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Management Options for Cavernous Malformations

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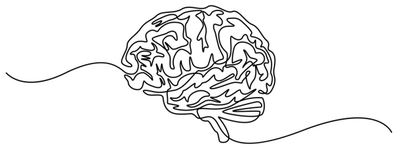

Financial Relationship Disclosure(s)

Curtis Doberstein, MD

- Nothing to disclose

Cerebral Cavernous Malformations (CCMs)

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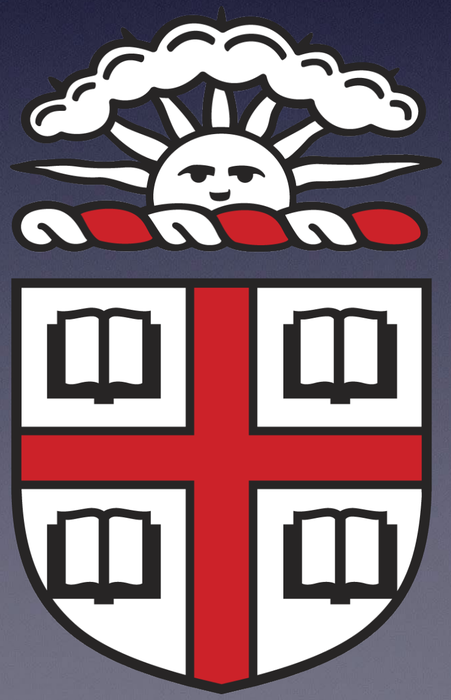

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CCM Nomenclature

- Cavernous malformation
- Cavernous Angioma
- Cavernous hemangioma
- Cavernoma

CCM Pathology

- Composed of clusters of dilated capillaries without intervening brain parenchyma and can occur in the brain or spinal cord
- Endothelium lacks tight junctions (leaky)
- Vessels lack normal smooth muscle and elastic tissue (thin walled)
- At surgery appear like blood filled bubbles, or grape clusters, and are low flow

3 Genetically Distinct Categories of CCMs

- Sporadic (80-85%)
- Familial (15%)
- Radiation induced (5%)

Incidence of CCMs

- 0.16 - 0.9% based on autopsy and routine MRI studies
- Flemming et al in a population based study of non-clinical MRIs found that 1/200 patients (0.5%) had a CCM.

Pathogenesis of Sporadic CCMs

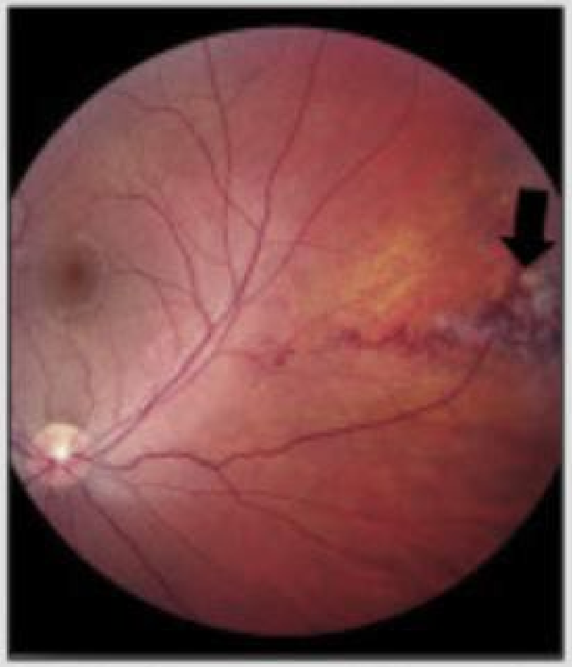
- Originally thought to be congenital, now known to be acquired
- Sporadic form (80-85%) typically have 1 lesion (10% can have multiple) and are often associated with a developmental venous anomaly (DVA)
- 30% of sporadic CCMs have an associated DVA although emerging data with 7T MRI suggest they all may be associated with a DVA
- Greater genetic heterogeneity than the familial form of CCMs
- Location (cerebral hemisphere 66%, brain stem 20%, basal ganglia or deep nuclei 8%)

Pathogenesis of Familial form of CCMs

- Associated with autosomal dominant germline variants with incomplete penetrance
- Loss of function of CCM1, CCM2, CCM3 results in endothelial cell overgrowth and poor adhesion to adjacent cells with proliferation of abnormal, dilated capillaries (bubbles)
- Do not usually have an associated DVA

Locus Name: CCM1

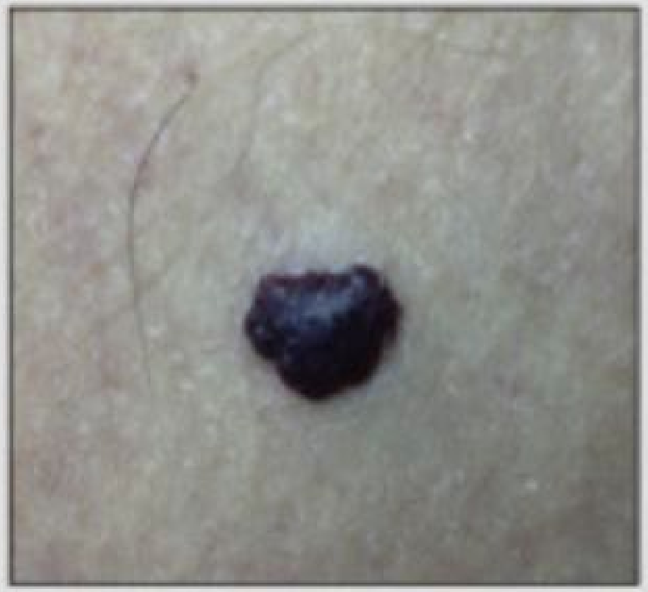
- Gene: *Krit 1*
- Chromosome 7q21.2
- Function: Angiogenesis, inhibit endothelial cells, apoptosis, migration



Retinal Cavernous Malformation

Locus Name: CCM2

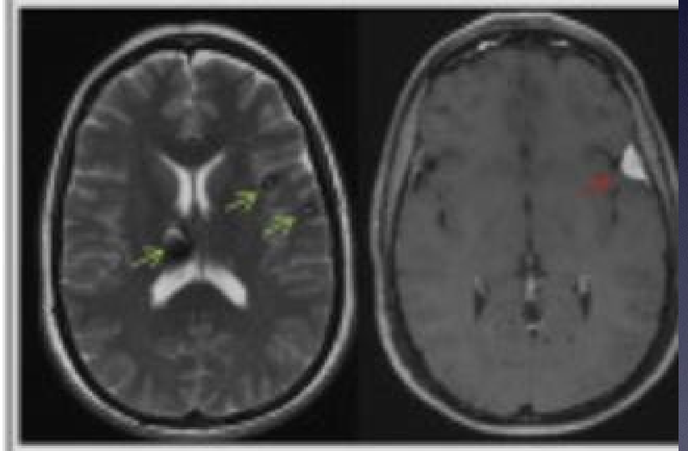
- Gene: *Malcavernin*
- Chromosome 7p13
- Function: Stabilize endothelial cell junctions and maintain endothelial integrity



Skin Venous Malformation

Locus Name: CCM3

- Gene: *PDCD10*
- Chromosome 3q26.1
- Function: Stimulate cell proliferation, regulate angiogenesis and vasculogenesis, regulate apoptotic pathway



Multiple Cavernous Malformations (green arrow) and Meningioma (red arrow) suggestive of CCM3

Radiation-Induced CCMS

- Develop in up to 8% of patients previously undergoing radiation
- Typically occur around 10 years after treatment
- Higher risk if treatment under 10 years of age to radiation dose over 3000 cGy
- May have a more indolent course

Symptoms and Presentation of CCMs

- Many are incidental (20-50%)
- Symptoms develop due to accruing hemorrhage in, or adjacent to, the CCM and to growth of the CCM
- Focal seizure (50%)
- Focal neurological deficit (25%)
- Brain stem and eloquent locations are more commonly symptomatic (small amount of bleeding can cause symptoms in these locations)

CCMs Risk of Bleeding

- Sporadic form, incidental : 0.1 - 1% annually
- Sporadic form presenting with bleeding: 3 - 10% annually
- The risk of subsequent bleeding after an initial single hemorrhage over 1-5 years is 14-56%
- Familial form of CCM has a higher risk and is associated with approximately 4% annual risk of bleeding
- Patients with familial form or previous hemorrhage require closer follow up and lower threshold for treatment

CCM Risk of Bleeding

Horne et al Meta Analysis

- **5 year risk of bleeding**

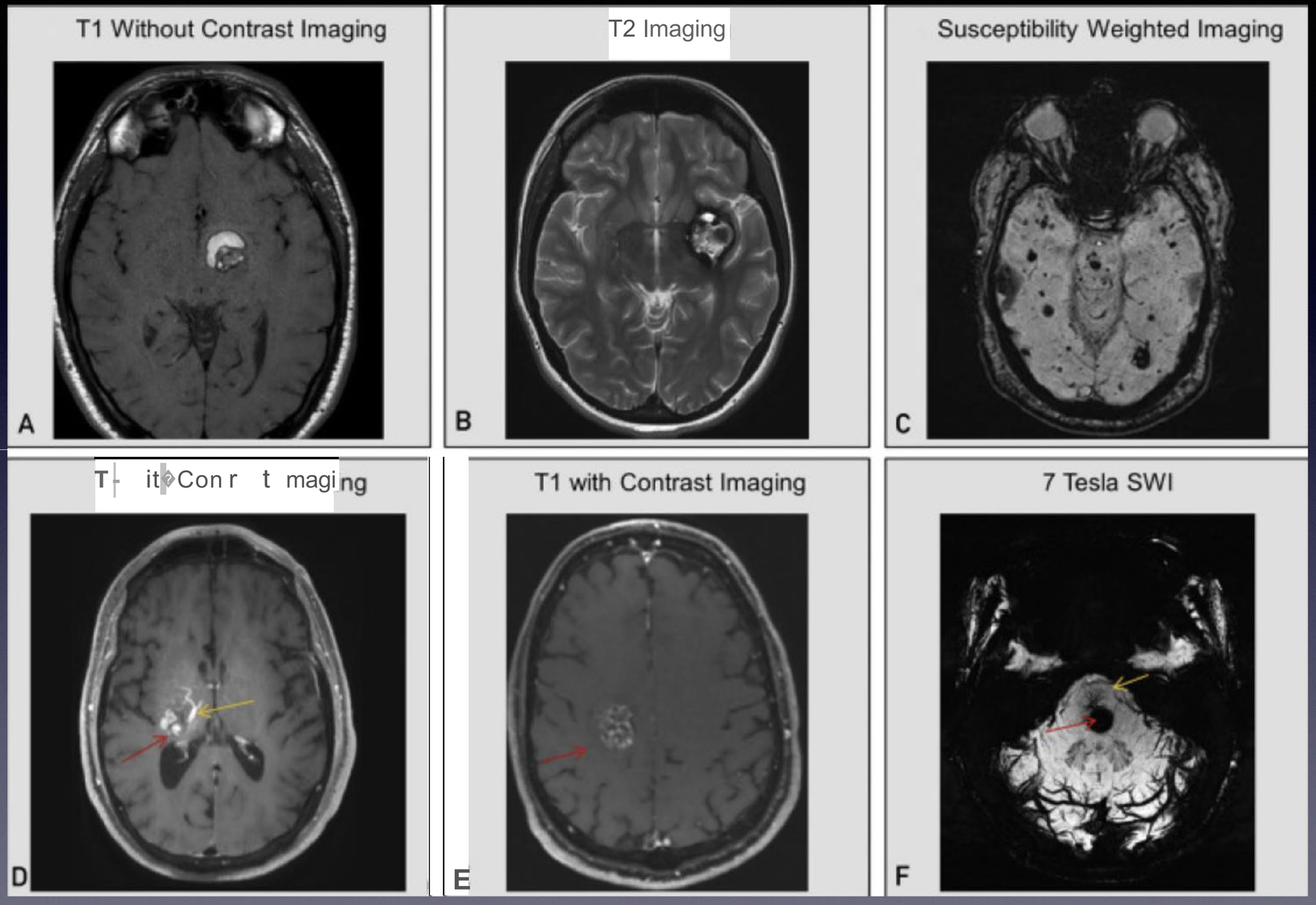
- 3.8% if no bleeding and non brain stem location
- 8% if brain stem and no bleeding
- 18.4% if bleeding or symptomatic in non brain stem location
- 30.8% if bleeding or symptomatic brain stem location
- Take away is prior bleeding and brain stem location or higher risk

CCM Natural History/Outcome

- CCMs are at the capillary level and are low flow so bleeding tends to be small. Unlike AVMs or aneurysms (high flow, arterial level)
- Because bleeding is low pressure it often displaces, rather than damaging, adjacent tissue
- Because of this low flow bleeding, patients often show clinical improvement as acute blood is absorbed.
- Taslimi et al found that 80% of patients showed complete recovery or had minor disability at 1 year after an initial hemorrhage
- Mortality after a CCM associated hemorrhage is very low

CCM Imaging

- CT scanning has poor sensitivity and specificity
- CCMs are angiographically occult
- MRI with 3T magnet and standard sequences and SWI (gradient echo) is the best modality
- Gadolinium is very useful in localizing an associated DVA
- Described as looking like popcorn or a mulberry


T1 Without Contrast Imaging
A
T2 Imaging
B
Susceptibility Weighted Imaging
C
T1 with Contrast Imaging
D
T1 with Contrast Imaging
E
7 Tesla SWI
F

Surgical Treatment of CCMs

- Indications for treatment include symptomatic lesions, hemorrhage, growth, intractable seizures
- Asymptomatic or high risk eloquent areas (brain stem, thalamus, etc…) typically are observed and require individual risk/benefit assessment
- Surgical resection is the gold standard
- Seizure control in over 80% (earlier resection is better)
- Approximately 4% risk of surgical intervention
- Lesion recurrence is about 1%

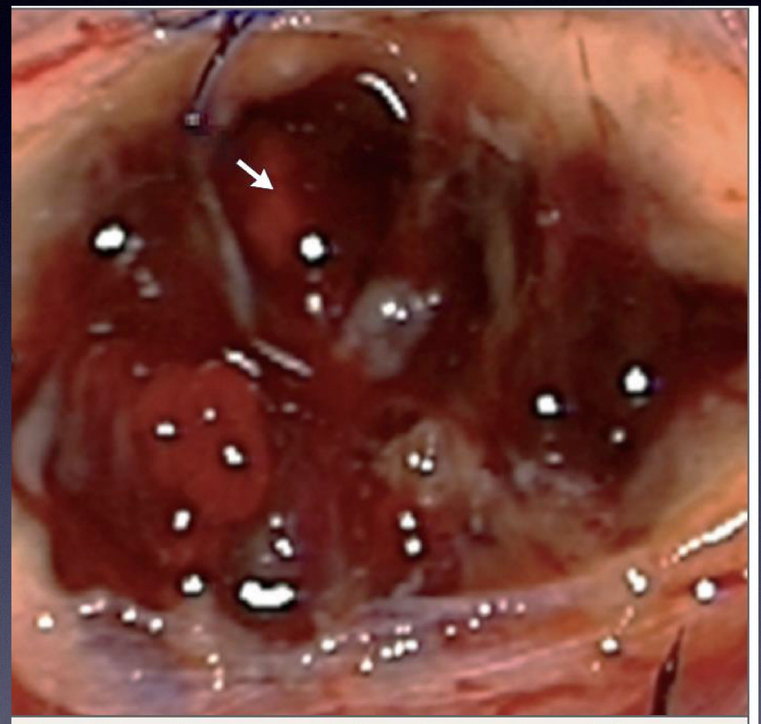
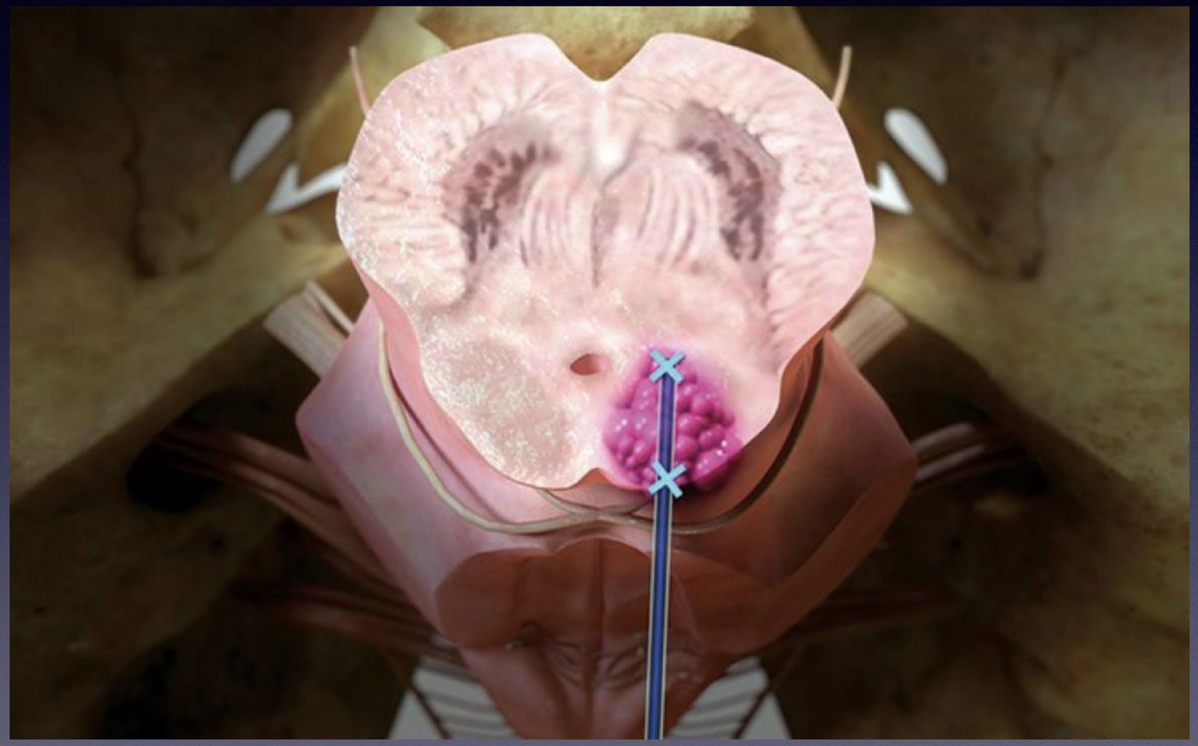


Figure 1. A Cerebral Cavernous Malformation (CMM) Seen during Surgery. Characteristic blood-filled bubbles (white arrow) are visualized through the operating microscope.

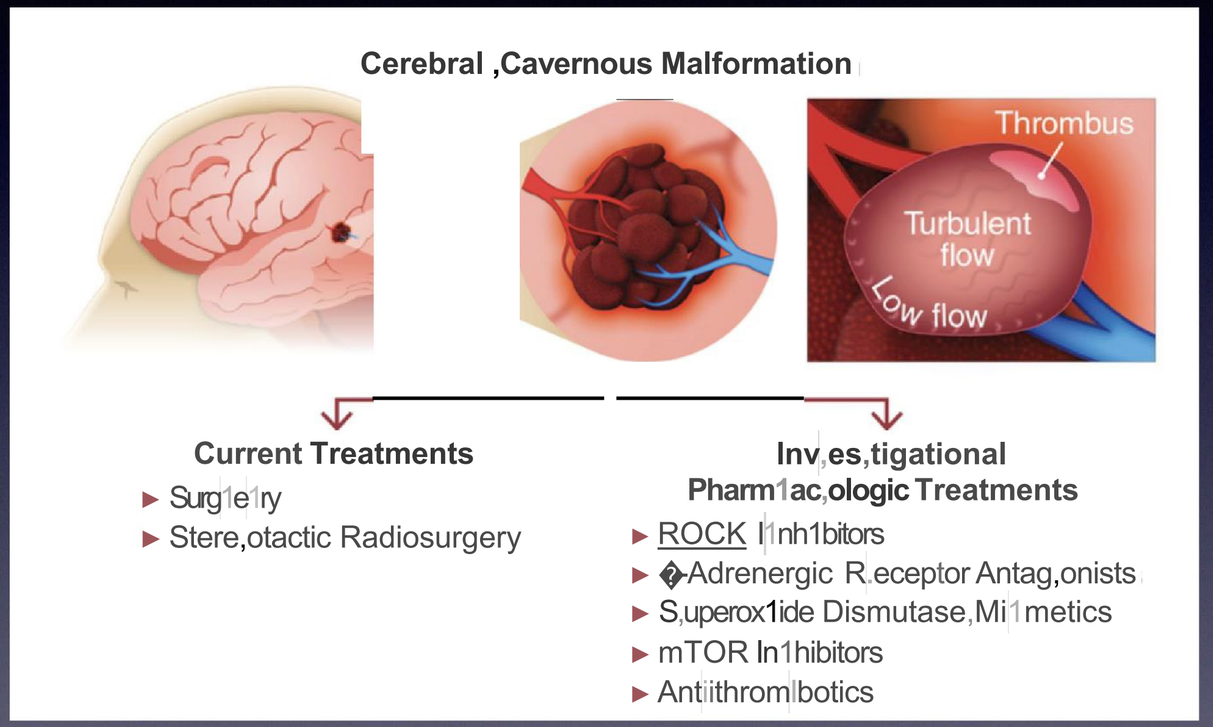


Stereotactic Radiation and Potential other therapies for CCMs

- SRS is best suited for surgically inaccessible lesions or those in the brain stem or in patients who are poor candidates for surgery
- SRS is controversial. It is debated whether it truly works or improvement is due to the natural history as no control groups in studies
- LITT, HIFU, and targeted medical therapies are being investigated

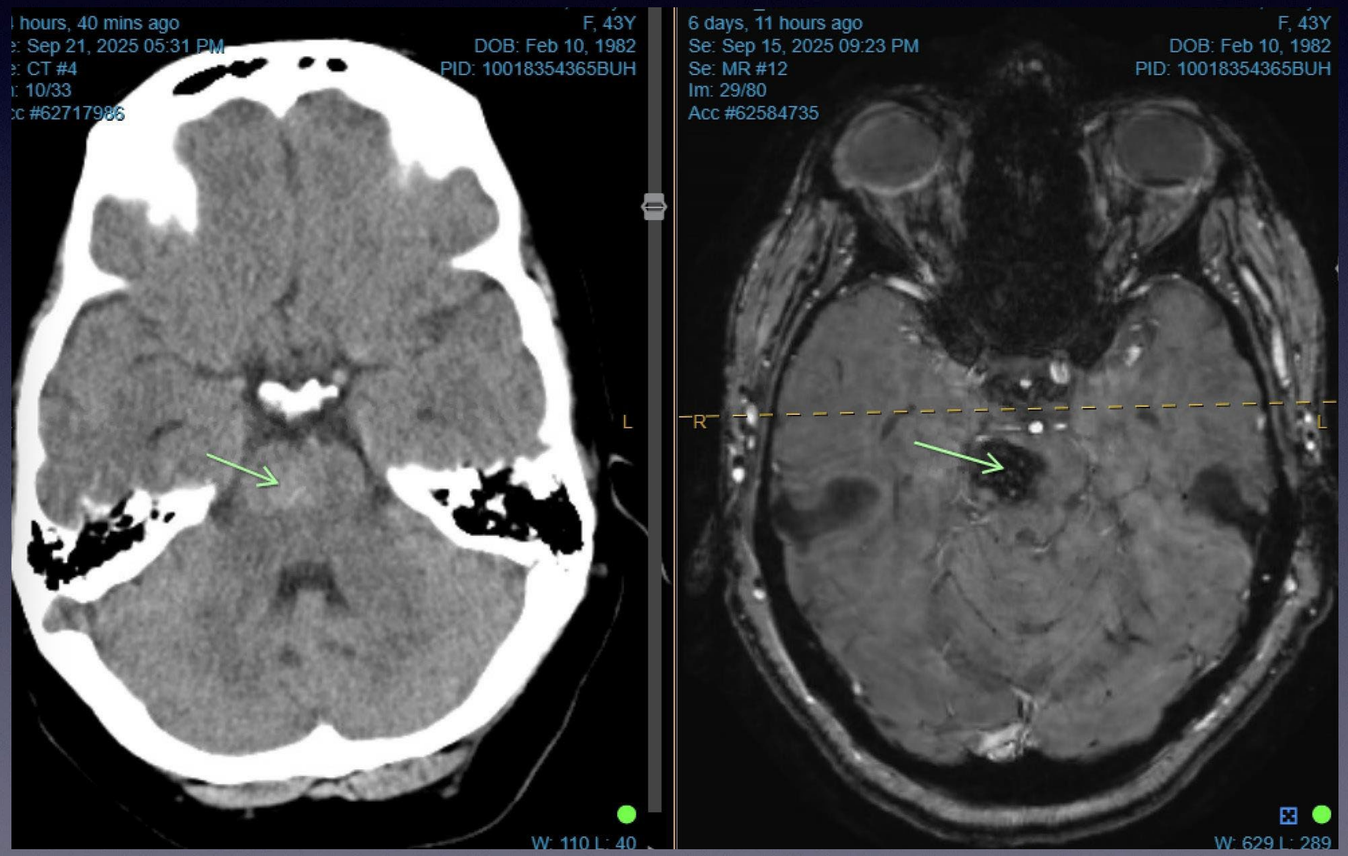
Study	Location	Enrollment	Eligible patients	Study medication	Primary outcome
Permeability MRI in Cerebral Cavernous Mafformations Type 1 in New Mexico: Effects of Statins NCT01764451	IJniversity of New Mexico	Closed	Familial CCM	Sirnvastatin	Effect of drug on permeability MRI
Atorvastatin Treatment of Cavernous Angiomas With Symptomatic 1--lemorrhage Exploratory Proof of Concept {AT CASH EPOC) Trial NCT02603328	University of Chicago	Recruiting	CM hemorrhage within 1 y	Atorvostatin	Mean change in lesional QSM MRI
Treat_CCM: Propranolol in Cerebral Cavernous Malformation NCT03589014	Italy	Recruiting	Familial CM	Propranolol	Lesion burden and clinical events

Table 4
Clinical Trials Assessing the Utility of Medication in Treating Patients With CMs



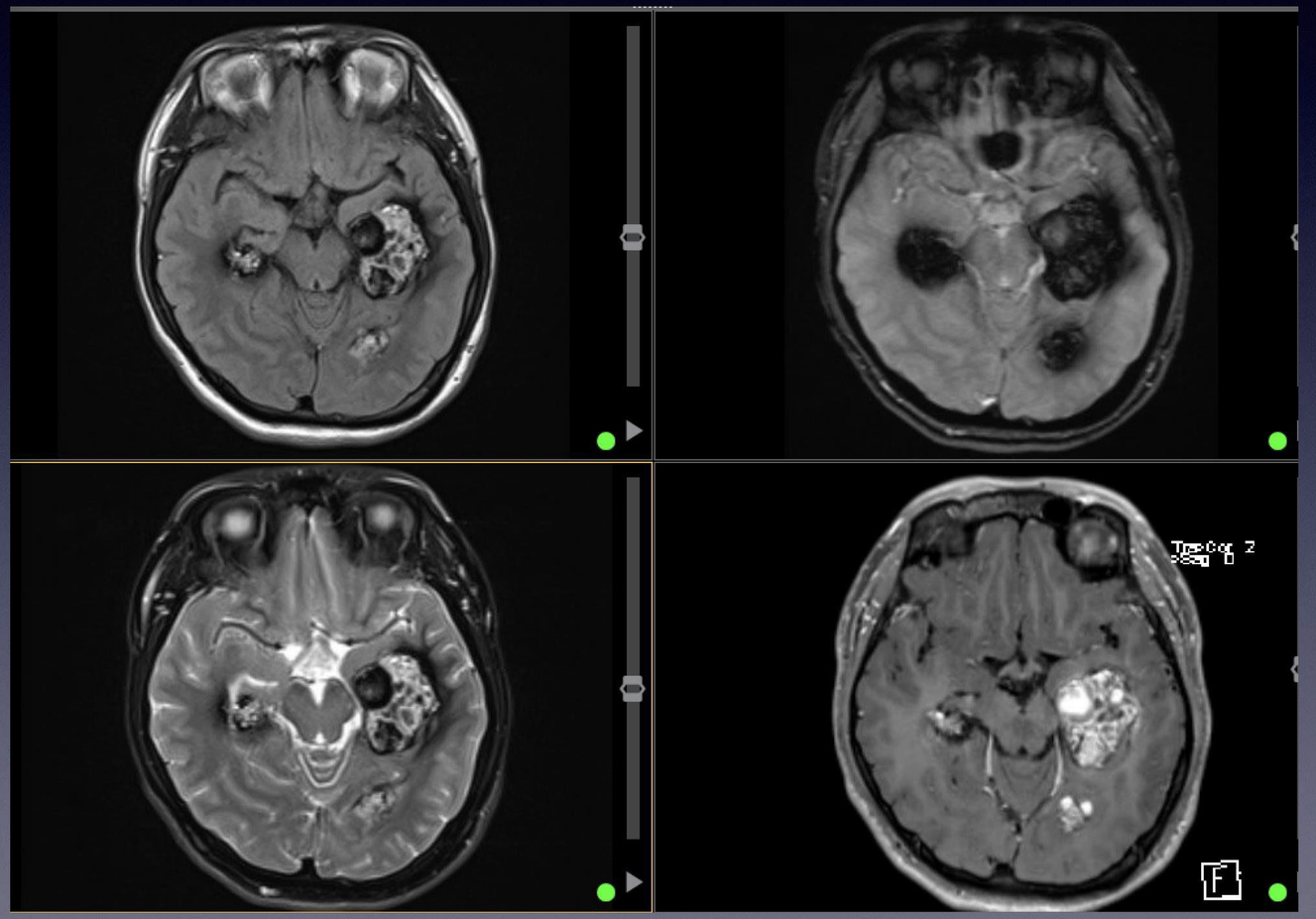
Recent Clinic Cases

43 yo female with right hemiparesis



Recent Clinic Cases

26 yo male with headaches



Summary CCMs

- Incidence around 0.5% in general population
- The majority of the sporadic form (85%) are solitary whereas multiple CCMs are usually associated with the familial with germline variants (CCM1, CCM2, CCM3) or prior radiation
- The greatest risk of hemorrhage is a previous bleed or brain stem location
- Susceptibility weighted, gadolinium enhanced, and T2 MRI is best mode of detection
- Treatment options: observation, surgical excision, stereotactic radiation. Other potential future options such as LITT, HIFU, targeted medical therapies