Adjunct mTOR Inhibition Improves Treatment Durability in PTEN Mutation-Associated Cranial Dural Arteriovenous Fistulas

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Learning Objectives

By the conclusion of this session, participants should be able to:

1) Recognize PTEN hamartoma tumor syndromes (PHTS) result from germline mutations to the PTEN tumor suppressor gene and can manifest in the brain as arteriovenous malformations or dural arteriovenous fistulae.

2) Consider PTEN mutation-associated arteriovenous malformations and dural arteriovenous fistulae are often not amenable to surgical ligation or endovascular embolization due to collateral formation and re-establishment of abnormal fistulae.

3) Be aware that PI3K/Akt/mTOR pathway inhibition is a safe and effective adjunct to surgical and endovascular management of cranial dAVF in PHTS patients and may improve treatment durability by mitigating curb abnormal endothelial proliferation

Methods

Three patients with PHTS who underwent cerebral angiography that demonstrated dAVF who subsequently received Onyx (ev3, Irvine, California) and coil embolization were included. Patient 3 received concurrent treatment with mTOR inhibition; Patient 1 and Patient 2 did not.

Results

Patient 1, a 38-year-old woman with Cowden's syndrome and dAVF, had continued recurrence two months after last embolization despite a good angiographic result and underwent craniotomy for surgical ligation of the dAVF. The patient developed venous hypertension and hydrocephalus and did not recover neurologically despite ventriculo-peritoneal shunt placement.

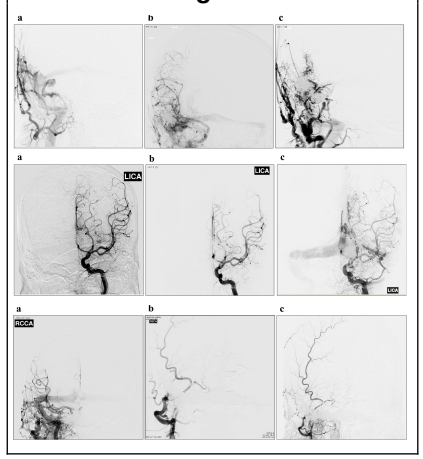
Patient 2, a 45-year-old man with Cowden's syndrome and a Cognard type III dAVF, underwent sub-occipital craniotomy for ligation of the residual dAVF, despite a good angiographic result following embolization. Post-operative worsening seizures and poor neurologic status resulted in care being withdrawn and the patient died.

Patient 3, a 20-year-old man with Bannayan–Riley–Ruvalcaba syndrome and a Cognard type IIa dAVF, demonstrated a small, stable dAVF without evidence of venous hypertension at 22 months following last embolization. He began 2 mg daily rapamycin (mTOR inhibitor) treatment to limit vascular proliferation two years before treatment and maintained this regimen following treatment.

Conclusions

PI3K/Akt/mTOR pathway inhibition is a safe and effective adjunct to surgical and endovascular management of cranial dAVF in PHTS patients and may improve treatment durability.

Figure



Patient 1: A diagnostic cerebral angiogram demonstrated a new and distinct Cognard type IIa dAVF involving the left jugular bulb, as well as progressive stenosis of the right transverse sinus with retrograde drainage (Top a). Despite a good angiographic result (Top b), she had continued recurrence two months after her last embolization (Top c).

Patient 2: A 45-year-old male with Cowden's disease presented with progressively-worsening headaches following two prior embolizations of a Cognard type III dAVF draining into the vein of Galen, straight sinus, and superior sinus (Middle a). Despite a good angiographic result (Middle b), his symptoms worsened over the next six months, with new-onset seizures and worsening headaches. Subsequent angiography demonstrated recurrence of his previously-embolized dAVF (Middle c).

Pt 3: A diagnostic cerebral angiogram demonstrated a Cognard type IIa dAVF with multiple arterial pedicles from bilateral external carotid arteries (Bottom a), with cortical venous reflux and drainage via the right sigmoid sinus. The patient underwent five-staged trans-arterial and trans-venous embolizations over a 10 month period using Onyx (ev3, Irvine, California) and platinum coils with eventual complete occlusion of the dAVF (Bottom b). He was maintained on rapamycin 2 mg daily and follow-up angiography at 22 months after the last embolization demonstrates a stable small dAVF from the occipital artery to the right jugular bulb without evidence of venous hypertension (Bottom c).