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Case Report

Empiric Treatment of Metameric Cerebrofacial Arteriovenous Malformation Syndrome with Trametinib-Mediated MEK Inhibition

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ABSTRACT

Background.

The genetic events involved in the pathogenesis of arteriovenous malformation (AVM) frequently involve somatic activating mutations in the KRAS/MAPK pathway. Prior reports have described the benefits of MEK inhibition therapy, informed by vascular malformation genotyping.

Clinical presentation.

Here we describe the empiric treatment of a high surgical grade, unruptured, symptomatic metameric brain AVM by MEK inhibition therapy, uninformed by lesion genotype. The rationale for such treatment was to alleviate symptoms, reduce high risk features predisposing to hemorrhage and achieve nidal volume reduction to enable definitive radiosurgical treatment. We observed a rapid progression of pre-existing focal steno-occlusive changes affecting the ophthalmic segment of ipsilateral internal carotid artery, resulting in a reduction of AVM and cerebral hemispheric blood flow. There was accompanying regression of high-risk AVM features (i.e. flow-related aneurysms). The volume of the AVM nidus did not change, though headache symptoms were transiently improved. During therapy the patient did not have any hemorrhagic events but did suffer an ischemic stroke prompting cessation of drug therapy.

Conclusion.

Our case shows that MEK inhibition in patients with metameric brain AVM can have unanticipated adverse effects. This emphasizes the experimental nature of such treatment, and the need for additional research. Our experience further suggests that carotid stenosis in the metameric distribution of the brain AVM is a risk factor for trametinib-related stroke complications in patients with metameric brain AVM.

INTRODUCTION

Drug therapies have recently emerged as promising treatment alternatives for vascular malformations. The PIK3CA inhibitor, Alpelisib, which is under investigation for the treatment of PIK3CA-related overgrowth syndromes (PROS), has been widely reported to improve vascular malformation outcomes in PROS when patients are properly selected on the basis of genotype1. Most recently, trametinib, a MEK inhibitor that targets the KRAS/MAPK pathway, was reported to achieve some therapeutic success in a patient with non-central nervous system (CNS) arteriovenous malformations (AVM) and in a patient with spinal metameric AVM2,3. These cases were informed by lesion genotype derived from biopsy samples. Trametinib is a MEK inhibitor which is approved by the United States Food and Drug Administration for the treatment of specific malignant neoplasms and low-grade gliomas carrying the BRAF V600E mutation, either as a single agent or as part of a multiagent treatment regimen4. MEK inhibitors, including trametinib, suppress a ubiquitous intracellular signal transduction pathway that is activated by the binding of mitogens to cell-surface receptors that control gene expression programs governing cell growth and proliferation through a cascade of intra-cellular GTP binding proteins and protein kinases. The phosphorylation targets of these protein kinases influence widespread modulation of gene

expression at the transcriptional and translational level5. Recent publications have shown that somatic activating mutations within the KRAS/MAPK/BRAF pathway play a leading role in AVM pathogenesis6,7. Endothelial cell-specific constitutive activation of the MAPK pathway in genetically engineered mice causes cerebral vascular malformations that are associated with altered endothelial cell expression of more than 1600 genes, many of which are involved in the regulation of vasculogenesis8.

Metameric AVMs are vascular malformations that develop within tissues of one or more adjacent embryonic segments containing a clonal population of vascular progenitor cells that harbor a somatic mutation conferring vulnerability9. A variety of metameric CNS AVMs have been described. The Wyburn Mason syndrome, or cerebrofacial arteriovenous metameric syndrome type-2 involves a type of metameric AVM affecting tissues of the diencephalon, optic tract, optic nerve and neural retina10. Most patients are not eligible for conventional treatments due to the large size and anatomical distribution of AVM within eloquent tissues.

Here we describe the empiric treatment of a symptomatic metameric brain AVM with the MEK inhibitor, trametinib. The intention of treatment was to relieve symptoms, lessen high risk features predisposing to hemorrhage and reduce nidal volume so that definitive radiosurgical treatment might be feasible.

CASE REPORT

A 17-year-old female with an unruptured Spetzler-Martin grade 5 metameric brain AVM expressing the Wyburn Mason phenotype presented to our institution for treatment recommendations

(Figure 1). Symptoms included complex migraine headaches with auras, poorly controlled with gabapentin, and chronic left monocular blindness. Catheter-directed angiography performed to evaluate high-risk features revealed flow related aneurysms of the left superior hypophyseal artery (SHA) and left anterior choroidal artery (AchA) and mild stenosis of the ophthalmic segment of the left internal carotid artery (LICA). Our multispecialty group concluded that microsurgical, endovascular and radiosurgical treatments were not indicated due to an unfavorable risk: benefit ratio. Initiation of trametinib was considered given recent reports of therapeutic success for spinal metameric AVM, though it was not possible to identify a biopsy target for AVM genotyping in our patient2. The patient was started on a daily dose of 1.5 mg (0.025 mg/kg/day) trametinib. The dose was reduced to 1 mg daily after 3 weeks due to grade 3 diffuse acneiform rash, which markedly improved but did not completely resolve. Although closely monitored for additional toxicities, none were detected. The toxicity monitoring regimen included physical exam, brain MRI/MRA, complete blood count and comprehensive metabolic panel every 3 months in addition to electrocardiogram, echocardiogram and ophthalmologic examination with optical coherence tomography every 6 months. Non-contrast brain MRI, Quantitative 4D flow magnetic resonance angiography (MRA) and time of flight (TOF) MRA were used to monitor the treatment response. We relied on Quantitative 4D flow MRA, a phase contrast technique, to characterize dynamic changes in flow (ml/sec) and on TOF MRA to assess dynamic changes in vascular structure. Quantitative 4D flow MRA studies were performed on an Ingenia Elition X Philips 3T magnet (Philips Healthcare, Andover, MA) by scanning a prespecified 8 cm slab volume extending from the roof of the

body of the lateral ventricles to the foramen magnum. Images were post-processed on a Lenovo workstation with an AMD Rizen Threadripper PRO 3955WX using GTFlow software v 4.18.1 (GyroTools, Zurich, Switzerland). At each exam, quantitative flow (ml/sec) was measured across an orthogonal plane bisecting the centerlines of the petrous internal carotid arteries, the basilar artery and the straight sinus (Video 1A, B and Table 1). A baseline exam was obtained prior to initiation of trametinib therapy and repeated 3 months later. After 3 months, there was a marked selective reduction of intracranial LICA flow (57%) on Quantitative 4D flow MRA and apparent LICA luminal diameter (28%) on TOF MRA without changes in overall AVM size. The apparent reduction in LICA diameter was generalized, affecting petrocavernous and intradural segments (Figures 2A and 2B).

Approximately 4 months after starting trametinib, the patient experienced a moderately disabling left primary somatosensory cortex infarction (Figure 2C). The stroke presented with progressively worsening left ear and retro-orbital pain which spread into the forehead over a 2-day period. This adverse event was associated with an additional incremental reduction of intracranial LICA flow (41%) on Quantitative 4D flow MRA. Straight sinus flow, which closely correlates with total AVM venous drainage, was also markedly decreased (54%) on Quantitative 4D flow MRA. The patient was hydrated with intravenous fluids and started on aspirin 81 mg daily. The trametinib dose was decreased to 0.5 mg daily, and gabapentin was increased to 600 mg three times per day. Over the following 3 months the patient remained asymptomatic without changes in quantitative blood flow or reference vessel diameters.

After 9 months of trametinib therapy, catheter-directed angiography was repeated. That study revealed progression of focal steno-occlusive changes involving the ophthalmic segment of LICA, not evident on TOF MRA (Figure 3). Conversely, the diffuse reduction in petrocavernous LICA luminal diameter suggested by prior TOF MRA exams was revealed to be a secondary flow-related manifestation of the ophthalmic segment stenosis, rather than a true structural narrowing. These changes were accompanied by a substantial reduction of blood flow to the anterior compartment of AVM as well as severely diminished cerebral perfusion in the left middle cerebral artery territory (Figure 3). The left AchA aneurysm markedly decreased in size, while the left SHA aneurysm, more proximal to the stenosis, showed no decrease in size (Figure 3). Notably, the posterior compartment of AVM supplied by the vertebrobasilar circulation did not show interval angiographic changes. Moreover, the overall size of AVM remained constant. The correlation of trametinib with progressive LICA stenosis and ischemic stroke raised concerns that continuation of trametinib might lead to further complications. Trametinib was discontinued. Interval follow-up imaging obtained 3 months later showed stabilization of LICA steno-occlusive changes and quantitative blood flow. Notably, straight sinus flow increased by 89%, closely approaching baseline levels. Six months after discontinuation of trametinib, the patient had not experienced stroke and for a period of several months had only mild headaches. At 7-months follow up, headaches had returned to pre-trametinib severity.

DISCUSSION

This report describes our experience with empiric treatment of a metameric brain AVM by MEK inhibition, uninformed by lesion genotype. The AVM was not considered curable, and conventional treatment approaches were regarded as having an unfavorable risk: benefit profile. Given the presence of high-risk features such as flow-related aneurysms, the long-term risk of hemorrhagic stroke was expectedly high. Encouraged by a prior report of MEK inhibition in a patient with spinal metameric AVM, we started our patient on a trial of trametinib. In contrast to prior reports of MEK inhibition for AVM, our therapy was not guided by AVM genotype since there were no cutaneous lesions safe for biopsy and sequencing of somatic mutations2,3. We reasoned that metameric AVMs might share somatic activating mutations clustered in specific gene families, and that the positive therapeutic responses (i.e. reduction in pain, nidal size and nidal flow) achieved by MEK inhibition in the previously reported case of spinal metameric AVM would be possible in our patient. The unanticipated adverse event experienced by our patient contrasts with experience previously reported in patients receiving genotype-directed therapy. It is unclear if differences in treatment response and clinical outcome are related to genetic, anatomical or other factors. In the future lesional genotyping should be prioritized to better contextualize drug response.

Although trametinib therapy was associated with a marked decrease in AVM blood flow and regression of flow-dependent high-risk features within a few months, these changes were attributable to progression of a focal intracranial LICA stenosis rather than involution of AVM nidus. Consequently, total AVM blood flow as reflected by straight sinus flow, initially decreased but then increased, likely as a

result of AVM flow demand being redistributed to alternative arterial feeders. The focal stenosis of the intracranial LICA and associated alterations of cerebral perfusion were not reversible after discontinuation of trametinib on short-term follow up. Longer term follow up will be needed, however. Although the left AchA aneurysm showed a remarkable decrease in size in response to trametinib-induced hemodynamic changes, there was no significant change in the left SHA aneurysm. These differences may relate to differential proximity of the aneurysms to the focal intracranial LICA stenosis and associated flow jet. Notably, although the position of the AchA aneurysm in relation to the stenosis was a modulating factor, the primary driver of aneurysmal involution was the reduction in aneurysmal flow accompanying the progression of upstream arterial stenosis.

It is remarkable that the largest effect of trametinib on vascular structure and function was isolated to a short focal segment of intradural LICA directly upstream to the AVM. The affected segment of internal carotid artery was shown to have mild narrowing on baseline imaging studies prior to the initiation of trametinib. It is possible that vascular cells in the affected ophthalmic segment of internal carotid artery (ICA) share a common progenitor cell origin with vascular cells giving rise to AVM and that both vascular tissues harbor a shared somatic mutation in the KRAS signaling pathway. Modern theories of vascular dysgenetic neurocristopathies associated with aberrant ICA development, such as the PHACES syndrome, are based on the concept that defective neural crest cells possessing somatic mutations contribute to aberrant vascular development in derivative tissues throughout their migratory pathway11. Concepts about the embryological basis of cerebrofacial metameric syndromes are based on similar mechanisms

of defective neural crest cell migration9. Cranial neural crest cells contributing to development of the forebrain and retinal vasculature also contribute to the development of the ICA12,13. Accordingly, it is possible that the drug-responsive segment of intracranial ICA possesses the same somatic activating mutation as diencephalic AVM and that differential effects of trametinib on the ophthalmic segment of ICA and AVM nidus are primarily a function of pharmacokinetics. Together with prior reports, our findings emphasize that the response of vascular malformations and other host tissues to MEK inhibition may be variable and depend not only on the nature of the mutation underlying AVM pathogenesis, but the distribution of the mutation in other host tissues outside of the AVM. Our results suggest that pre-existing arterial stenoses involving a major cerebral artery, within the metameric distribution of the AVM (i.e. internal carotid artery), could be an important biomarker of stroke risk in patients with metameric brain AVMs receiving trametinib. Future studies of MEK inhibition for AVM should rely on a detailed understanding of these factors.

The neuropathological effects and clinical complications of cerebral arteriovenous malformations (AVM) are direct manifestations of the pial hemodynamic derangements caused by arteriovenous shunting. Cerebral arteriovenous shunting 1) markedly elevates vascular wall tension stresses, causing a flow-dependent cumulative mural damage process that leads to the formation of flow-related aneurysms and venous ectasias that rupture, 2) steals perfusion from brain tissue and 3) elevates luminal pressure in regional veins causing cerebral venous hypertension and congestion. The combined effects of perfusion steal and venous dysfunction lead to pathological depolarization of cortical neurons and

seizures, as well as infarction and hemorrhage. The severity of vascular mural wall tension, cerebral perfusion steal and cerebral venous dysfunction are all directly related to the magnitude of arteriovenous shunting. Hence, the probability of clinical complications is proportional to the magnitude of blood flow directed through the AVM. This is a well-established guiding principle in the management of brain AVMs. Consequently, the primary endpoint for monitoring treatment response in our patient was quantitative blood flow through the AVM. Since the complex architecture of the AVM precludes direct, non-invasive, quantitative determination of AVM blood flow, we used quantitative 4D flow MRA measurements of internal carotid artery flow and straight sinus flow as surrogates. As the effects of MEK inhibition on AVM structure and function are unknown, and potentially non-uniform in distribution this global approach was favored and has been previously described in studies of trametinib therapy for metameric spinal AVM2. Our initial assessments based on these metrics confirmed that AVM flow was dramatically decreased, and that our treatment goals were being met. Unfortunately, the decrease in AVM blood flow was due to a generalized upstream reduction in flow through the internal carotid artery, which also reduced blood flow to normal brain tissue. Since MRI does not allow detailed evaluation of the structural changes within the AVM vasculature, the absence of changes in the overall size of the AVM was not necessarily an indication of treatment failure. The inability of MRI to accurately depict changes in AVM structure over time is well known, and definitive assessments are based on catheter-directed cerebral angiography. While the progression of focal internal carotid artery stenosis was not initially appreciated on MRI, this may not have compelled cessation of trametinib therapy in the absence of

clinical complications. At the time of our patient's arterial ischemic stroke, the severity of ipsilateral focal internal carotid artery stenosis was not yet understood. Since our therapeutic endpoints were being achieved, it was believed that a trametinib dose reduction would cause a sufficient increase in carotid blood flow to satisfy cerebral blood flow demand. The patient clinically stabilized on the lower dose of trametinib, and quantitative flow metrics also stabilized. When the severity of internal carotid artery stenosis was later revealed by catheter-directed angiography, our consensus was that the potential for further stenosis and recurrent stroke, even on the reduced dose of trametinib, outweighed the potential benefits of further non-specific AVM flow reduction. Notably, the highly focal steno-occlusive changes involving the ophthalmic segment of intracranial internal carotid artery in our patient were not evident on non-invasive vascular imaging studies, perhaps due to the unusually short segment of vessel involved and the widespread decrease in flow-related enhancement upstream to the index steno-occlusive lesion. Since MRA displays signal intensity proportional to flow, the structural nature and location of the underlying steno-occlusive changes were not accurately depicted. Although arterial spin labeling (ASL) sequences were routinely obtained as part of each imaging evaluation performed in our patient, these failed to accurately represent progressive changes in cerebral blood flow over time. Quantitative 4D flow MRA also lacks spatial and anatomical information. On the other hand, catheter-directed angiography and other contrast-based vascular imaging studies clearly demonstrate the nature of underlying focal steno-occlusive changes. Our experience emphasizes the indispensable role of accurate, reliable, high

fidelity contrast-based vascular imaging for monitoring and understanding treatment responses in patients receiving MEK inhibition therapy for vascular malformations.

Optimal AVM therapy should achieve a targeted involution of aberrant vessels within AVM nidus. Selective constrictive remodeling of arterial feeders supplying both AVM and brain may promote regression of flow-dependent high-risk AVM features, but this benefit will be counter-balanced by an increased risk of ischemic stroke due to increased competition for blood flow between brain and AVM, as observed in our patient. In such cases, a net benefit of drug therapy may be possible if the reduction in blood flow is sufficient to induce a regression of high-risk AVM features without precipitating cerebral ischemia. Future research directed at illuminating how quantitative changes in dosing can achieve predictable treatment responses may enable reliable dose titration for a net benefit.

CONCLUSION

Early experience with empirical treatment of metameric brain AVM by MEK inhibition reveals a temporary reduction in AVM blood flow, and selective regression of some flow-related aneurysms, attributable to rapid progression of a minor pre-existing internal carotid artery stenosis within the metameric distribution of the AVM rather than a direct effect on the AVM nidus. Decreased cerebral blood flow accompanying the progression of internal carotid artery stenosis led to an arterial ischemic stroke which offset the benefit of flow-related aneurysm regression in our case. Further study is needed to better characterize the effects of MEK inhibition in patients with metameric brain AVM so that

precision treatment selection can be guided by patient-specific and lesion-specific markers. Pre-existing carotid stenosis in the metameric distribution of the brain AVM should be considered a risk factor for stroke in patients with metameric brain AVM receiving trametinib.

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FIGURE, TABLE AND VIDEO LEGENDS

Figure 1. Baseline axial (A) and coronal (B) T1 weighted spin echo images of the brain through the level of the foramen of Monro show AVM distributed throughout the left thalamus (long black arrow), left internal capsule (long white arrow), left hypothalamus (white triangle) and left temporal stem (short black arrow). T2 weighted spin echo images (C, D) of the orbits show AVM distributed throughout the left optic tract, optic chiasm intradural left optic nerve (dashed white arrows). AVM distributed in the intra-orbital optic nerve is also shown (dashed black arrow). Fundoscopic image shows characteristic corkscrew tortuosity of central retinal artery branches indicative of AVM (E).

Figure 2. Reconstructed time of flight MRA images obtained at baseline (A) and after 4 months of trametinib therapy (B) show marked interval reduction in flow-related enhancement and apparent luminal diameter of the petrous, cavernous and intradural segments of the left internal carotid artery

(black arrows). Notably, it was later confirmed on catheter-directed angiography that LICA structural changes were strictly limited to the ophthalmic segment (see Figure 3). Axial B100 image of the brain (C) shows focal diffusion restriction indicative of acute infarction involving left primary somatosensory cortex.

Figure 3. Selective left internal carotid artery angiograms, in the arterial phase, lateral projection, before (A) and after 9 months of trametinib therapy (B) show rapid interval progression of severe focal stenosis involving the ophthalmic segment of the left internal carotid artery (long black arrows) and marked decrease in the size of a flow-related left anterior choroidal artery aneurysm (long white arrows). Selective left internal carotid artery angiograms, in the arterial phase, frontal projection before (C) and after 9 months of trametinib therapy (D) also show rapid interval progression of severe focal stenosis involving the ophthalmic segment of the left internal carotid artery (long black arrow). The flow-related left superior hypophyseal artery aneurysm is not significantly changed (dashed white arrow). Note interval decrease in perfusion of left middle cerebral artery branches supplying brain parenchyma within the dashed black ellipsoid.

Table 1. The average flow in milliliters per second, determined by quantitative 4D-flow Magnetic Resonance Angiography (MRA) is reported for the right internal carotid artery, left internal carotid artery, basilar artery and straight sinus at 5 different assessment timepoints (Baseline, 3-months after initiating

trametinib, 4-months after initiating trametinib, 6-months after initiating trametinib and 3-months after stopping trametinib).

Video 1. Post-processed quantitative 4D-flow Magnetic Resonance Angiograms (MRA) of the left (A) and right (B) internal carotid arteries showing the centerline of each vessel (red lines) and the plane of quantitative 4D flow measurements (white line).