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Low-grade spinal glioneuronal tumors with *BRAF* gene fusion and 1p deletion but without leptomeningeal dissemination

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Concurrent *KIAA1549-BRAF* fusion and chromosome 1p deletion with or without concomitant chromosome 19q loss are recurrent molecular alterations in the diffuse leptomeningeal glioneuronal tumor (DLGNT) [6,7,10], in which widespread leptomeningeal dissemination is a diagnostic feature [1,6,10]. We have reviewed five spinal cord tumors (Table 1) that show the morphologic and molecular genetic characteristics of DLGNT, but in which radiographically apparent leptomeningeal dissemination was not identified at presentation. At initial review, we sought to understand the relationship between these tumors and DLGNT by undertaking immunohistochemical analyses with a panel of neural markers: GFAP, OLIG2, and synaptophysin, and with antibodies to the BRAF V600E, histone H3.1/H3.3 K27M, and IDH1 R132H mutant proteins. Duplication of chromosome 7q34 (a surrogate marker for the presence of *KIAA1549-BRAF* fusion) and deletion of chromosome arms 1p and 19q were examined by interphase fluorescence *in situ* hybridization (iFISH). The presence of *KIAA1549-BRAF* fusion transcripts was also tested by reverse transcription polymerase chain reaction (RT-PCR). We collected relevant clinical information and follow-up radiologic studies to characterize the tumors' clinical behavior and tendency for leptomeningeal dissemination.

DLGNT presents most commonly in children and young adults [6]. Similarly, among the five patients in our series, four were children (5-14 years old) and one was a young adult (20 years old). There was no apparent gender predilection, although female patients were older in our series. Pre-operative imaging was not available for one child. While diffuse leptomeningeal enhancement was not identified by MRI in any of the five cases, extensive

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intramedullary involvement across multiple segments was typical (Supplemental Figure). Except for one distal thoracic tumor spanning three segments, all tumors spanned ≥7 segments, with holospinal involvement from obex to conus in two cases. All four pre-operatively imaged tumors appeared central within the cord, filling and expanding the central canal (Fig. 1). All were multicystic, with peripheral variably solid or nodular enhancement. This mixed solid/cystic appearance, with T1 hypointensity and T2 hyperintensity, matches the imaging characteristics of DLGNT with a spinal cord mass [3,6,8–10]. None of the five patients had documented leptomeningeal metastasis during follow-up (2 months – 7.5 years).

Tumor cells in DLGNT have a characteristic oligodendrocyte-like morphology and express OLIG2. Expression of GFAP or synaptophysin is more variable. Signs of neurocytic or ganglion cell differentiation are present in 10-20% of cases [6,10]. Neuropil-like hypocellular zones and glial foci that resemble a pilocytic astrocytoma are sometimes seen [10]. Mimicking DLGNT, the five spinal cord tumors in our series contained many oligodendrocyte-like cells (OLCs), which either infiltrated spinal cord parenchyma or grew in small nests (Table 1, Fig. 2). By immunohistochemistry, they expressed OLIG2 and synaptophysin, but not GFAP. All contained rare neuropil-like islands, which were often surrounded by tumor cells with neurocytic differentiation and had a rosette-like configuration, a feature distinct from conventional low-grade ganglion cell tumors. The rosetted neuropil islands were much larger than similar structures in the rosette-forming glioneuronal tumor. Glial foci resembling pilocytic astrocytoma (PA) were also evident. Mitotic counts (<1/10hpfs) and Ki-67 immunolabeling (<5%) were low, in line with our experience of DLGNTs. While leptomeningeal spread was not found radiographically, microscopic leptomeningeal involvement was identified at the site of biopsy in four cases.

Chromosome 7q34 duplication, a surrogate marker for the presence of *KIAA1549-BRAF* fusions, was identified in all five cases by iFISH (Table 2). The presence of fusion transcripts was further confirmed in four cases tested by RT-PCR. In two cases, exon 15 of *KIAA1549* was fused to exon 9 of *BRAF* (15-9), which is also commonly seen in extra-cerebellar midline PAs [2]. The 15-11 fusion seen in case #3 is occasionally found in supratentorial PAs [5]. Both 15-9 and 15-11 fusions have been detected in DLGNTs at our institution. The 13-11 fusion in case #4 occurs rarely in PAs [11]. Chromosome 1p loss was present in all five cases. Chromosome 19q loss was not identified in the four cases tested. Immunostains for BRAF V600E, histone H3.1/H3.3 K27M and IDH1 R132H mutant proteins were negative in tumors with sufficient tissue for testing.

The spinal tumors in our series share the patient demographics, radiologic characteristics, morphologic features, and genetic alterations of DLGNTs, but lack overt leptomeningeal dissemination at presentation and during follow-up. When a parenchymal mass is present in a DLGNT it is often in the spinal cord. Our findings suggest that a low-grade glioneuronal tumor with the same features can also present as a solitary spinal cord mass. Since DLGNTs demonstrate slow, but nonetheless relentless and debilitating clinical progression [1,4,6,8], it would be prudent to follow such intramedullary tumors closely to understand their long term clinical outcome. However, our findings suggest that DLGNTs form a spectrum with tumors

that have no obvious leptomeningeal dissemination at presentation, which has implications for the DLGNT's provisional status in the latest WHO classification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Statement of Human Rights

The study was approved by the appropriate institutional research ethics committees. All procedures were in accordance with their ethical standards and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

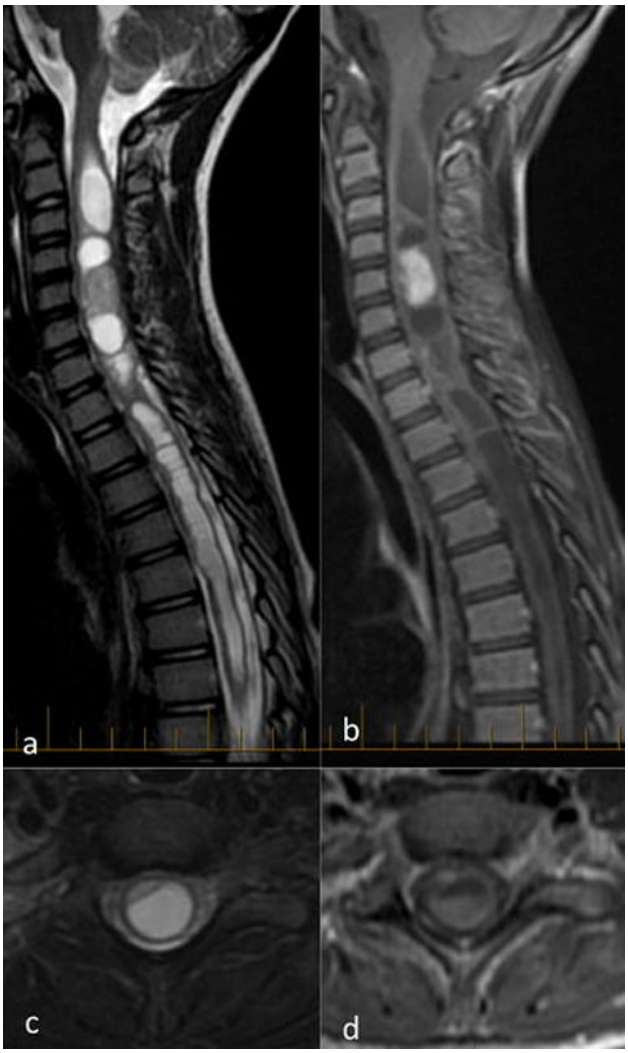

Figure 1. Imaging Features of Spinal *BRAF*-fused and 1p-deleted Glioneuronal Tumors

Sagittal (a, b) and axial (c, d) fat-saturated T2 (a, c) and contrast-enhanced T1-weighted images (b, d) show multi-cystic tumor with peripheral and nodular enhancement, filling and expanding the central canal of the spinal cord across multiple spinal segments.

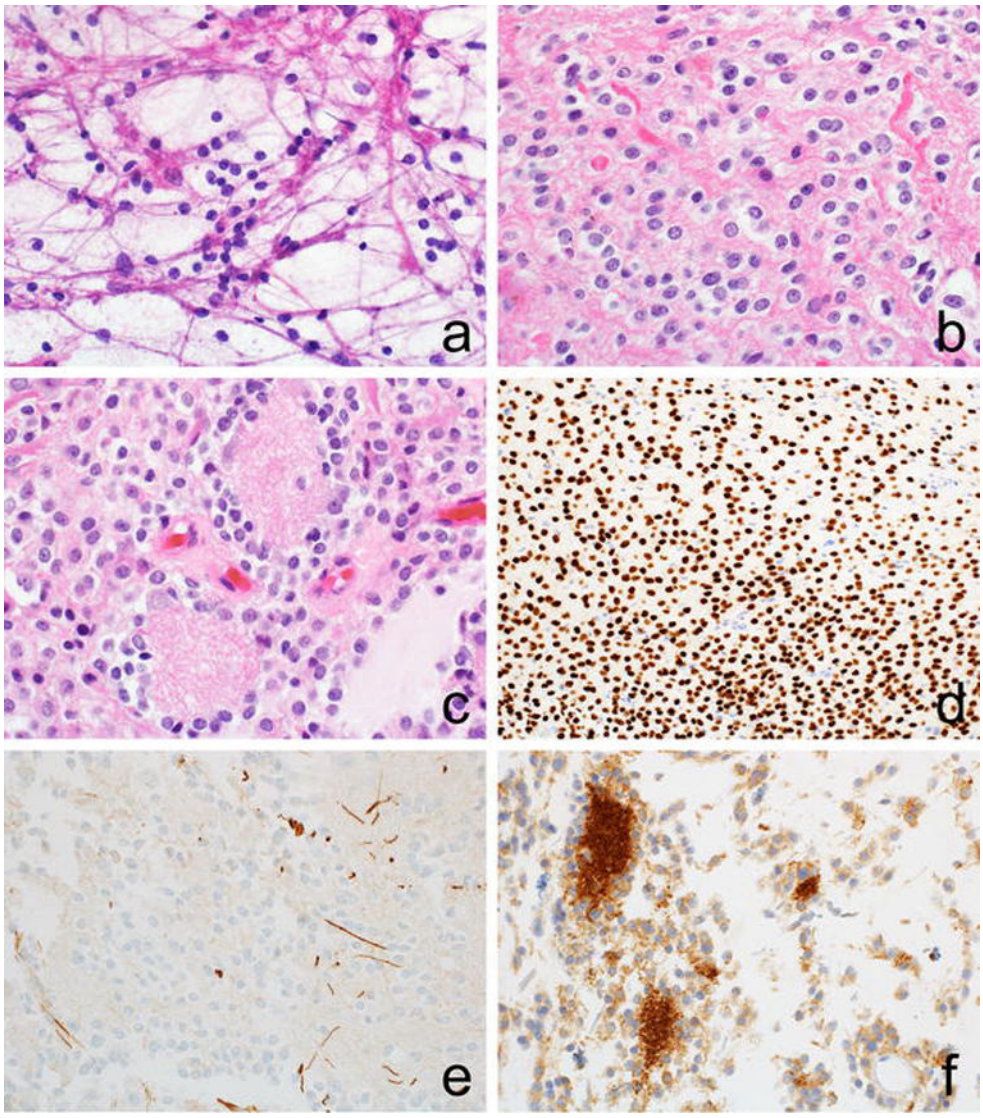

Figure 2. Histologic Features of Spinal *BRAF*-fused and 1p-deleted Glioneuronal Tumors

The oligodendrocyte-like cytology of the tumor is evident on both smear preparations (a) and fixed histologic sections (b). Axons are seen among oligodendrocyte-like cells (OLCs), giving away their infiltrative nature. Neuropil-like islands are often surrounded by tumor cells and have a rosette-like configuration (c). OLCs are immunopositive for OLIG2 (d) and immunonegative for GFAP (e). Synaptophysin immunoreactivity marks tumor cells and highlights neuropil islands (f).

Table 1

Patient Demographics, Tumor Locations and Pathologic Findings

Case	Age (yrs)	Gender	Site (spinal cord)	Follow-up	OLCs	NIs	LM	GFAP	Olig2	Syn
1	13	M	T10–12	5 m	+	+	+	−	+	+
2	20	F	Obex-Conus	10 m	+	+	−	−	+	+
3	5	M	C4-T4	4 y	+	+	+	−	n/d	+
4	14	F	Obex-Conus	2 m	+	+	+	−	+	+
5	5	M	C2-T9	7.5 y	+	+	+	−	+	+

Follow-up; m: months; y: years

OLCs: oligodendrocyte-like cells

NIs: neuropil-like islands

LM: microscopic leptomeningeal involvement

Syn: synaptophysin

n/d: not done

Table 2

Summary of Molecular Findings

Case	7q34 dup	Fusion	1p−	19q−	V600E	K27M	IDH1
1	+	15–9	+	−	−	−	−
2	+	15–9	+	−	−	−	−
3	+	15–11	+	−	n/d	n/d	n/d
4	+	13–11	+	−	−	−	−
5	+	n/d	+	n/d	−	−	n/d

dup: duplication

Fusion: *KIAA1549-BRAF* fusion; 15-9: *KIAA1549* exon 15 fused to *BRAF* exon 9; 15-11: *KIAA1549* exon 15 fused to *BRAF* exon 11; 13-11: *KIAA1549* exon 13 fused to *BRAF* exon 11

1p− chromosome arm 1p deletion; 19q− chromosome 19q deletion

V600E: immunostain for BRAF p.V600E mutant protein

K27M: immunostain for histone H3.1/H3.3 p.K27M mutant proteins

IDH1: immunostain for IDH1 p.R132H mutant protein

n/d: not done