H3 K27M-MUTATED GLIOMAS IN ADULTS

Is there a potential role for immunotherapy?

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OBJECTIVE

To describe an adult patient with a midline H3 K27M-mutated glioma treated with immunotherapy.

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BACKGROUND

When a point mutation arises in either the H3F3A or HIST1H3B genes that encode two histone H3 variants, a distinct subgroup of gliomas known as diffuse H3 K27M-mutant gliomas can arise. The mutation leads to an amino acid exchange from lysine to methionine at position 27 leading to an alteration in methylation and oncogenic gene expression.

Diffuse H3 K27M-mutant gliomas typically appear in children, but can occur in adults. They are localized to midline locations such as the thalamus, pons, and spinal cord and harbor a poor prognosis. The World Health Organization revised the classification of these tumors in 2016, adding "Diffuse midline glioma, H3 K27M-mutant" as a separate entity. These gliomas are considered WHO Grade IV regardless of their microscopic features. After surgical resection and radiotherapy, the optimal adjuvant treatment regimen for this exceptionally aggressive tumor remains unknown.

The field of immunotherapy has gained momentum in Oncology and has shown promise in the treatment of high grade gliomas such as Glioblastoma. For example, the use of checkpoint inhibitors such as pembrolizumab which target the Programmed death pathway is under study for high grade gliomas and has led to a durable response in select patients. Guidelines to standardize the response assessment criteria on imaging for patients with Glioblastoma were recently modified preventing premature discontinuation of immune-targeted therapies due to pseudoprogression. To date, there are no immunotherapies available to target histone mutations, but they serve as potential targets.

CASE

Our patient is a 43-year-old gentleman who presented with headache, visual distortion, and imbalance. He was found to have a thalamic mass. Biopsy was suspicions for an infiltrating glioma, with atypical glial cells staining positive for H3 K27M. Given his age, lack of resectability, and IDH1 wild-type status, he underwent radiation with concurrent temozolomide followed by adjuvant temozolamide. He required a treatment break due to intolerance, but exhibited radiographic stability. Surveillance MRI revealed progression in the form of new intraventricular lesions. He experienced a rapid decline physiologically and was treated with bevacizumab over surgery. When he progressed, he was switched to pembrolizumab. Further progression beckoned an alternate plan to be devised including pembrolizumab followed by radiotherapy then pembrolizumab. His repeat MRI was concerning for progression despite the propensity for immunotherapy to increase the volume of enhancement. After a difficult discussion, he declined further treatment and passed peacefully at home. At his request, his brain was harvested and his tumor cells are growing in culture. Review of the tissue revealed classic Grade IV characteristics representing true progression of disease versus treatment-related effects secondary to immunotherapy.

CONCLUSIONS

Diffuse H3 K27M-mutant gliomas are aggressive tumors classified as WHO Grade IV for which no optimal treatment has been identified.

Given the extremely poor prognosis, further investigation of the role of immunotherapy in treating these challenging tumors is paramount.

APRIL SCANS

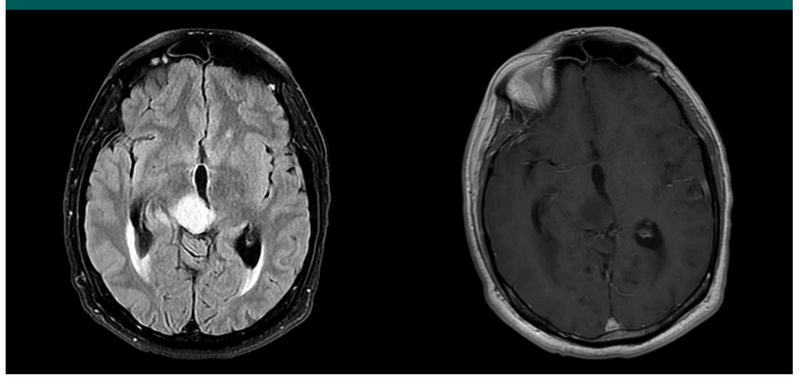

Figure 1. MRI brain with and without contrast showing a 2.5 cm T2-hyperintense lesion centered in the right thalamus and extending into the superior aspect of the right midbrain. There was an equivocal area of punctate enhancement along the posteromedial aspect.

AUGUST SCANS

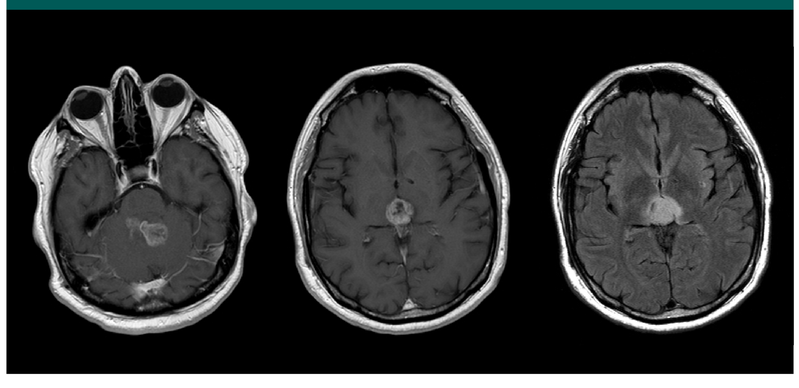

Figure 2. MRI head with and without contrast showing marked interval increase in size and abnormal enhancement of the mass in the region of the superior tectum and around the fourth ventricle consistent with progression.

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