

Cerebellar Ganglioglioma in Childhood: Histopathologic Implications for Management During Long-term Survival: A Case Report

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ABSTRACT

We report the case of a 19-year-old female with cerebellar ganglioglioma that was diagnosed at 4 years of age. Despite treatment with partial resection, radiation, and chemotherapy, residual tumor slowly expanded into the brainstem and upper cervical cord, resulting in nocturnal hypopnea, progressive tetraparesis, and feeding difficulty during 8–10 years of age. Initiation of temozolomide and bevacizumab was effective in preventing further expansion of the tumor, and the patient has been treated at home and in school with noninvasive positive pressure ventilation and gastrostomy. Histopathologic examination of the resected tumor tissue revealed phospho-S6-positive tumor cells of either neuronal or astroglial appearance. This suggests that a higher proportion of cells of glial lineage could be linked to the progression of cerebellar ganglioglioma in childhood. Possible treatment options with mammalian target of rapamycin inhibitors are discussed.

Key words childhood cerebellar tumor; Lhermitte–Duclos disease; mTOR; PTEN

Gangliocytoma (GC) and ganglioglioma (GG) are generally benign brain tumors, with a long-term recurrence-free survival rate of > 90%. The distinction between GC and GG is based on the absence or presence of glial tumor cell elements. Location in the temporal lobe, longstanding epilepsy, and complete surgical resection are associated with a good prognosis in GG.¹ Adult-onset dysplastic cerebellar GC, which is synonymous with Lhermitte–Duclos disease (LDD), is char-

acterized by a lack of progression in most cases.² In the absence of these particularly favorable conditions, the prognosis of cerebellar GG in childhood may be variable. Here we describe a case of cerebellar GG in childhood, which emphasizes the quality of life in patients with long-term survival along with moderate-to-severe neurological impairment.

Mutations in the phosphatase and tensin homolog (*PTEN*) gene with resulting activation of the mammalian target of rapamycin (mTOR) pathway are common in adult LDD but are not established in childhood GC or GG.² We conducted histopathologic examination of the surgical specimen from the patient to obtain the basis for a possible treatment option with mTOR inhibitors.

PATIENT REPORT

The patient was born and normally developed until 3 years of age, when she manifested with right torticollis, drooped right corner of the mouth, and excessive drooling for her age. Intention tremor, dysdiadochokinesis, scanning speech, and nystagmus were noted on examination at 6 years of age. Magnetic resonance imaging (MRI) revealed a tumor in the right cerebellar hemisphere, intruding into the vermis, brainstem, and upper cervical cord (Figs. 1A and E). Histopathologic examination of the partially resected tumor revealed a mixture of ganglion-like and less prominent astroglia-like cells, which was consistent with a diagnosis of GG (Figs. 2A and B). Despite postoperative radiation therapy of 44 Gy, the tumor mass slowly expanded (Figs. 1B and F). The patient developed a wide-based gait with repeated falls, dysarthria, left-sided hearing loss, and frequent sleep apnea at 8 years of age, resulting in the use of a wheelchair at 9 years of age and nighttime noninvasive positive pressure ventilation (NPPV) and gastrostomy at 10 years of age. Temozolomide 200 mg/m²/day for 5 days every 4 weeks was initiated at 12 years of age, which prevented further expansion of the tumor (Figs. 1C and G). However, swelling of the infiltrated upper cervical cord developed at 17 years of age (Fig. 1D

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Abbreviations: GC, gangliocytoma; GG, ganglioglioma; LDD, Lhermitte–Duclos disease; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; NPPV, noninvasive positive pressure ventilation; P-S6, phosphorylated S6 ribosomal protein

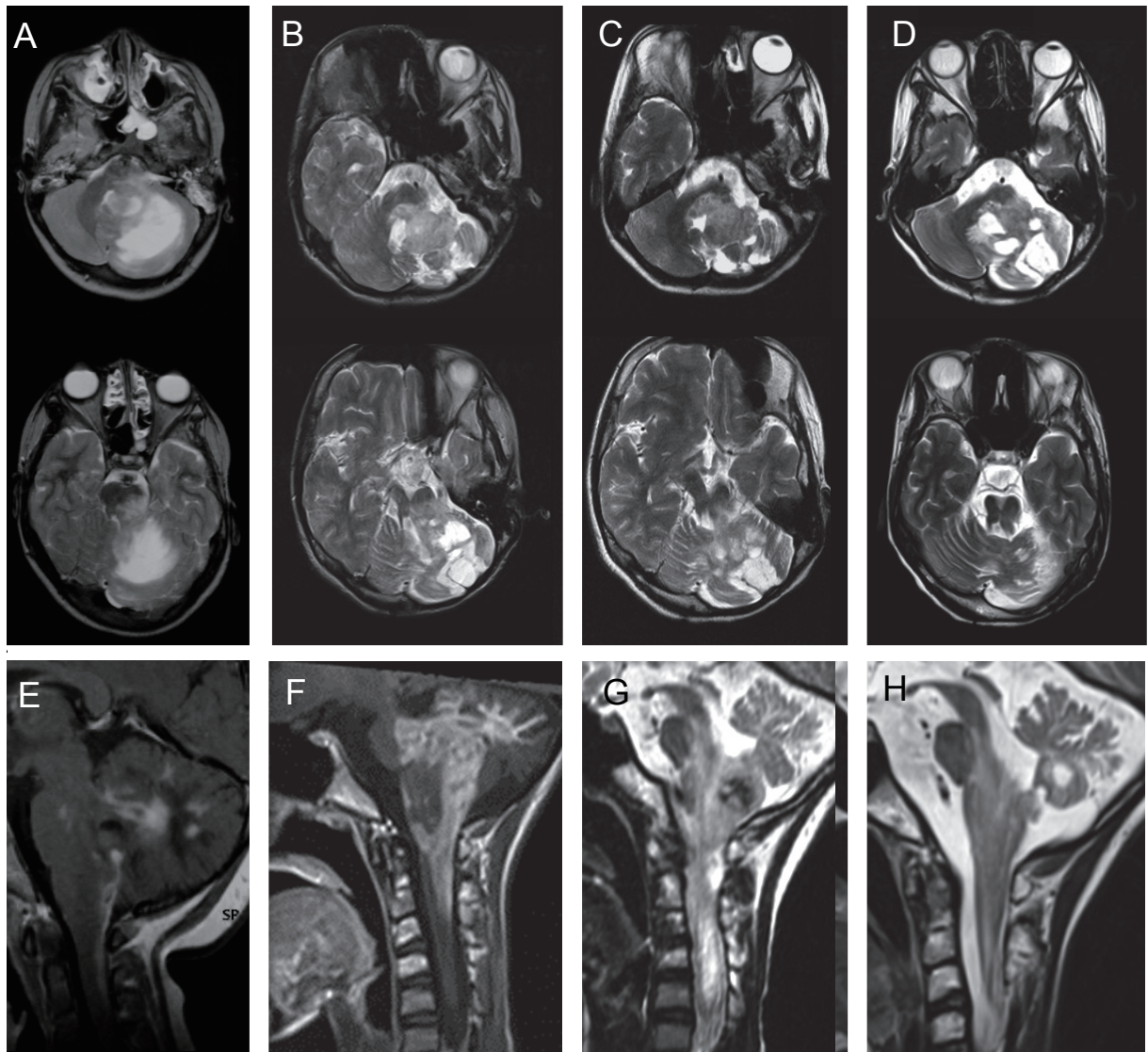


Fig. 1. Evolution of the infratentorial tumor on magnetic resonance imaging at the age of 6 years (**A, E**), 12 years (**B, F**), 13 years (**C, G**), and 18 years (**D, H**). **A–D, G**, and **H**: T2-weighted imaging; **E** and **F**: gadolinium-enhanced T1-weighted imaging.

and H). An additional administration of bevacizumab 10 mg/kg every 2 weeks resulted in amelioration of the edema and cavitation in the cervical cord. The patient has required recurrent hospital admission for bronchial asthma once or twice per year since the age of 12 years. She is currently 19 years old (height, 153 cm; weight, 38 kg). She has spastic tetraparesis with right-sided predominance and left facial paraplegia. Dysmetria in the left hand is also noted. She can stand up slowly from the supine position and walk by holding on to objects. Pharyngeal reflex is depressed, and tongue fasciculation is present. Her intelligence quotient at 15 years of age was assessed to be 51 (verbal, 56; performance, 55) using the Wechsler Intelligence Scale for Children (4th edition).

She graduated from a high school for disabled children and is now living with her family and participating in activities at local day-care centers.

Since the patient was 17 years old, we performed immunohistochemical investigation of the paraffin-embedded surgical specimen, with the hope of finding a basis for further treatment options. Surgical specimen was taken from the left posterior cerebellar hemisphere (see the square-shaped tissue defect at the left posterior cerebellum in the bottom image in Figs. 1B and C). Four-mm-thick sections were immersed in 3% hydrogen peroxide for 5 min to abolish endogenous peroxidase activity. The sections were incubated with the primary antibody against synaptophysin (mouse monoclonal, di-

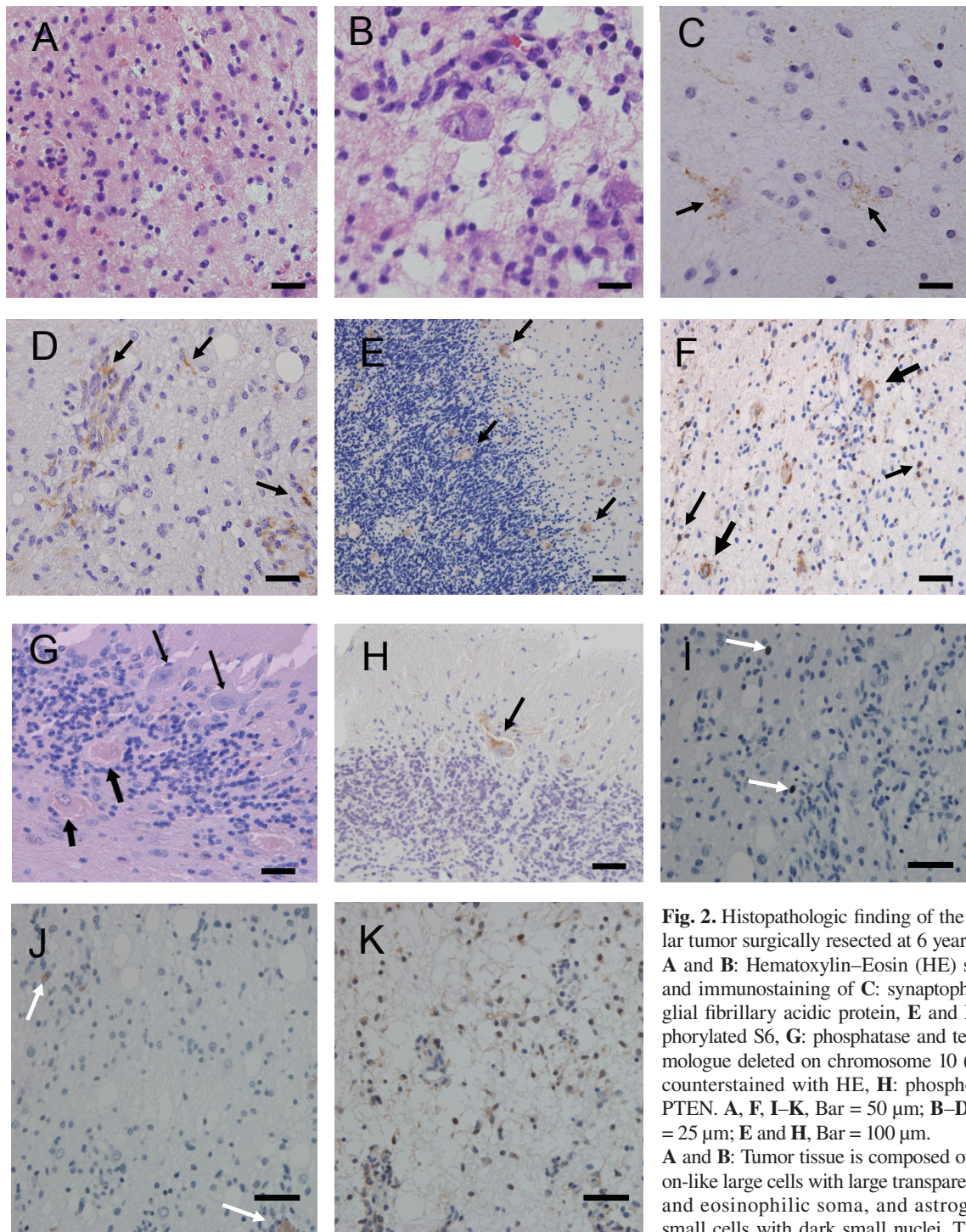


Fig. 2. Histopathologic finding of the cerebellar tumor surgically resected at 6 years of age. **A** and **B**: Hematoxylin–Eosin (HE) staining; and immunostaining of **C**: synaptophysin, **D**: glial fibrillary acidic protein, **E** and **F**: phosphorylated S6, **G**: phosphatase and tensin homologue deleted on chromosome 10 (PTEN); counterstained with HE, **H**: phosphorylated PTEN. **A**, **F**, **I–K**, Bar = 50 μ m; **B–D**, **G**, Bar = 25 μ m; **E** and **H**, Bar = 100 μ m.

A and **B**: Tumor tissue is composed of ganglion-like large cells with large transparent nuclei and eosinophilic soma, and astroglia-like small cells with dark small nuclei. These are compatible with the diagnosis of ganglioglioma [2].

Ganglion were immunopositive for synaptophysin (**C**, arrows), and astroglia-like cells are immunopositive for glial fibrillary acidic protein (**D**, arrows). **E**: Ganglion-like tumor cells (arrows) infiltrating from cerebellar white matter (right side) into the granular layer (left side), immunopositive for phosphorylated S6. **F**: Ganglion-like (thick arrows) and astroglia-like cells (thin arrows) replacing the cerebellar white matter, both immunopositive for phosphorylated S6. **G**: PTEN-positive ganglion-like tumor cells in the cerebellar white matter and granular layer (thick arrows). Note that the Purkinje cells (thin arrows) and granule cells are immunonegative for PTEN. **H**: Rare ganglion-like cells (arrow) are immunopositive for phosphorylated (inactivated) PTEN. **I–K**: Immunostaining in the deep white matter of the surgically resected specimen. **I**: Rare ovoid-shaped cells (arrows) are immunopositive for Ki-67. **J**: No cells are immunopositive for MGMT. Intravascular erythrocytes are falsely positive, presumably due to residual internal peroxidase activity (arrows). **K**: Many astroglia-like cells are immunostained with anti-P-S6 antibody (rabbit polyclonal, diluted at 1:200; Cell Signaling Technology, Danvers, MA). Bar = 50 μ m.

luted at 1:100; Boehringer-Mannheim, Indianapolis, IN), glial fibrillary acidic protein (mouse monoclonal, ready-to-use; BioGenex, San Ramon, CA), phosphorylated S6 ribosomal protein (P-S6) (rabbit polyclonal, diluted at 1:200; Cell Signaling Technology, Danvers, MA), PTEN (mouse monoclonal, diluted at 1:100; Santa Cruz, Dallas, TX), phosphorylated-PTEN (rabbit monoclonal, OriGene, Rockville, MD), Ki-67 (mouse monoclonal, ready to use, Clone MIB-1, DAKO, CA), or O6-methylguanine-DNA-methyltransferase (MGMT) (mouse monoclonal, ready to use, abcam, Cambridge, UK) overnight at 4 °C. The appropriate Vectastain Avidin-biotin-immunoperoxidase complex (ABC) kits (Vector Laboratories, Burlingame, CA) were used to detect bound the antibodies mentioned above. 3,3'-diaminobenzidine tetrahydrochloride (DAB) was the final chromogen. Between each step, the sections were thoroughly washed with phosphate-buffered saline 3 times.

As expected, the ganglion cell-like tumor cells were positive for synaptophysin (Fig. 2C), and the astroglia-like tumor cells were positive for glial fibrillary acidic protein (Fig. 2D). In addition, the ganglion cell-like and astroglia-like tumor cells were both immunopositive for P-S6, a downstream product of PTEN/mTOR pathway (Figs. 2E, F and K). In addition, most ganglionic cells were immunopositive for PTEN (Fig. 2G), and a small proportion of ganglionic cells were immunopositive for phosphorylated-PTEN (Fig. 2H). MIB-1 index was < 1% (Fig. 2I), and MGMT immunostaining was absent (Fig. 2J) in the surgical specimen.

DISCUSSION

Because the proportion of astroglia-like tumor cells was small in the surgical specimen, we were not confident that either GC or GG was the most appropriate pathologic diagnosis for the patient. However, the extension of the tumor into the brainstem and spinal cord and absence of the typical findings of GC in LDD, including the striated pattern in the cerebellar cortex on MRI and the thickened granular cell layer on histopathologic examination, were suggestive of a less favorable outcome. Progressive neurological impairment could be terminated only after initiation of combination therapy with temozolomide and bevacizumab, which is usually employed for treatment of anaplastic GG.³ Malignant transformation of GG preferentially occurs within the glial component.⁴ Evolution of a LDD-like tumor to GG, and subsequently to anaplastic GG,⁵ is consistent with this trend and suggests that glial proliferation can become obvious later in the course in childhood GC-like lesions. In the present case, mTOR activation in both the ganglion-like and astroglia-like cells on initial pathologic evaluation may further

support the primary gliomatous origin of glial cells and the diagnosis of GG. Retrospectively, the surgical specimen of tumor may have not reached the deep, possibly more malignant portion involving the brainstem (Figs. 1A and B). A second biopsy from the deep structure for assessment of MIB-1 index and MGMT immunostaining, along with genetic analysis of *CDKN2* deletion and *BRAF* V6000E mutation, might have revealed evidence of anaplastic transformation.^{7,8} However, we decided not to conduct the second biopsy before initiation of temozolomide and bevacizumab, considering the risk of surgical intervention at the advanced stage of illness.

In LDD, increased P-S6 immunoreactivity in GC tumor cells represents mTOR activation due to disruption of PTEN activity.^{2,6} However, PTEN expression was preserved and no *PTEN* mutation was detected in childhood cerebellar GC, in contrast to adult GC with LDD.^{2,6} This suggests that the pathological mechanism of childhood cerebellar GC is distinct from that in adult LDD. As in LDD, the mTOR pathway is activated in GG,^{9,10} as well as in low- or high-grade gliomas, in childhood.¹¹ *PTEN* gene methylation (inactivation) due to an unknown mechanism, accompanied by activation of the mTOR pathway, is linked to lower survival in cases of glioma.^{11,12} It remains to be elucidated whether mTOR activation and increased P-S6 expression in childhood GC or GG are caused by augmented *PTEN* methylation. The preserved PTEN immunoreactivity in our case suggests that childhood GG shares certain pathological mechanisms with childhood GC.² Interestingly, the mTOR inhibitor sirolimus was effective for refractory childhood ependymoma with augmented P-S6 expression proven by immunohistochemistry.¹³ Thus, mTOR inhibitors may be worth a trial in childhood gliomas and GG, particularly with findings of mTOR activation in the tumor tissue.

Childhood cerebellar GC or GG can have a slowly progressive course, as in the present patient. Treatment strategies and physico-social aids may need to be specifically planned in individual patients; atypical findings for LDD on neuroimaging, proliferation of glial components, and activation of the mTOR pathway on histopathologic examination of the surgical specimen may indicate a risk of progressive disease. We may need to be prepared for possible treatment options, including temozolomide, bevacizumab, and mTOR inhibitors. These regimens require only oral administration or short-term admission, thereby permitting outpatient treatment. To obtain a better quality of life in patients with long-term survival with moderate-to-severe neurological impairment, NPPV and gastrostomy could be helpful for children with cerebellar GC or GG and brainstem involvement.

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The authors declare no conflict of interest.

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