemotherapeutic regimes similarly to other LGG. RT's role remains uncertain, it could be considered as salvage therapy after tumor progression or as a first-line therapy (associated to ChT) in aggressive forms of DLGNT. Surgical resection is reserved in case of solid nodule causing mass effect and neurological impairment and it should not be considered a curative treatment (symptomatic effect). VPS positioning at any stage of the disease is mandatory in case of hydrocephalus, despite a high risk of shunt malfunction.

The observed results need further validation; larger clinical trials conducted with a reliable methodology seem advisable.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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