

# Anaplastic ganglioglioma arising from a Lhermitte–Duclos-like lesion

## Case report

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✓The authors report the case of a 7-year-old boy with a history of developmental delay who presented with aggressive behavior. A magnetic resonance (MR) image showed a mass lesion originating from the cerebellar vermis with an atypical folial pattern and contrast enhancement. Histologically, the subtotally resected specimen consisted mostly of neuropil with nodular foci of ganglion cells. Lhermitte–Duclos disease (LDD) was diagnosed in the patient. A retrospective review of the tissue sections showed a nidus of associated astrocytic proliferation, suggesting a diagnosis of ganglioglioma. Five years later, the patient experienced an altered mental state and a facial droop. An MR image revealed a cerebellar mass with cystic areas and an enhancing nodule. The resected tissue specimen consisted primarily of a mixed proliferation of glial and ganglion cells consistent with a ganglioglioma. Two years later, a third craniectomy was performed in the patient for worsening headache and ataxia. Histologically, the tumor showed progressive anaplasia and was most accurately classified as an anaplastic ganglioglioma. Immunohistochemically, most of the tumor cells were immunoreactive for anti-phospho-mammalian target of rapamycin (mTOR) and phospho-S6 ribosomal protein antibodies. In contrast, the subpopulation of neoplastic ganglion cells in the tissue, particularly from the first surgery, did not express phosphatase and tensin homolog deleted from chromosome 10 (PTEN). This immunohistochemical pattern suggests that the large dysplastic ganglion cells (the gangliocytomatous component) forming the greater part of the lesion were associated with activation of the phosphatidylinositol 3-kinase–PTEN/Akt/mTOR signaling pathway, a feature previously reported in LDD. This case represents the first report of an anaplastic ganglioglioma arising in an LDD-like lesion. (DOI: 10.3171/PED-07/08/137)

**KEY WORDS** • anaplastic ganglioglioma • cerebellum • immunohistochemistry • Lhermitte–Duclos disease • pediatric neurosurgery

**L**HERMITTE–DUCLOS disease, also known as dysplastic cerebellar gangliocytoma, is a rare, slowly enlarging, mass lesion of the cerebellum. More than 100 cases of LDD have been described in the literature since the first description in 1920 by Lhermitte and Duclos.<sup>13</sup> Clinical manifestations of LDD frequently include a longstanding history of vague neurological symptoms and cerebellar signs related to a progressive posterior fossa mass. Histologically, the lesion of LDD is composed of dysplastic ganglion cells that

are mostly confined to the internal granule cell layer. Although histopathological findings can confirm the diagnosis of LDD, MR imaging is often sufficient to demonstrate its characteristic features, which consist of a typically striated pattern of hyperintensity on T2-weighted images and hypointensity on T1-weighted images, with no enhancement following gadolinium–diethylenetriamine pentaacetic acid administration. The pathogenesis of LDD remains controversial, and the debate as to whether it represents a neoplastic, malformative, or hamartomatous lesion is still ongoing. It has recently been reported that LDD is associated with the autosomal-dominant, familial, multiple hamartoma-neoplasia syndrome (or CS)<sup>6,12,20,23</sup> and that both conditions are associated with germline mutations in the *PTEN* gene, a tumor suppressor gene, on chromosome 10q23.<sup>6,12,21,25,29</sup> Although several recurrent cases of LDD after subtotal resection have

*Abbreviations used in this paper:* CS = Cowden syndrome; GFAP = glial fibrillary acidic protein; ICP = intracranial pressure; LDD = Lhermitte–Duclos disease; MAP2 = microtubule-associated protein 2; MR = magnetic resonance; mTOR = mammalian target of rapamycin; PTEN = phosphatase and tensin homolog deleted from chromosome 10.

been reported.<sup>10,14,24</sup> To the best of our knowledge, the occurrence of other neoplasms within an LDD lesion have not been recorded.

Gangliogliomas may occur throughout the central nervous system, but the majority are supratentorial and involve the temporal lobe.<sup>22</sup> Gangliogliomas arising from the cerebellum are uncommon, however, and the anaplastic variant is much more rare in this location. We report a case of an anaplastic ganglioglioma arising against a background of a benign cerebellar gangliocytic tumor histologically similar to LDD (that is, an LDD-like lesion).

### Case Report

**History and Examination.** This 7-year-old boy with a history of developmental delay presented in 1998 with aggressive behavior during school. There were no signs of increased ICP or gait disturbances. An MR imaging study revealed a large nonhomogeneous mass lesion (low isointensity on T1-weighted images and high intensity on T2-weighted images) with patchy enhancement, originating in the vermis and measuring 6 cm at the largest dimension (Fig. 1A and B). The neuroradiological differential diagnoses included a primitive neuroectodermal tumor, an ependymoma, or an atypical pilocytic astrocytoma.

**Operations and Postoperative Course.** Subtotal resection of the lesion was performed. The impression of the frozen section and the intraoperative consultation, as well as the final histological diagnosis, was LDD. Two months after the craniotomy, the patient showed signs of increased ICP, for which a ventriculoperitoneal shunt was placed, and the patient has remained dependent on a ventriculoperitoneal shunt since that time.

In 2003, he experienced an altered mental state and a facial droop. An MR imaging study revealed a residual cerebellar mass, measuring approximately 6 cm in diameter, with cystic areas and an enhancing nodule (Fig. 2A). Suboccipital craniotomy with resection of the cerebellar lesion was performed. The histological diagnosis of the tumor was a ganglioglioma.

In 2005, a third craniotomy was performed for worsening headache and ataxia. A preoperative MR image showed a rapidly enhancing mass involving the entire cerebellar ver-

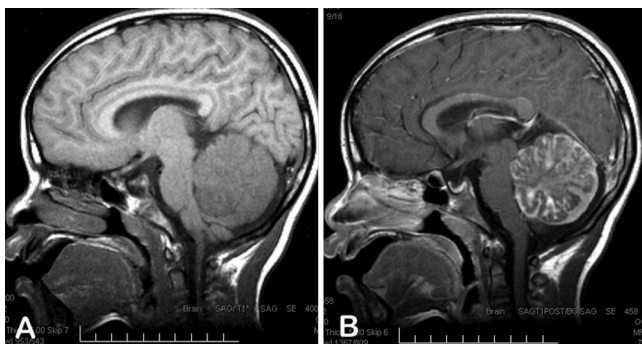


FIG. 1. Sagittal T1-weighted MR images of the patient at presentation showing a large nonhomogeneous mass lesion with low isointensity, originating in the cerebellar vermis and measuring 6 cm at the greatest dimension (A), and demonstrating patchy contrast enhancement (B).

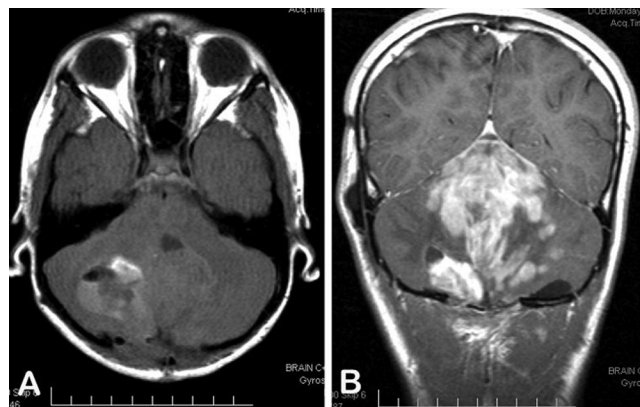


FIG. 2. A: Axial T1-weighted contrast-enhanced MR image obtained at the 5-year follow-up showing a residual cerebellar mass measuring approximately 6 cm in diameter with cystic areas and an enhancing nodule. B: An MR image obtained at the 7-year follow-up revealing a rapidly enhancing mass involving the whole of the cerebellar vermis and paramedian cerebellar hemispheres. The mass measures  $8 \times 7 \times 6.7$  cm.

mis as well as the paramedian cerebellar hemispheres, measuring approximately  $8 \times 7 \times 6.7$  cm (Fig. 2B). The cerebellar tonsils were also noted to be herniating through the foramen magnum. The histological diagnosis of the lesion was an anaplastic ganglioglioma. The patient received radiation therapy but experienced further tumor progression 5 months after completing the therapy. He is currently receiving an experimental treatment of a Phase 1 study protocol. Clinical follow-up information revealed no signs or symptoms suggestive of CS.

### Pathological Findings

**First Resection and Biopsy Procedure.** Histological examination of the tissue sample resected in 1998 showed loss of the normal cerebellar architecture with thickened cerebellar folia, loss of Purkinje cells, and poorly defined white matter. For the most part, the tissue consisted of neuropil in which there were foci of dysplastic ganglion cells with abundant cytoplasm, large nuclei, prominent nucleoli, and occasional multinucleation (Fig. 3A). There were also scattered vacuoles interspersed in the neuropil. The tissue appeared lobulated in some places. These features were histologically compatible with the diagnosis of LDD. In addition, there was a minor component with slightly increased cellularity consisting of a mixture of ganglion and glial cells (Fig. 3B). A special stain (Luxol fast blue) revealed isolated myelinated fibers and some bundles of myelinated fibers separating the clusters of ganglion cells. Axonal stains identified many axon bundles coursing throughout the tissue in a relatively organized pattern.

**Second Resection and Biopsy Procedure.** Histologically, the specimens resected in 2003 consisted predominantly of a proliferation of glial cells with fibrillary cytoplasm, admixed with scattered ganglion cells as well as numerous eosinophilic granular bodies (Fig. 4). Mitotic figures were not seen. There were chronic inflammatory cell infiltrates in some places. These histological features were characteristic of a ganglioglioma. In addition, there was a minor component with residual LDD-like features.

## Anaplastic ganglioglioma arising from an LDD-like lesion

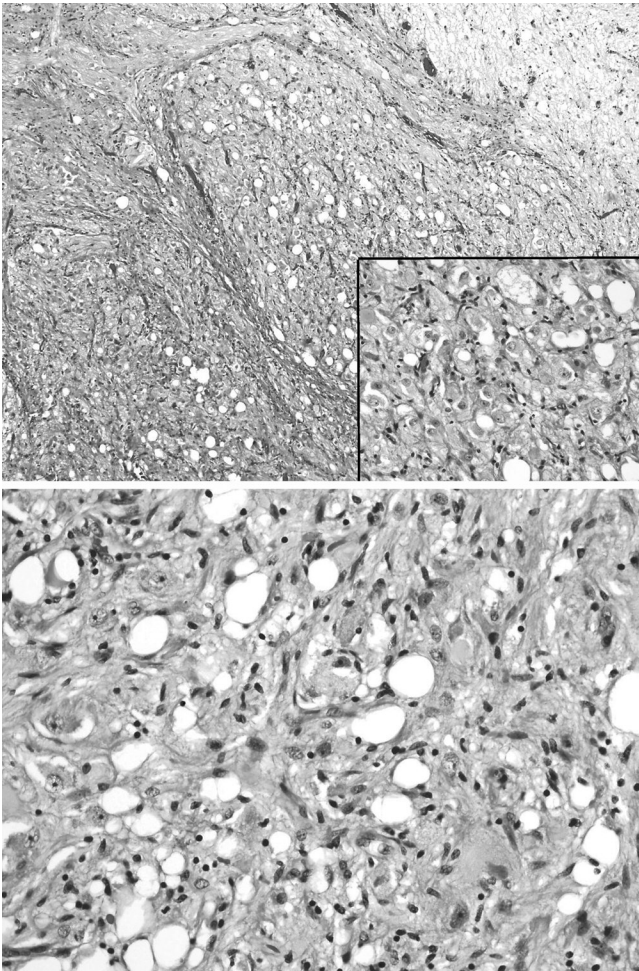


FIG. 3. Photomicrographs showing histological features of the tissue specimen from the first surgery at presentation. *Upper*: The LDD-like area is characterized by a small lobular architecture composed of vacuolated neuropil with randomly distributed dysplastic ganglion cells. *Lower*: A focal area with a mixture of ganglion cells and glial cells is demonstrated. H & E, original magnification  $\times 100$  (*upper*),  $\times 200$  (*lower*), and  $\times 400$  (*inset*).

**Third Resection and Biopsy Procedure.** Histologically, the tumor resected in 2005 showed progressive anaplasia including cellular pleomorphism, hypercellularity, and a few typical and rare atypical mitotic figures (Fig. 5). Scattered eosinophilic granular bodies were also noted. The tumor was most accurately classified as an anaplastic ganglioglioma. In addition, there was a minor component with residual LDD-like features.

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tissue specimens using the avidin-biotin complex method. Antigen retrieval was undertaken using steam heat. Primary antibodies against the following antigens were used: synaptophysin (clone SY38, dilution 1:30; Dako); phosphorylated neurofilament protein (clone 2F11, dilution 1:25; Dako); GFAP (clones 4A11, 1B4, and 2E1, dilution 1:500; BD Biosciences Pharmingen); Ki 67 (clone MIB-1, dilution 1:500; Dako); MAP2 (clone AP20, dilution 1:1000; Roche Molecular); human PTEN (clone 6H2.1, dilution 1:200; Cascade Bioscience); phospho-mTOR (clone 49F9, dilution 1:30; Cell Signaling Tech-

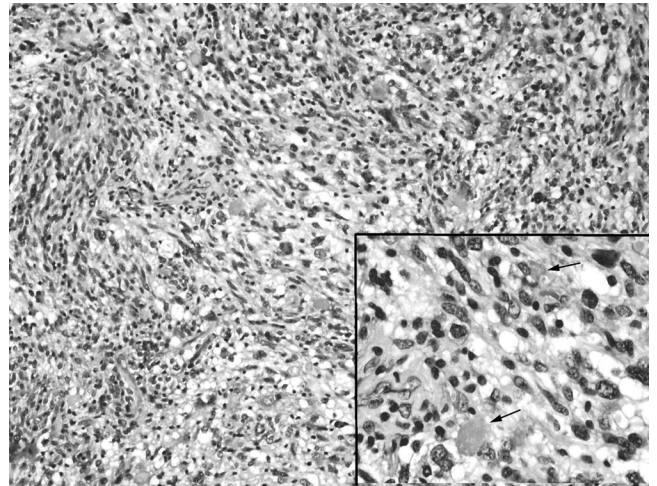


FIG. 4. Photomicrograph showing histological features of the tissue specimen from the second surgery at the 5-year follow-up. A proliferation of glial cells admixed with scattered ganglion cells is seen as are numerous eosinophilic granular bodies (*inset, arrows*). H & E, original magnification  $\times 100$  and  $\times 400$  (*inset*).

nology); and phospho-S6 ribosomal protein (clone 2F9, dilution 1:30; Cell Signaling Technology).

The glial component in the ganglioglioma/anaplastic ganglioglioma was labeled with anti-GFAP antibody (Fig. 6A). Some neoplastic ganglion cells in these tumors were highlighted using antisynaptophysin (Fig. 6B), phosphorylated neurofilament protein, and MAP2 antibodies (Fig. 6C). These cells did not express PTEN (Fig. 6D). Most of the neoplastic ganglion cells were immunoreactive for anti-phospho-mTOR (Fig. 6E) and phospho-S6 ribosomal protein (Fig. 6F) antibodies. In the anaplastic ganglioglioma the Ki 67 labeling index was approximately 5%, counted in the most mitotically active areas.

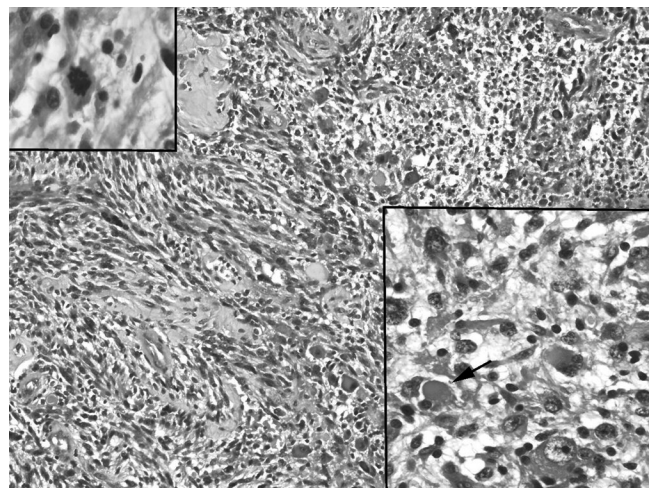


FIG. 5. Photomicrograph showing histological features of the tissue specimen from the third surgery at the 7-year follow-up. The tumor demonstrates progressive anaplasia with cellular pleomorphism and hypercellularity. *Upper left inset* shows a mitotic figure; *lower right inset* shows an eosinophilic granular body (*arrow*). H & E, original magnification  $\times 100$  and  $\times 400$  (*insets*).

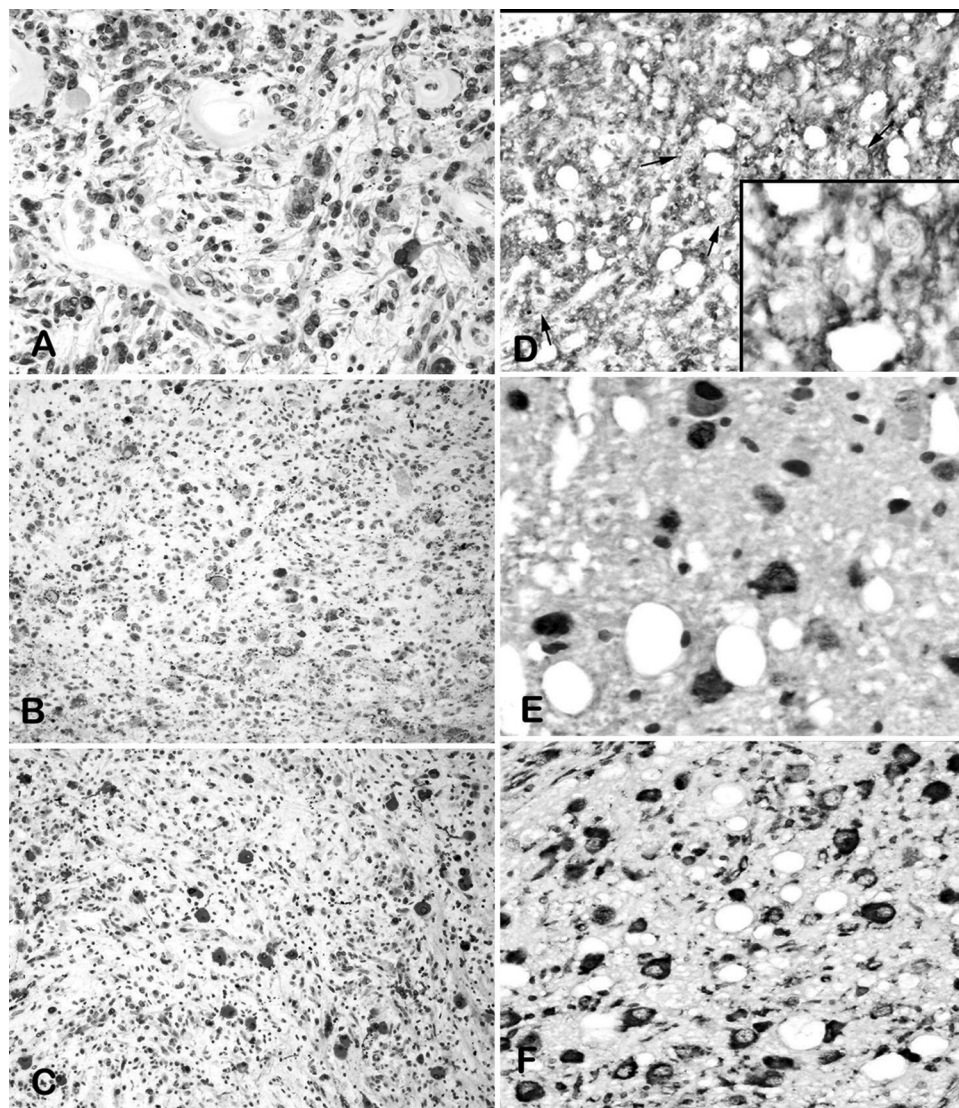


FIG. 6. Photomicrographs showing immunohistochemical findings. A: Tissue specimen showing the glial component in ganglioglioma expressing GFAP. B: Many neoplastic ganglion cells labeled with synaptophysin. C: Neoplastic ganglion cells highlighted with MAP2. D: Some ganglion cells with no immunoreactivity with PTEN antibody (*arrows*). E and F: Many of the neoplastic ganglion cells were strongly immunoreactive for anti-phospho-mTOR (E) and phospho-S6 ribosomal protein (F) antibodies. H & E, original magnification  $\times 200$  (A–D) and  $\times 400$  (E, F, and *inset*).

### Discussion

This is a case in which a very small nidus of gangliogliomatous component against a background of dysplastic cerebellar gangliocytoma progressively replaced a large area of the cerebellar tumor with increasing anaplasia over an 8-year follow-up period. Gangliocytoma in the cerebellum is used synonymously for LDD, and it has not been reported to occur outside of this disease. The present case is unique because the astrocytic proliferation within the tumor was so limited in the specimen from the first surgery that the histological features closely mimicked those of a dysplastic cerebellar gangliocytoma, or LDD. The tumor also showed an atypical folial pattern on MR imaging.

It is well known that occasionally gangliogliomas may demonstrate areas almost entirely devoid of an obvious gliomatous component, thereby resembling a gangliocytoma.<sup>26</sup>

Handa and colleagues<sup>8</sup> reported a very similar case of a cerebellar hemispheric ganglioglioma with a small astrocytic component in a 53-year-old patient. In their case, the disappearance of Purkinje cells or hypertrophy of the internal granular cell layer, which are characteristics of LDD, was not observed. These investigators noted that differentiation from LDD was possible based on these histological findings. Our case was more complicated because the internal granular layer was almost totally effaced by gangliocytic proliferation with loss of the overlying Purkinje cells. It is generally believed that the typical MR imaging findings of LDD, such as a nonenhancing mass in the cerebellar hemisphere with an alternating striated pattern of corresponding low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, are so distinctive<sup>28</sup> that it is unlikely that LDD will be confused with other diseases.

## Anaplastic ganglioglioma arising from an LDD-like lesion

Chen and coworkers,<sup>5</sup> however, reported a case of a medulloblastoma in which the MR imaging findings were indistinguishable from those of LDD with the exception of the laminated/foveal pattern, which showed contrast enhancement. Our case demonstrated a cerebellar tumor with an atypical foveal pattern that was highlighted on T1-weighted images with contrast enhancement, probably reflecting a diffuse leptomeningeal infiltration of tumor cells. The absence of typical MR imaging features of LDD may have been the only clue to the correct initial histological diagnosis in our case.

Although gangliogliomas may occur at almost any location of the central nervous system, those arising from the cerebellum are uncommon and only approximately 35 cases have been reported so far in the literature.<sup>4,7-9,11,15,17,18</sup> Gangliogliomas occurring in the cerebellum and in other more common locations (such as the temporal lobes) tend to be found in pediatric and young adult populations at presentation, with the patient age ranging from 3 months to 53 years (mean 16.2 years). The most common presenting symptoms in patients are those related to increased ICP and/or cerebellar dysfunction, in contrast to patients with supratentorial gangliogliomas, who commonly present with a long history of seizures.<sup>26</sup> Neuroradiologically, it was reported that the majority of these lesions with well-described neuroimaging findings were contrast enhancing and that nearly half demonstrated cyst formation and the presence of calcification. The main differential diagnoses include pilocytic astrocytoma and dysplastic cerebellar gangliocytoma/LDD. Malignant transformation of cerebral ganglioglioma has been reported to be as high as 10% of cases;<sup>16,27</sup> however, to our knowledge this is the first documented case of cerebellar ganglioglioma with anaplastic transformation.

Lhermitte-Duclos disease was recently recognized as a phenotypic variant of CS, and over 80% of patients with CS reportedly carry germline mutations in *PTEN*.<sup>29</sup> Zhou et al.<sup>29</sup> reported that a *PTEN* mutation was detected in all tissue samples (15 cases) from patients with adult-onset LDD. In contrast, three tissue samples from patients with childhood-onset LDD were all found to be without mutations. The *PTEN* gene is a tumor suppressor gene that codes for a phosphatase that negatively regulates the phosphatidylinositol 3-kinase/Akt/mTOR pathway, thereby inducing cell cycle arrest and/or apoptosis.<sup>3</sup> The mTOR kinase phosphorylates ribosomal S6 kinase, which leads to increased levels of phospho-S6. A novel function for *PTEN* in the control of cell size has recently been discovered,<sup>2</sup> and several recent *in vivo* studies indicate that S6 kinase plays an essential role in the regulation of cell size using this signaling pathway.<sup>19</sup> Abel et al.<sup>1</sup> studied 11 cases of LDD using immunohistochemistry and reported that most of the lesions were negative for *PTEN* and that high levels of immunoreactivity against phospho-Akt and phospho-S6 were observed in the large ganglion cells forming the lesions, indicating activation of the *PTEN*/Akt/mTOR signaling pathway. The absence of *PTEN* immunoreactivity is presumed to reflect the loss of the inhibitory influence of this protein on this pathway, which may or may not be due to mutation of the *PTEN* gene. It has also been suggested that mTOR may play a central role in the pathogenesis of LDD.<sup>1</sup> The results of the immunohistochemical analysis of our case showing loss of *PTEN* immunoreactivity, in the presence of phospho-S6 and phospho-mTOR positivity in the large ganglion cells,

suggest that the large dysplastic ganglion cells (the gangliocytomatous component) forming the greater part of the lesion in the first surgical specimen have activated mTOR and S6 kinase, probably as a result of the loss of the *PTEN* inhibitory effect on the *PTEN*/Akt/mTOR signaling pathway.

The pathogenesis of LDD remains an enigma and the controversy as to whether it represents a malformation (such as hypertrophy of granule cells), hamartoma, or neoplasm is still ongoing. Although tumor regrowth is rare after appropriate initial treatment, several cases of recurrent LDD have been reported.<sup>10,14,24</sup> The close similarity of the histological features and immunoprofile of the lesion we are describing to those of classic gangliocytoma/LDD raises the intriguing possibility that it may represent a case of a ganglioglioma arising from a true LDD; that is, the nidus of ganglioglioma was already present in the LDD at the time of the first presentation and surgery. The results of the immunohistochemical study of our case support this possibility.<sup>29</sup> Because the diagnosis of LDD is, in general, confirmed by histology, it is extremely difficult or impossible to prove this possibility retrospectively.

In summary, we presented a case of a cerebellar ganglioglioma in which the gliomatous component (astrocytic proliferation) was so limited that the histological features closely mimicked those of LDD, and this component showed increasing anaplasia over an 8-year follow-up period. This tumor demonstrated an atypical foveal pattern on MR imaging with contrast enhancement. This enhancing foveal pattern is unusual for classic LDD and may be of help in differentiating classic LDD and mimics (LDD-like lesions). This immunohistochemical pattern (*PTEN* negative, phospho-S6 positive, and phospho-mTOR positive) of immunoreactivity in large ganglion cells suggests that the large dysplastic ganglion cells (gangliocytomatous component) forming most of the lesion demonstrate activation of the *PTEN*/Akt/mTOR signaling pathway.

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