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CASE STUDY

Molecularly targeted treatment of recurrent anaplastic astrocytoma – a case report

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Abstract

High-grade astrocytomas are malignant and aggressive, with limited treatment options. Treatment is geared not only toward increasing patient's overall survival but also in delaying or preventing neurological disability, a cause of significant morbidity. Increasingly, targeted and customized treatment approaches, especially for recurrent disease, are being explored. Here we present a successful outcome in a young patient with rapidly progressive disease who responded to targeted treatment based on genetic sequencing and circulating tumor DNA markers, given the inaccessibility of the tissue to biopsy. Molecular testing on tissue, serum or CSF may be helpful in identifying unique targets in these complex patients.

Introduction

Anaplastic astrocytomas (AA) are malignant glial tumors that carry a World Health Organization (WHO) grade III. Overall, 5-year median survival can range from 22% to 50%, depending on various prognostic features including patient's age, tumor location and genetics, resection, etc.[1,2] Given the higher grade and increased likelihood of transformation to WHO grade IV tumors (glioblastomas), these tumors are generally treated aggressively upfront. Standard treatment involves surgical resection, radiotherapy, and chemotherapy, but treatment options are greatly limited for progression and recurrence. Brainstem location increases complications given the technical challenge in achieving a radical resection without causing morbidity and limitations in radiation due to toxicity.

Case Presentation

A 16-year-old female with no significant medical or family history presented with a 1-month history of headaches and diplopia. Imaging revealed an enhancing lesion of the brainstem measuring 1.7 × 1.9 × 4.9 cm (Figure 1A1-3). A limited stereotactic biopsy of the lesion was undertaken which demonstrated features consistent with WHO Grade III AA, with a Ki-67 index of 10%. The tissue was evaluated at an outside pediatric oncology center, and Foundation One© next-generation sequencing was performed on the tissue, demonstrating negative isocitrate dehydrogenase (IDH) status and no mutation in the histone (H3) gene, O6-methylguanine-DNA methyltransferase (MGMT) status was not assessed on this panel. This testing also detected alterations in genes encoding the following proteins: phosphatidylinositol 3-kinase (PI3KCA – R140), neurofibromin 1 (NF1 – R816), fibroblast growth factor receptor (FGFR – N548K), and cyclin-dependent kinase 2a/b (CDKN2A/B - deletion). The patient received focal radiation and was treated with carboplatin and etoposide. She progressed 6 months after radiation and was started on combination treatment with temozolomide, bevacizumab, and irinotecan. Disease progression 2 months later resulted in a trial of pembrolizumab, but the tumor progressed again after two cycles of treatment. Clinically, the patient was rapidly declining, with an exam revealing dysphagia, diplopia, gait imbalance, and lower extremity weakness to the point that she was wheelchair-bound. She was on 8mg daily of dexamethasone with no improvement in clinical function.

The patient presented for a second opinion to our center at this point. Imaging revealed an expansile, T2-

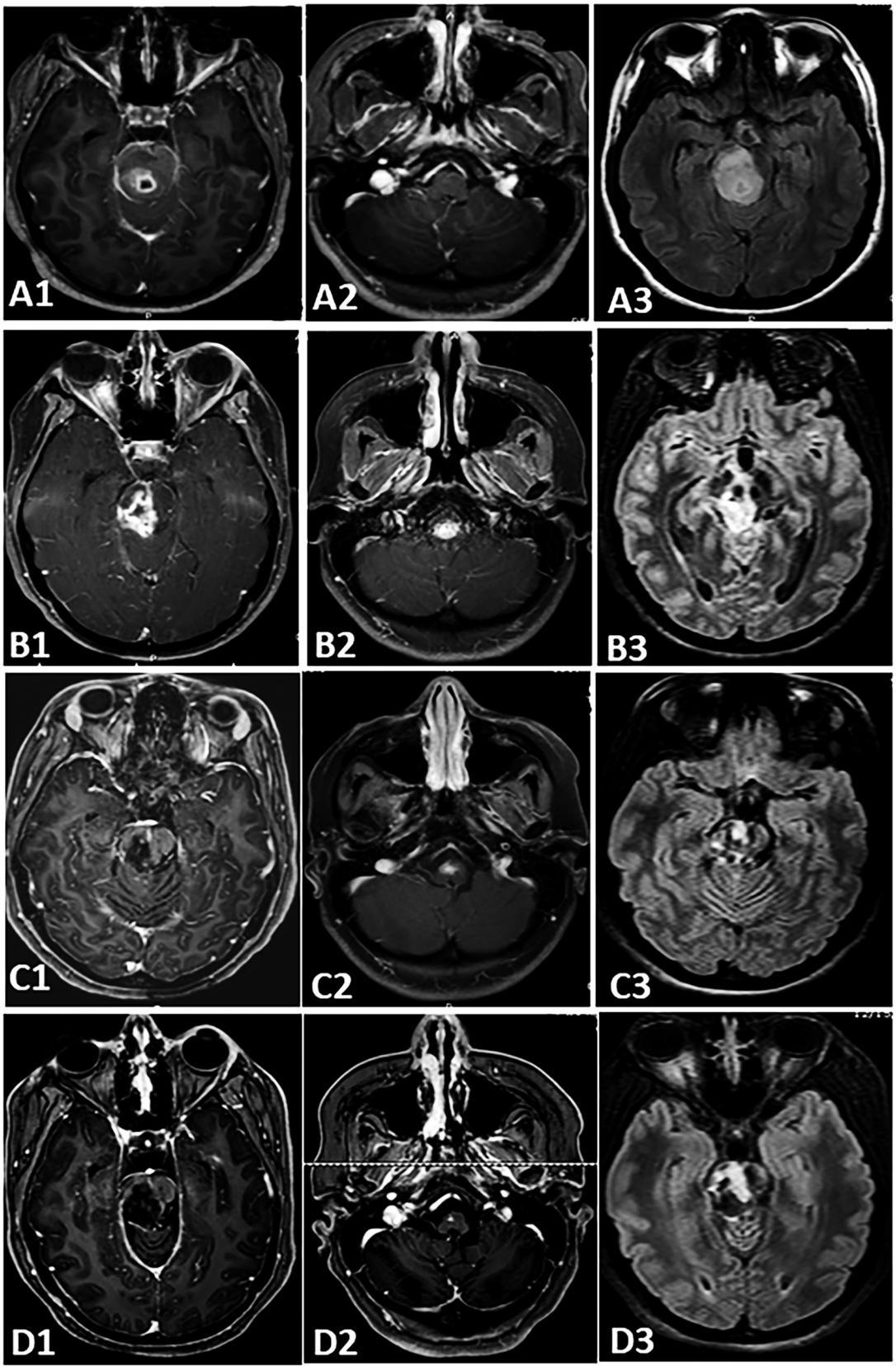

Figure 1. MRI Brain – Disease evolution over time. A1–3: 10/3/2014: Post-contrast and FLAIR MRI axial sequences when the patient was first diagnosed, revealing a midbrain lesion (A1) and no disease in the medulla (A2) with significant FLAIR effect (A3). B1–3 10/29/2015: Imaging when patient first established care with us, prior to everolimus treatment, with enhancing disease in the midbrain (B1) now extending down to medulla (B2) with associated FLAIR signal (B3). C1–3 9/25/2017: Over a year after treatment onset, there is notable improvement in the lesion in the midbrain (C1) and the medullary extension is smaller (C2). D1–3 12/15/2020: Most recent MRI demonstrates a continued lack of enhancement in the midbrain (D1) and a residual speck of enhancement lower down (D1) with evolving FLAIR signal.

hyperintense mass involving the tectum, right cerebral peduncle, right medial thalamus, midbrain, and pons, with progression lower down in the medulla (Figure 1B1-3). No disease was identified in the cerebrospinal fluid and spinal axis imaging did not reveal leptomeningeal disease. Repeat biopsy of the lesion was not considered safe given its location. Instead, advanced genetic testing was obtained with Guardant360© testing of the plasma. The testing confirmed that there were still tumor mutations that could be picked up peripherally—a mutation in the PI3KCA gene (specifically, an alteration in the R140 codon) and the CDKN2A/B loss. This was also confirmed with Foundation One© liquid biopsy testing. One month after the initial appointment and approximately 14 months after the initial diagnosis, the patient was started on everolimus at 5mg daily. The dose was increased to 10mg after 1 week. The patient has been on this dose for 5 years now with dramatic tumor shrinkage and without further progression of disease (radiographically or clinically) (Figure 1C1-3, D1-3). She was weaned off dexamethasone over a period of 9 months after the initiation of everolimus and has not required it again. The patient's neurological exam has been stable with no further decline. Primary side effects attributable to the treatment have been acneiform rash and mucositis, which occurred in the first year of treatment.

Of note, Guardant360© was repeated about 1 year after treatment was initiated and PI3KCA somatic mutation was still detected. Repeat testing over the last 4 years, with the most recent test in October 2020, has not revealed any detectable amount of mutated tumor DNA at all.

Discussion

Anaplastic astrocytomas can be highly aggressive with a high risk of tumor recurrence. Younger patients tend to have a better prognosis and overall survival, likely in part due to better functional status and tolerance of treatment.[3] Brainstem location of high-grade gliomas adds an additional layer of complexity—infiltrative growth in this area can rapidly impact key function and result in significant neurological morbidity. Resection here is almost impossible for the same reasons, unlike hemispheric lesions that may at times be able to undergo maximal resection (thus further improving prognosis). Standard therapy has been used in these gliomas, largely due to a lack of better options and an insufficiency understanding of the tumor biology and differences here. Over the last several years the field has made progress in this area, with increased understanding of the varied genomic alterations within this subgroup itself. Histone mutations—primarily noted in histone 3 (H3)—can be evaluated for, along with consideration of location, patient age, and several other mutations (isocitrate dehydrogenase (IDH), tumor protein 53 (TP53), etc.) to gather additional information on the behavior of the lesion. Chen et al integrate much of this genetic data to group the brainstem gliomas into different categories in their 2020 study.[4] In AAs in general, various mutations have been increasingly characterized for prognostic and treatment implications, including CDKN2A/B and P13KCA.

In this patient with high-grade brainstem glioma and an NF-1 mutation, everolimus, a rapamycin derivative and mammalian target of rapamycin (mTOR) kinase inhibitor was used to target the NF-1 mutation. Everolimus is an inhibitor of the mTOR pathway which successfully treats subependymal giant cell astrocytoma (SEGA).[5] The drug has been investigated as a treatment for various solid tumors, with mixed result.[6] Studies in glioma have thus far been discouraging but the prospective matching of molecular mutations to treatments has been challenging in the field.[7] With this case, we aimed to target treatment to available molecular information, but had to rely on other options for testing and monitoring given the challenges in obtaining a viable tissue sample.

Circulating tumor DNA (ctDNA) and cell-free DNA (cfDNA) testing options are becoming increasingly available and are being studied in brain tumor patients, where they offer the ability to identify targets for treatment and monitoring without invasive biopsies.[8] Dying and viable tumor cells release ctDNA which may be extracted, amplified, and sequenced in plasma and cerebrospinal fluid. While the technology is still early, has low sensitivity, and may be confounded by sample processing and storage, ctDNA does have the potential of specifying key mutations that may be targeted and/or followed. Here, we identified key mutations that had therapeutic and prognostic implications.

To start, NF1-deficient astrocytes exhibit greater levels of protein synthesis compared to wild-type astrocytes.[9] Moreover, NF-1 functions as a negative regulator of RAS, a protein involved in cellular signal transduction. One downstream target of activated RAS is the PI3KCA

signaling pathway. Loss of neurofibromin is not only associated with hyperactivation of RAS, but also the hyperactivation of the PI3K-AKT (protein kinase B) signaling pathway. The mammalian target of the rapamycin (mTOR) pathway, which is activated by this PI3K-AKT signaling pathway, has a role in cell growth and proliferation by its role in the phosphorylation of ribosomal S6. This phosphorylation machinery and hyperproliferative signals to the ribosomal machinery increases protein synthesis, contributing to the uncontrolled cell growth seen in NF-1 deficient astrocytes.[9]

Mutations in the PI3KCA gene observed in 6%–15% of glioblastomas are correlated with shorter survival (both progression-free and overall) and were more likely to occur in younger patients with more aggressive, disseminated disease at presentation.[10] Mutations in the tumor suppressor gene NF-1 also portend a worse overall prognosis, given they allow for uncontrolled proliferation of cells as discussed above.[11] We also know that CDKN2A also encodes key proteins that are involved in tumor suppression; mutations in this gene are associated with various types of cancer. In the patient described here, we were able to follow response not just by imaging and clinical response, but also by noting that tumor fragments identifying these abnormal mutations were no longer present in the circulating tumor DNA on repeat testing after prolonged treatment.

Conclusion

While this is a single case report, it illustrates successfully the movement of glioma treatment toward a precision approach with targeted therapy for each patient based on their molecular markers. The approach is exciting but poses challenges since large, randomized control trials powered to significance will be difficult to undertake since the molecular signature of each tumor is unique and may also change with radiation and treatment. Here, personalized treatment with everolimus has successfully aborted progression and stabilized and regressed an aggressive tumor in a young person.

Conflict of Interest

The authors report no conflict of interest relevant to the manuscript.

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