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Rebecca P. Bystrom
Maine Medical Center

Pavalan Selvam

Jens Rueter
The Jackson Laboratory

Honey Reddi
The Jackson Laboratory

Christine Lu-Emerson
Maine Medical Center

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CASE REPORT

Clinical Utility of Molecular Profiling in Recurrent Glioblastoma Multiforme

Rebecca P Bystrom MD,[1] Pavalan Selvam MBBS,[2] Jens Rueter MD,[3] Honey V Reddi PhD,[4] Christine Lu-Emerson MD[1]

[1]Department of Neurology, Maine Medical Center, Portland ME, [2]The Jackson Laboratory for Genomic Medicine, Farmington, CT, [3]The Maine Cancer Genomics Initiative, The Jackson Laboratory, Augusta, ME, [4]Medical College of Wisconsin, Milwaukee, WI

Introduction: Glioblastoma multiforme (GBM) is the most common and aggressive primary malignant brain tumor found in adults. GBM has limited therapeutic options. Initial tumor sampling establishes the histopathologic diagnosis, identifies prognostic and therapeutic biomarkers, and provides an opportunity for molecular profiling. By contrast, the utility of repeat tumor sampling and molecular profiling in recurrent GBM is not well established.

Clinical Findings: We present a 69-year-old woman with GBM whose tumor recurred after standard treatment with temozolomide (TMZ) and concurrent radiation, followed by adjuvant TMZ. This patient had a methylated O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter, which ordinarily predicts a favorable response to TMZ.

Main Diagnosis, Therapeutic Interventions, and Outcomes: Our patient's recurrent tumor was rechallenged with TMZ based on persistent methylation of the *MGMT* promoter. However, her tumor was refractory to TMZ, and she floridly progressed through multiple treatments. We performed retrospective molecular profiling using next-generation sequencing (NGS) on her recurrent tumor. The NGS results showed a TMZ hypermutation signature that confers resistance to TMZ. This signature impacted our patient's treatment plan in real time and prompted an immediate discontinuation of TMZ.

Conclusions: Advances in NGS provide further insight into the molecular landscape of GBM. As NGS becomes more timely and cost-effective, molecular profiling of recurrent tumors could impact treatment decisions through either avoiding a particular treatment paradigm or identifying a potential targetable mutation. For this reason, we suggest that clinical practice routinely consider repeat biopsy and molecular profiling for recurrent GBM.

Keywords: glioblastoma, temozolomide, next-generation sequencing

A 69-year-old woman presented with weakness and paresthesia in her right lower extremity. Magnetic resonance imaging (MRI) of the brain showed enhancing lesions at the left fronto-parietal junction and in the left occipito-parietal lobe (Figure 1A and 1B). Complete resection of the left occipital lesion revealed a isocitrate dehydrogenase 1 (*IDH1*) wildtype glioblastoma multiforme (GBM) with a methylated O^6-methylguanine-DNA methyltransferase (*MGMT)* promoter. Sequencing was not performed as it was not routinely available at that time. The patient proceeded with 6 weeks of chemoradiation with TMZ and 12 cycles of adjuvant TMZ. Bevacizumab, a recombinant humanized monoclonal antibody against vascular endothelial growth factor, was added for pseudo-progression.

Four months after treatment cessation, a surveillance MRI showed a new enhancing lesion in the contralateral frontal lobe (Figure 1C). Repeat biopsy showed an *MGMT* methylated *IDH1* wildtype recurrent GBM. Due to *MGMT* methylation status, the patient was rechallenged with a hypo-

Correspondence: Christine Lu-Emerson MD
Department of Neurology, Maine Medical Center
49 Spring Street
Scarborough, ME 04038
cluemerson@mmc.org

fractionated course of chemoradiation with TMZ. Yet the next MRI showed frank progression. Bevacizumab was initiated as monotherapy before reintroducing adjuvant TMZ. The patient progressed with new enhancement in the left temporal lobe (Figure 1D).

Molecular profiling (ActionSeq Plus/ActionSeq Plus 2.0 by the Jackson Laboratory for Genomic Medicine, Farmington, CT) of the patient's recurrent tumor revealed a 'TMZ hypermutation signature.'[1] This signature had an MSH6 mutation and 153 variants of unknown clinical significance and 261 genomic events with C>T transitions compared to 175 genomic events with C>T transitions in the original tumor. Based on this hypermutation profile, we discontinued TMZ and started pembrolizumab (an antibody against programmed cell death protein-1 and approved for *MSH6* mutations) and bevacizumab. Unfortunately, the tumor became too invasive, with diffuse involvement of the brain. After 6 weeks of treatment, the patient was transitioned to hospice.

DISCUSSION

Initial tumor sampling after surgical resection of GBM enables histopathologic diagnosis and molecular testing that assesses prognostic and therapeutic biomarkers. The methylation status of the *MGMT* promoter is one of the strongest prognostic and predictive biomarkers in GBM.[2] This *MGMT* promoter methylation is associated with a more favorable response to TMZ and improved overall survival.[2,3] When methylated, the *MGMT* promoter silences the *MGMT* gene, which leads to fewer successful repairs of O^6-meG, the byproduct of TMZ treatment.[1]

In recurrent GBM, there are limited treatment options and no prognostic or therapeutic biomarkers. Treatment often consists of adjusting chemotherapeutic or biologic agents, and it may involve reintroducing alkylating agents, such as TMZ or lomustine. Bevacizumab, an antiangiogenic agent, has also been approved for use in recurrent GBM.[4]

Repeating a brain biopsy solely for the purpose of molecular analysis of recurrent GBM is not routine clinical practice. Surgery is reserved for significant debulking as it confers a survival advantage.[5,6] In clinical practice, it is often assumed recurrent GBM tumors harbor the same molecular features as the initial tumor. For instance, if the newly diagnosed GBM has a methylated *MGMT* promoter, the assumption is that the *MGMT* promoter will remain methylated at recurrence and confer the same prognostic and predictive value. However, different molecular phenotypes can emerge at recurrence and only be revealed with repeat molecular profiling.

To illustrate, the TMZ hypermutation phenotype is associated with TMZ resistance. This phenotype can emerge in recurrent GBMs that are initially exposed to TMZ. When tumors with a methylated *MGMT* promoter are treated with TMZ, the increased O^6-meG adducts are funneled toward the mismatch repair pathway[1]. If tumor cells acquire mutations in any component of this pathway, such as the *MSH6* gene, then G:C>A:T transitions can accumulate, preventing tumor cell death. This 'TMZ hypermutation signature'[1] creates a survival advantage for the recurrent tumor. This hypermutation signature can only be identified by repeat biopsy and molecular profiling in the recurrent tumor. Uncovering the hypermutation signature can prevent further exposure to TMZ and may dictate new treatment paradigms, including those that incorporate immunotherapy.[7]

The TMZ hypermutation signature cannot be detected using conventional laboratory testing. Its detection requires molecular profiling using high-throughput technologies such as next-generation sequencing (NGS), which is now readily available through academic and commercial laboratories. NGS typically analyses 50 to 500 cancer-related genes in parallel. It enables the identification of new comprehensive biomarkers and also assesses a tumor's mutational burden. Various applications of NGS can be developed to bypass concerns regarding the timely application of this technology in the clinical setting. For instance, to identify the TMZ hypermutation phenotype, a rapid assessment of the number of G:C>A:T transitions and tumor mutational burden may suffice. Our local laboratory estimates that the presence or absence of the hypermutation phenotype could be communicated to clinicians as quickly as 7 to 10 days.

There are technical limitations to using NGS sequencing in GBM, including the amount of tissue needed for testing and the degree of neoplastic content in tumor samples. Cost is also a consideration if incorporating additional molecular testing into the management algorithm. While NGS

can be cost-effective, the reimbursement model in clinical practice has not been fully established.[8]

The utility of repeat biopsy for molecular profiling in recurrent GBM has not been previously established. We present a case in which repeat molecular profiling could have provided guidance for treatment. Despite the change in treatment, the patient rapidly progressed, underscoring the challenges in treating recurrent GBM. Earlier application of pembrolizumab may have been more beneficial. Timely incorporation of molecular profiling for recurrent GBM may guide appropriate targeting of mutations or avoidance of specific chemotherapeutic agents.

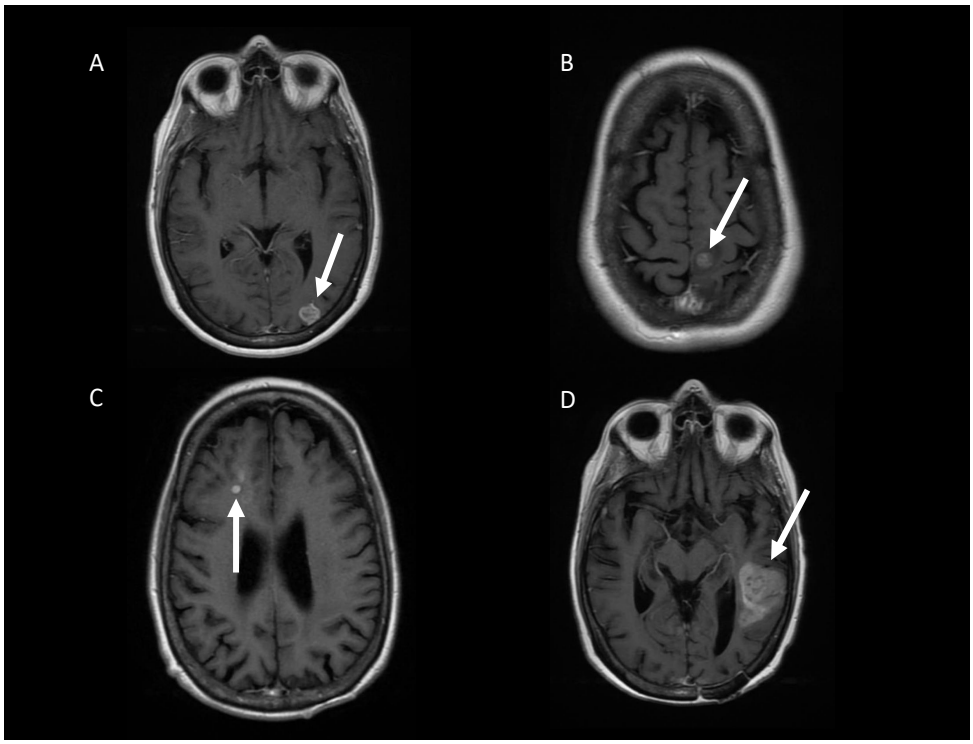

Figure 1. Axial post-contrast T1 MRI brain. (A) Original MRI showed enhancing lesion in left occipital lobe. This was treated with gross total resection. (B) Original MRI showed separate enhancing lesion in the left frontal lobe in the original MRI brain. (C) Surveillance MRI showed first recurrence in the right frontal lobe. Review of prior radiation map showed that this area was outside of the radiation field. This lesion was treated with gross total resection. (D) Surveillance MRI showed second recurrence in the left temporal lobe. MRI, magnetic resonance imaging.

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