Radiologic Response to MEK Inhibition in a Patient with a WNT-activated Craniopharyngioma

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Abstract

Craniopharyngiomas are benign brain tumors that can often be cured surgically. A small fraction of unresectable tumors can progress and cause significant morbidity and even death. Unfortunately, WNT activated tumors lack clinically-validated targeted therapies in the pediatric population. Herein, we describe a patient with a multiply recurrent adamantinomatous craniopharyngioma with WNT activation. We utilized the MEK inhibitor binimetinib with noted interval decrease in tumor size. This demonstrates the possible utility of MEK inhibitors in WNT activated craniopharyngiomas.

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Abstract

Craniopharyngiomas are benign brain tumors that can often be cured surgically. A small fraction of unresectable tumors can progress and cause significant morbidity and even death. Unfortunately, WNT activated tumors lack clinically-validated targeted therapies in the pediatric population. Herein, we describe a patient with a multiply recurrent adamantinomatous craniopharyngioma with WNT activation. We utilized the MEK inhibitor binimetinib with noted interval decrease in tumor size. This demonstrates the possible utility of MEK inhibitors in WNT activated craniopharyngiomas.

Introduction

Craniopharyngiomas (WHO grade I) are histologically benign neuroepithelial tumors of the sellar/suprasellar region. Pathologically, craniopharyngiomas are subdivided into adamantinomatous, papillary, and mixed types. The adamantinomatous type occurs more commonly in the pediatric population while the papillary type is more common in older adults. The microscopic structure of adamantinomatous craniopharyngiomas (ACPs) consists of a basal layer, an intermediate layer of stellate cells, and a top layer of keratinized squamous cells that face a cyst cavity. The cyst cavity is filled with lipids and keratin that has an appearance of motor oil (Figure 2). On the other hand, papillary craniopharyngiomas (PCPs) consist of layers of squamous

epithelium with papillary projections grossly forming a solid mass. Mixed craniopharyngiomas have both ACP and PCP components (8).

Due to sellar/suprasellar location of craniopharyngiomas, variable degrees of vision loss, endocrine abnormalities, and/or mental disturbances can occur. Craniopharyngiomas can cause elevated intracranial pressure (ICP) from obstructive hydrocephalus secondary to the mass effect. Presenting signs and symptoms can include seizures, papilledema, vision abnormalities, headaches, nausea, vomiting, and/or lethargy. Endocrine abnormalities can be variable and are related to dysregulation of the hypothalamic-pituitary axis. Most complications of craniopharyngiomas are due to space occupation and rarely due to malignant transformation (4).

WNT (wingless) signaling is important in normal cell proliferation and growth but it has been closely linked with carcinogenesis. WNT signaling is divided into two pathways – canonical (beta-catenin dependent) and non-canonical (beta-catenin independent). Beta-catenin is a transcriptional coactivator that is stabilized in the presence of WNT ligands allowing it to enable the expression of target genes. This pathway is important in normal cell development including terminal differentiation of pituitary gland cells. Over-activation of WNT signaling pathway is closely associated with tumorigenesis including with adamantinomatous craniopharyngiomas (ACPs). WNT signaling pathway targeted therapies could be potentially useful for reducing morbidity and mortality from ACPs. Unfortunately, WNT/beta-catenin targeted agents have not been well studied in children (5, 7, 8, 9).

Mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) is another important signaling pathway in normal cell proliferation, growth, and survival. When dysregulation occurs cancer cells proliferate and grow uncontrollably. Molecules such as EGFR, Ras, Raf, and MEK are involved in the regulation of the MAPK/ERK pathway and are targets for therapeutic interventions. The MAPK/ERK activation has been recently shown to be activated in beta-catenin dependent ACP tumor cells, with preclinical efficacy of MEK inhibitors reported (2, 3, 5, 9). Current therapies such as vemurafenib/dabrafenib and trametinib/binimetinib – BRAF V600E and MEK inhibitors, respectively – have been used for adult malignancies such as melanomas and non-small cell lung cancers and pediatric gliomas. This case report describes our successful experience of using a MEK inhibitor to treat a WNT-activated ACP (5).

Case Presentation

A 26 year-old female was initially diagnosed with an ACP at the age of 6 years old (Figure 2). She had a resection and ventriculoperitoneal shunt placement at the time of initial diagnosis. Unfortunately, over the years her tumor recurred and progressed. She developed panhypopituitarism and almost complete vision loss. In addition to direct tumor-related morbidities, she developed obesity (hypothalamic obesity; with subsequent sleeve gastrectomy), insulin-independent diabetes mellitus, hepatic cirrhosis (status post liver biopsy in 2018 - unknown etiology) with secondary splenomegaly and cytopenias, and stasis dermatitis. Over her long clinical course, the patient had a total of 8 surgical resections, chemotherapy (vinorelbine), radiation therapy, and gamma knife radiosurgery (last in February 2016) without sustained benefit. Due to continued tumor growth and progression, binimetinib was considered for off-label use based on the existing preclinical data (2). After clearance from dermatology and ophthalmology, binimetinib was initiated in April 2019 at 45 mg twice daily. Patient did have binimetinib held for brief periods and had dose reductions to 30 mg twice daily and subsequently to 30 mg in the morning and 15 mg in the evening due to furuncles/papulopustular rash on thighs and buttocks, nail dystrophy, hyponatremia, venous stasis with poor wound healing, fatigue/daytime sleepiness, and weight gain. Brain MRI in December 2019 showed remarkable decrease in size of ACP in comparison to pre-binimetinib MRI in late February 2019 (Figure 1). Patient has continued to do well on binimetinib (still requiring occasional interruptions in therapy) and the size of ACP has been stable since December 2019. Molecular pathology testing of ACP tissue revealed CTNNB1 (beta-catenin gene) c.97T>C, p.S33P mutation (Tier 1) (with Variant Allele Frequency (VAF) of ˜33%) and KRAS c.380C>A, p.T127K mutation (Tier 3) (with VAF of 54%). Tier 1 mutations are of strong clinical significance and Tier 3 mutations are of unknown clinical significance. The KRAS mutation has not been reported in the Catalogue of Somatic Mutations in Cancer (COSMIC) database and appears to be a

single nucleotide polymorphism (SNP).

Discussion

Craniopharyngiomas are histologically benign tumors of sellar/suprasellar region. They are divided into three types – adamantinomatous, papillary, and mixed. Adamantinomatous craniopharyngiomas (ACPs) are the most common type in pediatrics and are characterized by a lipid and keratin filled cyst (Figure 2). Based on location of craniopharyngiomas – variable vision loss, endocrine abnormalities, and/or mental disturbances can occur. The majority of signs/symptoms/morbidities that occur from craniopharyngiomas are due to space occupation/mass effect and elevated ICP (4, 8, 9).

Various signaling pathways in human body are associated with normal cell proliferation, growth, and survival. Mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and WNT (wingless; specifically canonical (beta-catenin dependent)) signaling pathways are two major pathways in oncologic patients considering the therapeutic target potentials. Dysregulation of these pathways can lead to uncontrollable cell proliferation and growth and tumor formation. Benign and malignant tumors such as melanomas, non-small cell lung cancers, gliomas, and craniopharyngiomas are associated with one or both of these pathways. Molecular pathway targeted therapies such as vemurafenib/dabrafenib and trametinib/binimetinib – BRAF V600E and MEK inhibitors respectively – have been used successfully in controlling tumor growth and progression. WNT/beta-catenin targeted agents have not been well studied or used in children, despite the absence of WNT/beta-catenin targeted agents, MEK inhibitors are potentially beneficial in WNT-activated tumors (5, 7).

This case presentation provides evidence that MEK inhibitors (binimetinib) have therapeutic potentials in patients with WNT-activated tumors such as ACPs. Our patient had years of tumor progression and recurrences with secondary morbidities despite surgery, chemotherapy, radiation, and radiosurgery. This case's tumor molecular pathology has the CTNNB1 mutation that is of clinical significance as expected and the KRAS mutation appears to be a SNP. Activating KRAS mutations are frequent oncogenic events in human cancers with residues 12, 13, and 61 most commonly involved. In recent years a number of KRAS activating variants have been described occurring at various codons (such as K117 and A146) with lower frequencies (1, 6). The T127K variant identified in this case is a missense variant that has not been previously reported in COSMIC, OncoKB, or My Cancer Genome cancer databases. Furthermore, this variant is not present in the individuals in GnomAD population database. However, the variant allelic frequency of 54% might suggest that this variant may be a rare germline variant. The clinical significance of this variant is uncertain. Despite the mutational findings of the tumor (Tier 1 CTNNB1 and Tier 3 KRAS mutations), binimetinib has led to decreased ACP size. This case provides evidence for and potential insight into the utility of MEK inhibitors in WNT-activated tumors (early or late in the disease course).

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K;Ricarte Filho JC;Persaud Y;Levine DA;Fagin JA;Jhanwar SC;Mariadason JM;Lash A;Ladanyi M;Saltz LB;Heguy A;Paty PB;Solit DB; "Genomic and Biological Characterization of Exon 4 KRAS Mutations in Human Cancer." Cancer Research, U.S. National Library of Medicine, 2010, pubmed.ncbi.nlm.nih.gov/20570890/.

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