

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

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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 dabrafenib led to shrinkage of a BRAF-mutant craniopharyngioma that had recurred even after four surgical procedures. More than a year after dabrafenib 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 dabrafenib, 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 possibly 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 craniopharyngiomas 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."

Provided by Massachusetts General Hospital

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