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Targeted treatment produces rapid shrinkage of recurrent, BRAF-mutant brain tumor

BRAF inhibition stops regrowth of debilitating craniopharyngioma, suggests new treatment options

MASSACHUSETTS GENERAL HOSPITAL

A team led by Massachusetts General Hospital (MGH) investigators has reported the first successful use of a targeted therapy drug to treat a patient with a debilitating, recurrent brain tumor. In a paper published online in the *Journal of the National Cancer Institute*, the researchers report that treatment with the BRAF inhibitor dabrafinib led to shrinkage of a BRAF-mutant craniopharyngioma that had recurred even after four surgical procedures. More than a year after dabrafinib treatment, which was followed by surgery and radiation therapy, the patient's tumor has not recurred.

"This is the first time that a systemic therapy has shown efficacy against this type of tumor," says Priscilla Brastianos, MD, of the MGH Cancer Center, co-lead author of the JNCI report. "This has the potential of completely changing the management of papillary craniopharyngiomas, which can cause lifelong problems for patients - including visual defects, impaired intellectual function, and pituitary and other hormonal dysfunction.

Craniopharyngiomas are pituitary tumors that, while technically benign, can cause serious problems because of their location near critical structures, such as optic and other cranial nerves and the hypothalamus. Not only does the growing tumor compromise neurological and hormonal functions by impinging on these structures, but treatment by surgical removal or radiation therapy can produce the same symptoms by damaging adjacent tissues. In addition, since the tumor can adhere to nearby brain and vascular structures, complete removal is difficult, leading to often rapid recurrence.

The patient described in the JNCI paper came to the MGH Emergency Department with confusion, impaired vision, severe headaches and vomiting seven months after he had been surgically treated for a brain tumor in another country. A CT scan revealed a 4 cm cystic tumor - tumor enclosed in a fluid-filled sac - that was pressing against midbrain structures and blocking drainage of cerebrospinal fluid. While his symptoms improved after surgical removal of part of the tumor, they did not disappear; and six weeks later he returned to the MGH, this time in a nearly comatose condition.

MGH neurosurgeons again removed the tumor, which was confirmed to be a BRAF-mutant craniopharyngioma. But two weeks later, before planned radiation therapy could be carried out, his condition again deteriorated into a minimally responsive state, leading to a fourth emergency

surgery. Seven weeks later he was back at the hospital with progressive vision loss, and an MRI showed that the tumor had once again recurred. Since the growth of this tumor was likely driven by the BRAF mutation, which is known to drive the growth of melanomas and other malignant tumors, the team decided to try treatment with dabrafinib, which is FDA approved for the treatment of BRAF-mutant melanomas.

After only four days of treatment, the patient's tumor was around 25 percent smaller; and by day 17 the tumor was half the pretreatment size, and the surrounding cyst was 70 percent smaller. On day 21, the treatment team added the MEK inhibitor trametinib, which is known to enhance the effects of BRAF inhibition, to the protocol; and by day 35 both the tumor and the cyst had lost more than 80 percent of their pretreatment size. Endoscopic surgery to remove accessible tumor was performed on day 38, and drug treatment was stopped a week later, soon followed by radiation treatment. At the time the paper was written, the patient had remained symptom-free for seven months and continues to do so more than a year after his last treatment.

In addition to finding evidence of the antitumor effects of dabrafinib in the removed tumor tissues, the investigators were surprised to find the BRAF mutation circulating in blood samples taken at several times during the course of the patient's treatment. "That result was absolutely novel," says William Curry, Jr., MD, of MGH Neurosurgery, a co-senior author of the JNCI paper. "Finding evidence of the BRAF mutation in the blood raises the hope of potentially diagnosing this mutation and perhaps shrinking these tumors with targeted therapy before surgery, which could make surgical removal safer and possible unnecessary for some patients." He also notes that, since craniopharyngiomas are less molecularly complex than malignant tumors, they may be less likely to develop resistance to BRAF inhibition, a problem that has plagued targeted therapy for several types of cancer.

Sandro Santagata, MD, PhD, of Brigham and Women's Hospital's Pathology Department, a co-senior author of the JNCI paper, adds,"It is quite remarkable how quickly we have been able to go from identifying the genetic driver of papillary craniopharyngiomas to testing the idea in a patient that needed help. It was only last year that, along with Dr. Brastianos and colleagues, we first described in Nature Genetics that nearly all papillary cranionpharyngiomas have mutations in BRAF. This is the same mutation that is found in many melanomas, allowing us to use treatment strategies that have been so promising in melanoma patients."

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To further investigate the impact of this treatment in a larger group of patients, Brastianos is conducting a National Cancer Institute-sponsored, multicenter trial of BRAF and MEK inhibitor treatment for papillary craniopharyngiomas. She is an instructor in Medicine, Curry is an associate

professor of Neurosurgery, and Santagata is an assistant professor of Pathology at Harvard Medical School.

Ganesh Shankar, MD, PhD, MGH Neurosurgery, and Corey Gill, MGH Neurology are co-lead authors, and Daniel Cahill, MD, PhD, and Fred Barker II, MD, both MGH Neurosurgery, are co-senior authors of the JNCI paper. Additional co-authors are Naema Nayyar, MGH Cancer Center; Ryan Sullivan, MD, MGH Medicine; Dennie Frederick, MGH Surgery; Pamela Jones, MD, and Brian Nahed, MD, MGH Neurosurgery; Javier Romero, MD, MGH Radiology; David Louis, MD, and Gad Getz, PhD, MGH Pathology; Malak Abedalthagafi, MBBS, and Ian Dunn, MD, Brigham and Women's Hospital; David Panka, PhD, Beth Israel Deaconess Medical Center; and Amaro Taylor-Weiner, Broad Institute. The study was supported by National Institutes of Health grant 2K12 CA090354-11, and grants from the Brain Science Foundation, Susan G. Komen for the Cure, Terri Brodeur Breast Cancer Foundation, Conquer Cancer Foundation, and the American Brain Tumor Association.

Massachusetts General Hospital, founded in 1811, is the original and largest teaching hospital of Harvard Medical School. The MGH conducts the largest hospital-based research program in the United States, with an annual research budget of more than $760 million and major research centers in AIDS, cardiovascular research, cancer, computational and integrative biology, cutaneous biology, human genetics, medical imaging, neurodegenerative disorders, regenerative medicine, reproductive biology, systems biology, transplantation biology and photomedicine. In July 2015, MGH returned into the number one spot on the 2015-16 U.S. News & World Report list of "America's Best Hospitals."