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A role for early surgical intervention in childhood low-grade glioma? Illustrative case

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BACKGROUND *IDH*-mutant diffuse gliomas are considered low grade, albeit with a propensity for malignant behavior over time, distinguishing them from pediatric-type low-grade gliomas. *IDH*-mutant tumors have astrocytic or oligodendrocytic phenotypes associated with *TP53* and *ATRX* mutations or *1p/19q* deletions, respectively. *TP53* mutations are associated with a tumor that acquires malignant properties characteristic of glioblastoma with subsequent very poor survival.

OBSERVATIONS The authors present the case of a 12-year-old female who presented with an incidental T2-FLAIR bright lesion in the right frontal lobe. Although clinically asymptomatic, there was interval minimal but definite growth on serial imaging over 5 years, and she underwent resection. Molecular pathology indicated an isolated *IDH1* mutation, without cooperating molecular changes.

LESSONS *IDH*-mutant gliomas, although typically an adult disease, may be diagnosed in childhood or adolescence. This early diagnosis of a tumor before it has acquired cooperating events suggests childhood origin and long latency for this more typical adult tumor. Early recognition and treatment of these tumors, before they reach their full malignant potential, may yield therapeutic benefit. Surgery may also play a key role to eliminate neoplastic cells and the acquisition of more fully malignant clones that may become more aggressive and drive disease progression many years later.

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KEYWORDS pediatric; astrocytoma; low-grade glioma

Low-grade gliomas are the most common childhood and young adult tumors. While management can be challenging related to their location and heterogeneity, increasingly sophisticated molecular diagnostics are modifying medical and surgical decision-making for these tumors.

Compared with adults, children with low-grade gliomas generally have a favorable long-term prognosis, with a lower propensity for malignant transformation.[1] We have learned that some lower-grade pediatric tumors harboring specific mutations, such as *BRAF V600E*, are best treated in the earliest stages of the disease. These tumors tend to become aggressive with time, suggesting benefits for early medical or surgical efforts to completely eliminate the disease and prevent or delay transformation.[2,3] Pediatric-type gliomas are typically driven by alterations in the RAS–mitogen-activated protein kinase pathway;[4] in contrast, adult-type lower-grade gliomas harbor *IDH1/2* mutations, which have a greater tendency to evolve into high-grade gliomas. Emphasis on early intervention has increased in an era in which tumors can be identified incidentally and early on in the disease process.[5]

Illustrative Case

We present the case of a previously healthy 12-year-old female who was presented with a T2 hyperintense cortical right frontal lesion (Fig. 1). This was first discovered during a workup for intermittent headaches and self-limiting diplopia, but otherwise no focal neurological deficits; the lesion was thought to be asymptomatic. She was diagnosed at the time with idiopathic intracranial hypertension by neurology and was treated with a brief course of acetazolamide (Diamox), with complete symptom resolution.

ABBREVIATIONS GBM = glioblastoma.

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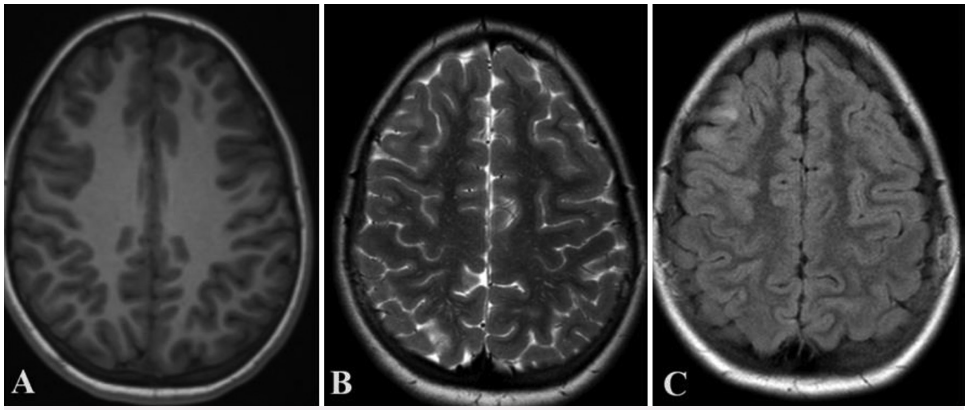

FIG. 1. Baseline axial T1-weighted (**A**), T2-weighted (**B**), and FLAIR (**C**) MR images demonstrating an ill-defined T2-FLAIR hyperintense lesion in the right middle frontal gyrus.

Her lesion was then monitored with serial imaging. Although she remained asymptomatic, 5 years later she demonstrated interval growth of her lesion on MRI from 21 × 21 × 22 mm to 25 × 24 × 24 mm (Fig. 2). The patient was left-handed, but functional MRI demonstrated bilateral language representation. The lesion was assessed to be above Broca's area based on typical right-sided dominant anatomy. After discussion with the multidisciplinary neuro-oncology team, the decision was made to proceed with resection of the lesion to obtain tissue for diagnostic clarification and prognostication. She subsequently underwent a right frontal craniotomy for resection of the lesion (Fig. 3). Her postoperative course was remarkable for several episodes of seizures, for which she was treated with dexamethasone and levetiracetam. Final pathology was consistent with a WHO grade 2 diffuse astrocytoma with an isolated *IDH1* mutation. No additional alterations were detected by copy number analysis or next-generation sequencing including *ATRX*, *TP53*, and *1p/19q*. Several months later, a routine postoperative MRI was concerning for some T2-FLAIR thickening along the posterior resection margin (Fig. 4). Given the concern of disease progression and potential mutational evolution to a more aggressive entity, the patient underwent an uneventful repeat resection of the abnormal region approximately 1 year after her initial surgery (Fig. 5). The final surgical pathology was identical to the initial diagnosis, with an isolated *IDH1* mutation and no evidence of other cooperating genetic events. She has subsequently had no progression on imaging after a further 2 years of follow-up (Fig. 5).

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Observations

IDH is a catalytic enzyme in the Krebs cycle; *IDH1*-mutant proteins, acting in concert with wildtype protein, result in a buildup of 2-hydroxyglutarate, an oncometabolite thought to promote tumorigenesis via alteration of the epigenetic methylation state of the cell.[6] *IDH1* mutations are present in the majority of adult low-grade gliomas, and although, in comparison with glioblastoma (GBM), they have a better prognosis, these tumors are associated with significant mortality over 10–15 years. Recently, *IDH*-specific inhibitors have been suggested to have an impact on the survival of these patients, as well as delaying transformation to more aggressive forms typical of GBM.[7]

While the precise timing remains unclear, it is thought that *IDH1* is the inciting oncogenic hit in gliomagenesis, followed by *TP53* and

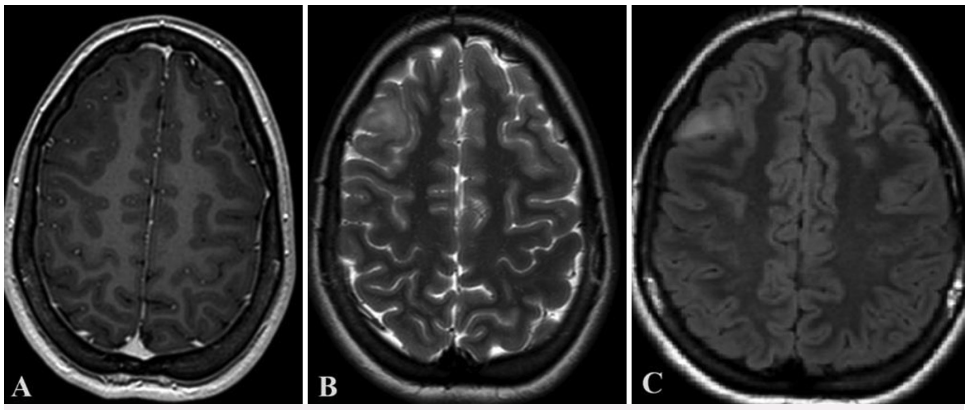

FIG. 2. Follow-up axial T1-weighted (**A**), T2-weighted (**B**), and FLAIR (**C**) MR images demonstrating interval development of the previous T2-FLAIR hyperintense lesion in the right middle frontal gyrus.

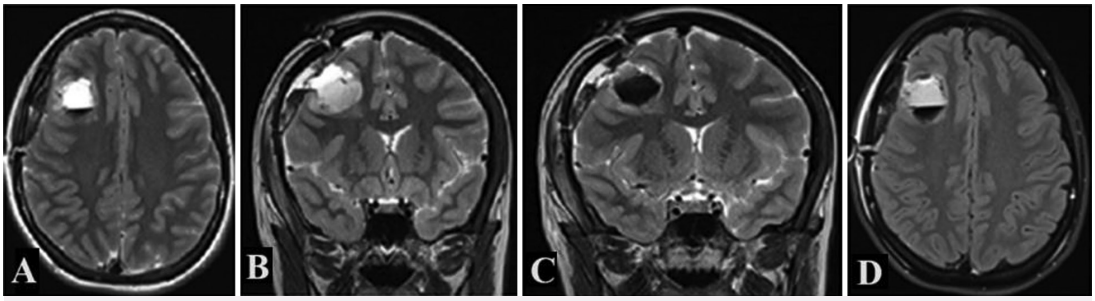

FIG. 3. Immediate postoperative axial T2-weighted (**A**), coronal T2-weighted (**B and C**), and axial FLAIR (**D**) MR images demonstrating air-fluid levels in the postsurgical cavity and an extra-axial hemorrhagic collection.

then *ATRX*, which are involved in genomic stability.[8] *TP53* mutations are seen in approximately 94% of *IDH1*-positive astrocytoma cases, and *ATRX* inactivation in approximately 86% of cases.[9] It is unknown over what time period cells acquire these additional mutations. The presented case suggests that the inciting oncogenic event may occur in childhood or adolescence. Interestingly, GBM-associated mutations have been reported in normal brains,[10] where cells of both neuronal and glial lineage harbor the same mutations, suggesting that adult glioma may have origin in the embryonic period. The occurrence of *IDH* mutations in childhood also raises important questions about the developmental origins of these alterations.

The fifth edition of the World Health Organization classification of CNS tumors marked the incorporation of molecular biomarkers in tumor diagnosis and classification. This paradigm shift is attributed to the improved uniformity of biomarkers across tumors and the ability to offer more detailed information for prognostication. The clinical importance of *IDH* is reflected by the grouping of adult gliomas, which consist of three categories: astrocytoma *IDH*-mutant, oligodendroglioma (*IDH*-mutant and *1p/19* deletions), and GBM (*IDH*-wildtype).[11] *IDH* mutations have also been reported associated with hereditary mismatch repair deficiency and *1p/19q* co-deletion, where they are associated with worse prognosis.[12,13] While the majority of *IDH*-mutant low-grade glioma cases can be further characterized by co-occurring alterations, the present case was unusual in that pathology was consistent with a diffuse astrocytoma with an isolated *IDH1* mutation. In one study, 4 of 40 adult patients (mean age 37.0 ± 10.0 years) also presented with a lone *IDH1* mutation on an initial biopsy, with the second follow-up biopsy demonstrating subsequent *TP53* mutations.[14] However, the time lapse between the biopsies was not specified, and resection was not performed in these patients.

The management of low-grade pediatric gliomas has undergone a paradigm shift with the rising era of molecular diagnostics. Historically, slow-growing tumors in the pediatric age group have often been treated expectantly, as large-cohort studies have demonstrated that pediatric low-grade gliomas tend to remain quiescent with time and do not undergo malignant transformation.[1] However, the growing emphasis on incorporating targeted therapeutics as a part of the treatment regimen for pediatric low-grade gliomas has created a new impetus for tissue diagnosis (e.g., optic pathway gliomas were typically treated based on radiographic features due to the risks and challenges associated with a biopsy), and surgical biopsies are now being performed more frequently to facilitate therapeutic options.[15] While rare in children, the ultimate malignant and treatment-refractory behavior of *IDH*-mutant pediatric tumors suggests that more aggressive approaches should be considered at earlier stages of disease This suggests the potential clinical utility of early resection of low-grade gliomas with lone *IDH1* mutations or otherwise small but more molecularly advanced tumors.

Cancer biology strongly supports that malignant tumors arise from molecular events in single cells, and these cells then undergo clonal growth and tumor evolution. Malignant clones may also arise from a larger field of abnormal premalignant cells. Specifically, early

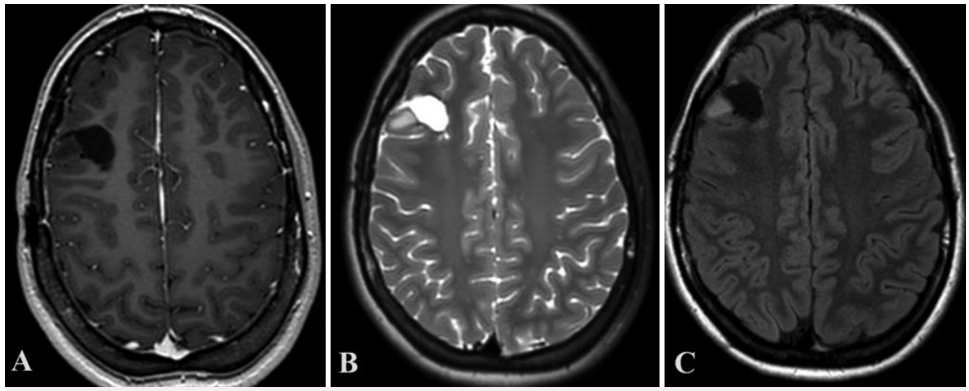

FIG. 4. Delayed postoperative axial contrast-enhanced T1-weighted (**A**), T2-weighted (**B**), and FLAIR (**C**) MR images demonstrating local recurrence.

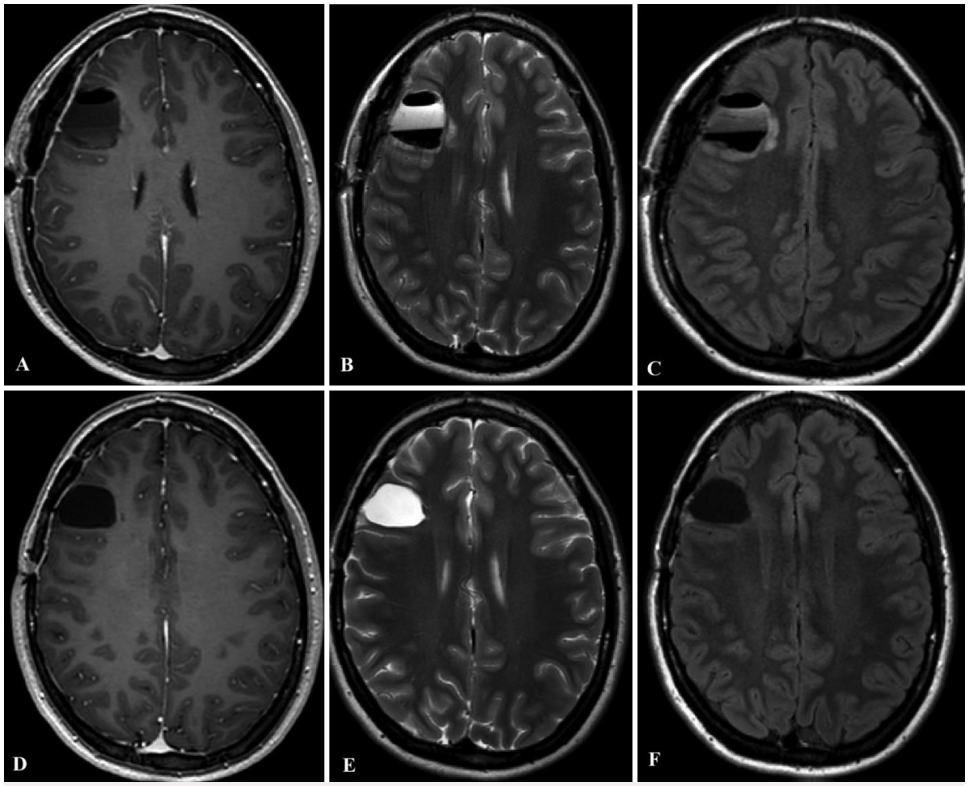

FIG. 5. Postoperative axial contrast-enhanced T1-weighted (A and D), T2-weighted (B and E), and FLAIR (C and F) images after the redo resection. **A–C:** Initial scans obtained on postoperative day 2, demonstrating a fluid-filled right frontal resection cavity with minimal diffusion restriction and T2-FLAIR hyperintensity along the rim of the resection cavity. **D–F:** Delayed scans obtained 6 months postoperatively, demonstrating reduction in the size of the surgical cavity with reduction in the surrounding signal abnormality and no new signal abnormality or abnormal enhancement at the surgical site.

resection of superficial lesions, maybe even considered "premalignant," in noneloquent regions theoretically may allow surgical cure prior to molecular progression and the development of a second or third oncogenic hit. This is of particular interest as *IDH1*-positive astrocytomas have a propensity for the frontal lobe, wherein gross-total resection with minimal morbidity is often possible, and thus there is potentially a better survival benefit without high morbidity.[16] *IDH1/2* mutations are less common in the pediatric age group, occurring in less than 1% of patients younger than 9 years of age and in approximately 16% of patients between 10 and 21 years.[17] Given their rarity, there is uncertainty as to their natural history among this population. In their multicenter study, Yeo et al. found that 25 of 58 pediatric cases with an initial low-grade diagnosis recurred or progressed to a higher-grade glioma at follow-up.[17] Pediatric low-grade gliomas with *IDH1/2* mutations may represent a unique population and be relatively early in their molecular course compared with their adult counterparts, and may benefit from aggressive early treatment to intercept later more malignant behavior.

Another consideration is the role of liquid biopsies in this unique population, which would facilitate early detection and intervention. This may serve as a useful tool in monitoring tumor evolution along with postoperative monitoring in cases with subtotal resection or evidence of early disease recurrence. A challenge may be that lower-grade tumors may be harder to capture with liquid biopsy, which is also an area for further exploration.

Lessons

Isolated *IDH1* mutations in the setting of a pediatric astrocytoma are an uncommon phenomenon. Suspicious lesions need molecular diagnosis and consideration of treatment, particularly as targeted therapy is being developed that shows promise in delaying progression.[18,19] However, removal of all potential malignant clones by resection may offer advantages over medical therapy when surgery has relatively low risks. Therefore, early resection, especially of noneloquent lesions, may play a critical role in the interception of an otherwise aggressive disease that plays out over many years.

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Disclosures

Dr. Hawkins reported personal fees from Servier outside the submitted work. Dr. Das reported personal fees from Servier Canada for participating on an advisory board outside the submitted work. Dr. Bennett reported personal fees from Servier Canada for participating on an advisory board on two occasions outside the submitted work.

Author Contributions

Conception and design: Jung, Tabori, P Dirks, Quon. Acquisition of data: Hawkins, Tabori, Quon. Analysis and interpretation of data: Jung, Hawkins, Tabori, Das, P Dirks, Quon. Drafting the article: Jung, J Dirks, Quon. Critically revising the article: Jung, Tabori, Das, Bennett, P Dirks, Quon. Reviewed submitted version of manuscript: Tabori, Bennett, P Dirks, Quon. Approved the final version of the manuscript on behalf of all authors: Jung. Statistical analysis: Quon. Administrative/technical/material support: Quon. Study supervision: Tabori, Quon. Performed literature review: J Dirks.

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