

Cerebral Cavernous Malformation: What a Practicing Clinician Should Know

Kelly D. Flemming, MD, and Giuseppe Lanzino, MD

Abstract

Cavernous malformations (CMs) are angiographically occult, low-flow vascular malformations of the central nervous system. They are acquired lesions, with approximately 80% of patients having the sporadic form and 20% the familial form of the disease. The lesions may also develop years after radiotherapy. At the microscopic level, they consist of endothelium-lined cavities (or “caverns”) containing blood of different ages. The endothelium proliferates abnormally, and tight junctions are absent or dysfunctional, resulting in leakiness of the endothelium and clinical manifestations in some patients. Cavernous malformations can be an incidental finding or can present with focal neurologic deficits, seizures, or headache, with or without associated hemorrhage. Management of the CM lesion requires knowledge of the natural history of the disease compared with the risk of surgical intervention. Surgery is often considered for symptomatic patients with lesions in a noneloquent location. Medical management is warranted for symptoms related to the CM. Research aimed at understanding the genes and signaling pathways related to CMs have provided potential drug targets, and clinical trials are underway to determine whether medications reduce the risk of future bleeding without surgery or modify the disease course. In addition, recent epidemiologic data have aided practitioners in determining how to treat comorbid conditions in patients with a potentially hemorrhagic lesion. This review provides an overview of the epidemiology, presentation, and clinical management of CMs.

© 2019 Mayo Foundation for Medical Education and Research ■ Mayo Clin Proc. 2019;■(■):1-16

DEFINITION

Cavernous malformations (CMs) are low-flow, central nervous system vascular malformations that may occur in the brain, spinal cord, or, rarely, the dura. They are also referred to as *cavernomas* or *cavernous angioma*. Although sometimes the term *cavernous hemangioma* is used interchangeably with *cavernous malformation*, cavernous hemangiomas are pathologically distinct vascular tumors rather than a vascular malformation.¹

Cavernous malformations are composed of caverns or clusters of dilated capillaries with no intervening brain. At the microscopic level, the endothelium lacks normal tight junctions, resulting in “leakiness” (Figure 1). Macroscopically, the lesion is likened to a mulberry or raspberry. The underlying pathology is reflected radiographically on magnetic resonance imaging (MRI). Standard T2-weighted sequences demonstrate a reticulated central portion of

the lesion (“popcorn” appearance). The T2 hyperintense signal in the central portion reflects blood and thrombosis in the caverns. The central hypointense regions may reflect aging blood or calcium. The typical T2 hypointense rim around the lesion reflects surrounding hemosiderin.²⁻⁴

EPIDEMIOLOGY

The precise prevalence of CM is not known because the diagnosis can be made only with brain imaging or autopsy. Estimates from autopsy studies, clinical MRI studies, and studies performing brain MRI for nonclinical purposes suggest a prevalence of 0.16% to 0.9%.⁵⁻⁹ In a population-based study of patients 50 to 89 years old undergoing MRI for nonclinical purposes, the prevalence of CMs was approximately 1 in 200 patients, but only 1 in 2700 had symptoms.¹⁰

Patients most commonly present for medical attention between the third and fifth decades of life, but patients may present in

From the Department of Neurology (K.D.F.) and Department of Neurosurgery (G.L.), Mayo Clinic, Rochester, MN.

infancy and childhood. There is an equal prevalence in women and men.¹¹⁻¹⁵

PATHOGENESIS

Although initially thought to be congenital lesions, CMs are now known to be acquired, as confirmed by many reports of patients with normal MRI findings who later developed a CM.¹⁶⁻²⁴ Data demonstrating an increasing prevalence of CM with age also support an acquired etiology.²⁵

Approximately 80% of patients have the sporadic form of the disease. Typically a patient will have a single CM lesion, often with a concomitant developmental venous anomaly (DVA). In approximately 10% of cases, patients with the sporadic form will have more than 1 CM, but the CMs cluster around a DVA. Not only has the DVA been implicated in the pathogenesis of the CM, but it may also influence its natural history. Some data support a potential role of the DVA in influencing hemorrhage risk. Thrombosis in a DVA radicle could result in outflow obstruction into the drainage of the lesion with subsequent CM rupture.^{26,27} Approximately 30% of patients with sporadic CM will have an associated DVA on standard MRI sequences. Evolving data using 7-T susceptibility-weighted imaging (SWI) suggest that all sporadic CMs have an associated DVA.^{28,29}

Up to 20% of patients have the familial form of the disease.¹⁴ There are 3 known protein-encoding genes resulting in familial CM disease: *KRIT1* (*CCM1*), *malcavernin* (*CCM2*), and *PDCD10* (*CCM3*) (Figure 2). These genes regulate signaling pathways involved in endothelial tight junction stability, cell proliferation, and angiogenesis. Each form is autosomal dominant with variable penetrance. The inherited mutation is not sufficient for lesion (CM) genesis. It is suggested that a “second hit” or somatic mutation is necessary for lesion development to occur.³⁰⁻³²

Familial CM can occur in people of any race or ethnicity, but there is a higher prevalence of cerebral CM (CCM) type 1 in Hispanic Americans from the southwestern United States due to a founder mutation in

CCM1 (Q455X, also known as the “common Hispanic mutation”). Familial CM is commonly characterized by multiple CMs without associated DVAs, although rare cases of familial CM disease associated with DVAs exist. Patients with multiple lesions or a single lesion and a family history should be considered for genetic counseling and testing.³³ Results of gene testing may be negative in up to 5% of patients with presumptive familial CM based on imaging and family history. Routine genetic testing in patients with a single lesion and no family history results in low yield of finding a mutation. Patients with the familial form may also have skin lesions (capillary venous malformations) and retinal hemangiomas.^{14,34-37} Patients with the familial form may develop a new CM lesion at a rate of approximately 1 every 2 years. Often, CCM type 3 manifests a more severe disease course than CCM type 1 or 2.^{38,39} Patients often present in childhood, are more likely to develop brain hemorrhage, and may have other systemic conditions, including scoliosis, meningioma, astrocytoma, and vestibular schwannoma.^{14,39,40}

Capillary telangiectasia and CMs may develop 2 to 20 years after brain or spinal irradiation, including stereotactic radiosurgery.⁴¹ The CM often develops in the port of radiotherapy or more diffusely in the setting of whole-brain irradiation. It is common for patients with radiation-induced CM to form multiple lesions.

CLINICAL PRESENTATION

Patients may come to clinical attention with an incidental finding or due to symptoms. Symptoms may include focal neurologic deficit, seizure, or acute headache in isolation.¹² These symptoms may or may not be associated with acute hemorrhage. Up until 2008 there was not a standard definition for acute hemorrhage or for patients with focal deficits that either did not have early MRI or did have MRI and no hemorrhage. Standard definitions were put forth in 2008 defining an acute hemorrhage from a CM as acute or subacute symptoms (eg, headache, seizure, impaired consciousness, or new/worsened

focal neurologic deficit referable to the anatomical location of the CM) accompanied by radiologic, pathologic, cerebrospinal fluid, or surgical confirmation of hemorrhage. Non-hemorrhagic focal neurologic deficit was defined as a focal neurologic sign or symptoms without evidence of hemorrhage.⁴² Chronic headache is common in patients with CM,¹⁴ but in the absence of associated acute bleeding by imaging, chronic headaches are not considered symptomatic sequelae of CM requiring surgery.

In the familial form, up to 50% of patients present without symptoms, perhaps due to increased screening of family members. In the familial form, seizure presentation is most common, followed by hemorrhage and nonspecific headaches.³⁴

In a large cohort of prospectively recruited patients (n=202) who underwent structured interview, questionnaire, and medical record and MRI review, 37.1% presented with acute clinical hemorrhage, 6.5% with focal neurologic deficit without hemorrhage, 14.8% with seizures without hemorrhage, and 40.6% with an incidental finding.⁴³ Unlike arterial pathology (eg, arteriovenous malformation or aneurysm), patients with CM presenting with hemorrhage most commonly progressed over 2 to 30 or more days after the new symptoms first appeared. Patients with a brainstem-located CM were more likely to present with hemorrhage. Patients presenting with seizure were more likely to have a supratentorial cortical lesion, with the temporal lobe being most prevalent.⁴⁴

Spinal cord CMs more commonly present with symptoms rather than as incidental findings. However, in the familial form, incidental CMs may be detected in patients undergoing evaluation and surveillance. Patients with spinal cord CM hemorrhage often present with incomplete or complete myelopathy with or without associated pain.^{45,46}

DIAGNOSIS

Computed tomography of the head is often performed in acute situations and may demonstrate bleeding from a CM or calcifications. However, computed tomography of

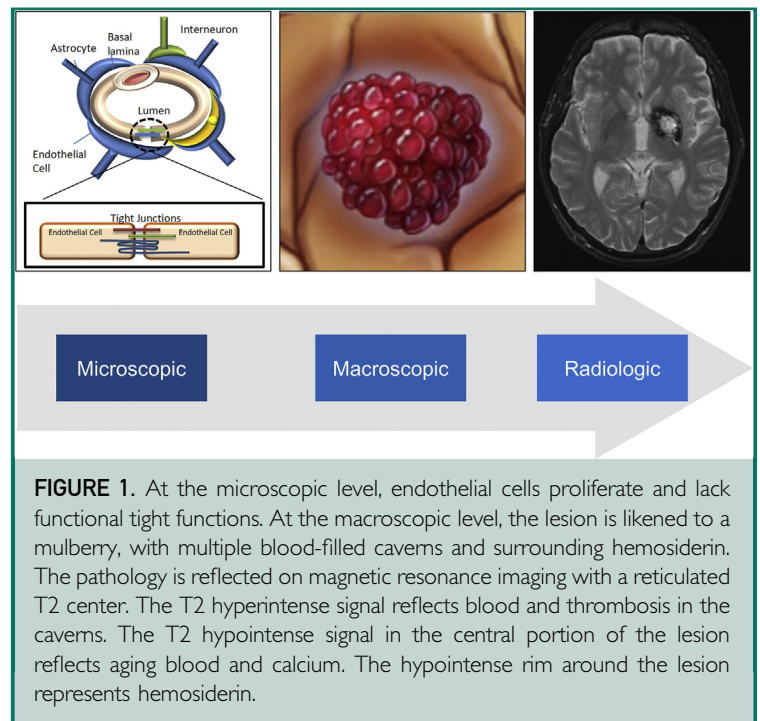
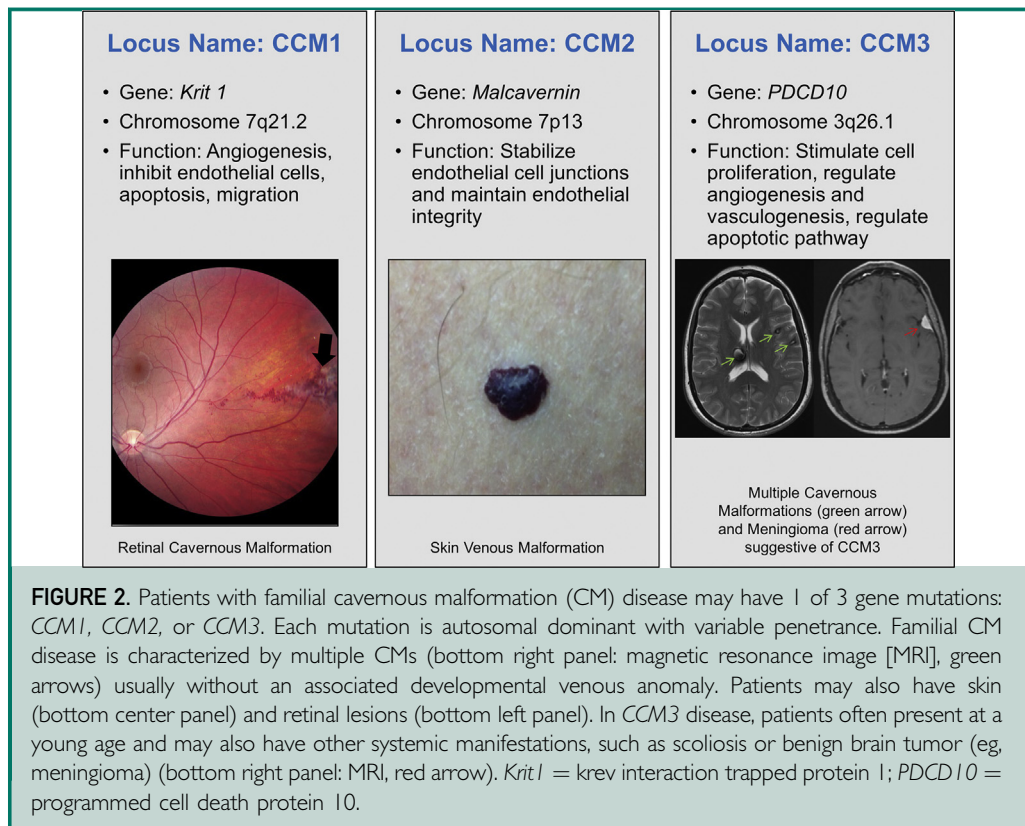


FIGURE 1. At the microscopic level, endothelial cells proliferate and lack functional tight junctions. At the macroscopic level, the lesion is likened to a mulberry, with multiple blood-filled cavities and surrounding hemosiderin. The pathology is reflected on magnetic resonance imaging with a reticulated T2 center. The T2 hyperintense signal reflects blood and thrombosis in the cavities. The T2 hypointense signal in the central portion of the lesion reflects aging blood and calcium. The hypointense rim around the lesion represents hemosiderin.

the head has poor sensitivity and specificity to make a diagnosis of CM.^{4,47,48}

Brain MRI, preferably 3 T with standard sequences and SWI, is the diagnostic test of choice.³³ T1-weighted sequences may demonstrate hyperintensity associated with recent subacute hemorrhage (Figure 3A), or the lesion may be isodense if no recent hemorrhage has occurred.^{2,4} T2-weighted sequences generally demonstrate a reticulated central lesion likened to a mulberry, with hypointensity surrounding the lesion reflecting the hemosiderin ring (Figure 3B). Hemosiderin-sensitive sequences, including gradient recalled echo or SWI, aid in confirming the diagnosis by demonstrating hypointensity at the CM site and possibly showing additional CMs (Figure 3C). Multiple CMs without DVAs may be suggestive of familial CM but can also be seen in patients with radiation-induced CM. In addition to T1-weighted MRI with contrast, SWI can help identify associated DVAs (Figure 3D). The CM may diffusely and minimally enhance on contrast-enhanced sequences (Figure 3E) but should not intensely enhance or have ring enhancement.⁴⁹ The latter, when associated with SWI changes, would be more suggestive



of a hemorrhagic metastasis, infectious process, or, rarely, inflammatory/demyelinating disease. The Zabramski classification system is commonly used to describe CM types I through IV based on imaging (Table 1).² Our understanding of the commonly associated DVA and its angioarchitecture has improved due to 7-T MRI SWI sequences (Figure 3F).²⁹

Zabramski type II (eg, Figure 3B) and III lesions are fairly characteristic on MRI; however, type I and type IV lesions are not specific (Table 2). The diagnosis of a CM may not be obvious on imaging in the presence of a sizable associated acute hemorrhage, type 1 lesion. Follow-up imaging may be necessary to ensure typical evolution of a CM hemorrhage.⁴⁹

NATURAL HISTORY AND OUTCOME

Multiple natural history studies and 3 meta-analyses have been performed to determine the prospective risk of bleeding from a CM.^{2,11,13,15,50-56} Based on these studies, patients with hemorrhage as their initial

presentation to medical attention and brainstem location have the highest risk of future hemorrhage. Based on one meta-analysis, the 5-year risk of future hemorrhage or focal neurologic deficit is 3.8% for non-brainstem location presenting without hemorrhage, 8.0% for brainstem location presenting without hemorrhage, 18.4% for non-brainstem location presenting with hemorrhage or focal neurologic deficit, and 30.8% for brainstem location presenting with hemorrhage or focal neurologic deficit.¹⁵ For those presenting with hemorrhage, the highest risk of recurrent hemorrhage was within the first 2.5 years. Others have similarly demonstrated a reduced risk of hemorrhage after the first 2 or 3 years.^{13,57,58} These observations have important practical implications for treatment recommendations.

Although brainstem location and previous hemorrhage seem fairly consistent among natural history studies, other risk factors for bleeding have been less consistent, including female sex,^{59,60} male sex,¹³ deep location,⁵⁶ and multiplicity.¹³

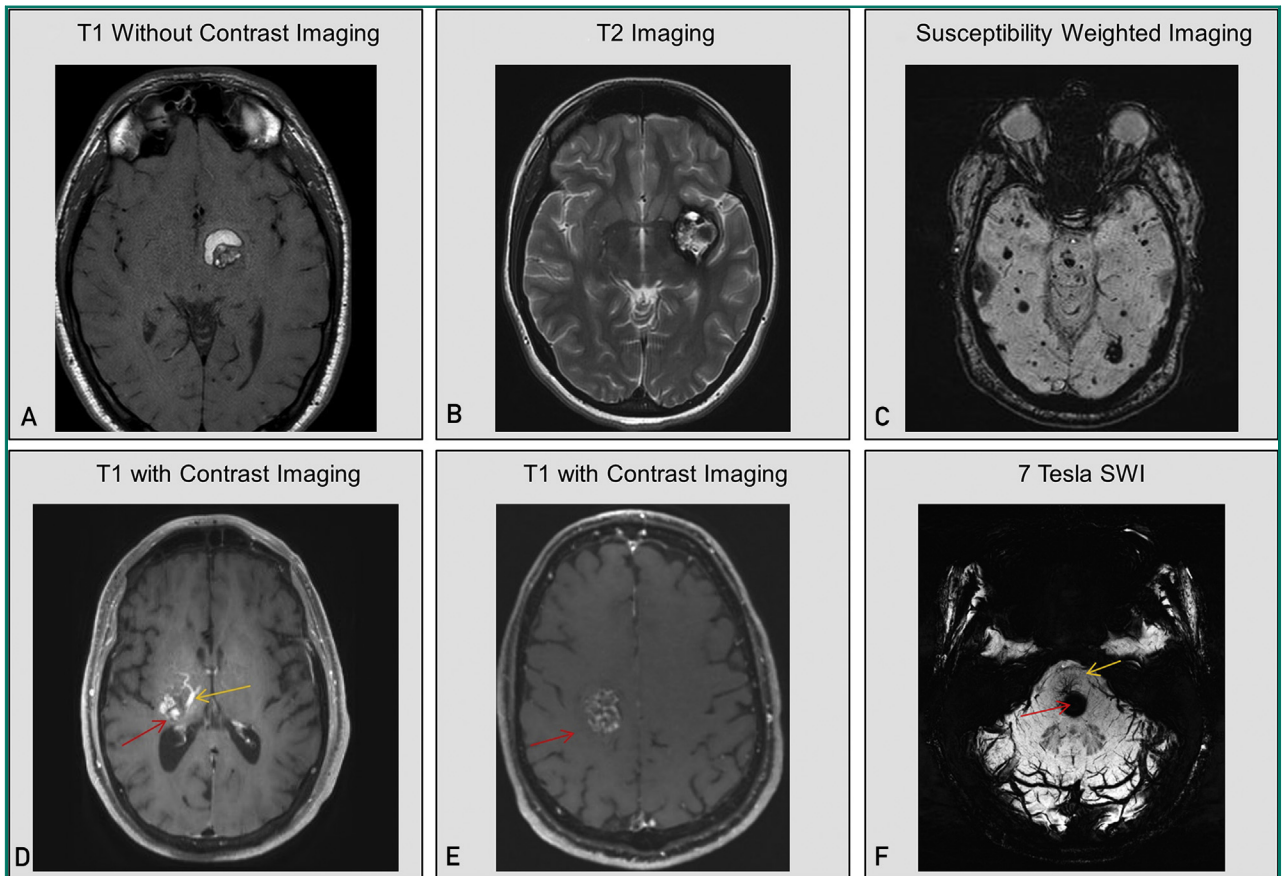


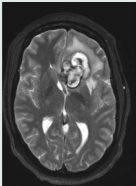
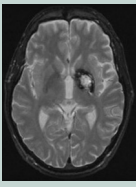
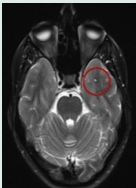
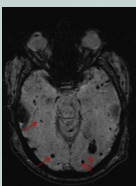
FIGURE 3. Magnetic resonance imaging (MRI) is the diagnostic test of choice in patients with cavernous malformation (CM). A, T1-weighted MRI is useful for assessing for subacute blood, as seen in this young patient with sudden right-sided hemiparesis. B, T2-weighted MRI sequences commonly demonstrate the characteristic reticulated central portion with hypointense hemosiderin surrounding the lesion. C, In patients with the familial form, hemosiderin-sensitive sequences such as gradient recalled echo or susceptibility-weighted imaging (SWI) are helpful in determining the lesion burden. Here you see innumerable dark lesions, each representing a small CM. D, T1-weighted imaging with contrast is helpful to determine whether there is an associated developmental venous anomaly (DVA) (yellow arrow). The CM is indicated by the red arrow. E, T1-weighted imaging with contrast also may show mild, mottled enhancement of the lesion (red arrow). Significant enhancement or ring enhancement is atypical for CM, and other pathologic conditions should be considered. F, A 7-T SWI demonstrates a CM (red arrow) and an associated DVA (yellow arrow). The detailed angioarchitecture of the DVA was not well visualized on standard MRI sequences at 1.5 or 3 T.

Although the bleeding risk is high in those presenting with hemorrhage, many patients have significant improvement in clinical symptoms after a first hemorrhage. Because CM are at the level of the capillary, blood flowing through them are under very low pressure. Thus, bleeding from a CM usually displaces rather than damages surrounding parenchyma; hence, the likely clinical recovery in the absence of recurrent bleeding as the acute blood is reabsorbed. Taslimi et al⁵¹ found that almost 80% of patients had full recovery

or minimal disability 1 year after a first hemorrhage, and mortality after hemorrhage from a CM is very low.

If a patient with CM presents with a seizure, the risk of recurrent seizure over 5 years can be as high as 94%.⁶¹ If the seizure is associated with acute hemorrhage and edema, it is not clear whether the risk of seizure goes down as the acute blood and edema resorb because most are treated with antiseizure medication. In a patient who presents with hemorrhage or focal neurologic deficit without hemorrhage, the 5-year risk

TABLE 1. Zabramski Types of Cavernous Malformation Based on MRI Characteristics

Lesion type	T1-weighted MRI characteristics	T2-weighted MRI characteristics	Hemosiderin sequence	Pathologic characteristics	Image
Type I	Hyperintense	Hyperintense or hypointense with surrounding hypointensity	Hypointense	Subacute hemorrhage surrounded by hemosiderin-stained macrophages and gliotic brain	
Type II	Reticulated core	Reticulated core with a hypointense rim	Hypointense	Loculated areas of hemorrhage and thrombosis of varying age surrounded by hemosiderin-stained brain and gliosis	
Type III	Isointense or hypointense	Hypointense with a hypointense rim	Hypointense	Chronic resolved hemorrhage with hemosiderin staining in and around the lesion	
Type IV	Poorly seen	Poorly seen	Hypointense	—	

MRI = magnetic resonance imaging.

Adapted from *J Neurosurg*.² Used with permission.

of seizure is approximately 4%. Seizures usually develop only in patients with supratentorial, cortically based lesions.⁴⁴

CLINICAL MANAGEMENT

In patients with CM, the goals of management include (1) determining treatment for the CM lesion itself, (2) treating symptoms and addressing issues associated with the CM (eg, seizures), and (3) managing the patient's other comorbid conditions (eg, headaches, pregnancy) (Figure 4). Clinical, nonsurgical management items are also summarized in Table 3.

There are presently no clinical trials published to guide the management of patients with CMs. Recommendations come from epidemiology and natural history

studies, large uncontrolled surgical and radiosurgical series, and large cohort studies. With the limitations of the available literature, the Scientific Section of the Angioma Alliance published consensus guidelines for the management of patients with CMs in 2017 based on the Delphi method.³³ These guidelines, in addition to other clinical considerations and recommendations, are addressed later herein.

Treatment of the CM Lesion

As with other conditions, the risk of intervention must be weighed against the natural history and outcome of the disease. Treatment recommendations in patients with CMs require the collaboration of neurologists and neurosurgeons with experience in

TABLE 2. Differential Diagnosis of Cavernous Malformations

Cavernous malformation, large lesions	Hypointensity on hemosiderin-sensitive sequences
Hemorrhagic metastases	Cavernous malformation (type IV)
Granuloma	Calcium
Infectious/inflammatory nodules	Microbleed due to cerebral amyloid angiopathy
Thrombosed arteriovenous malformation	Microbleed due to hypertension
Calcified primary brain tumor	Trauma
	History of radiation to the brain
	Foreign body: metal/glass
	Cardiac surgery

management of the disease. Current invasive treatment options for patients include surgery, radiosurgery, and stereotactic laser ablation, with open excision being the most commonly performed procedure. In the near future, new medical therapies may modify the course of the disease and the risk of CM hemorrhage and/or growth (see the "Research and Future Directions" section later herein).

What Are the Indications and Anatomical Considerations for Surgery? In general, invasive treatment is not indicated for incidentally discovered lesions because the risk of future hemorrhage in such patients is

negligible.³³ Surgery is indicated in select patients to reduce future hemorrhage risk (Figure 5) and seizure risk. Patients with a symptomatic hemorrhage related to a CM in a surgically accessible region of the brain can be considered for surgery understanding that the surgical risk is similar to the morbidity and mortality of living with the lesion for 2 years.³³ Patients in whom the CM is in the deep part of the brain (eg, thalamus, basal ganglia) or brainstem are commonly observed after even a single presenting hemorrhage, and surgery is reserved for recurrent hemorrhage or progressive deficits. However, this approach is

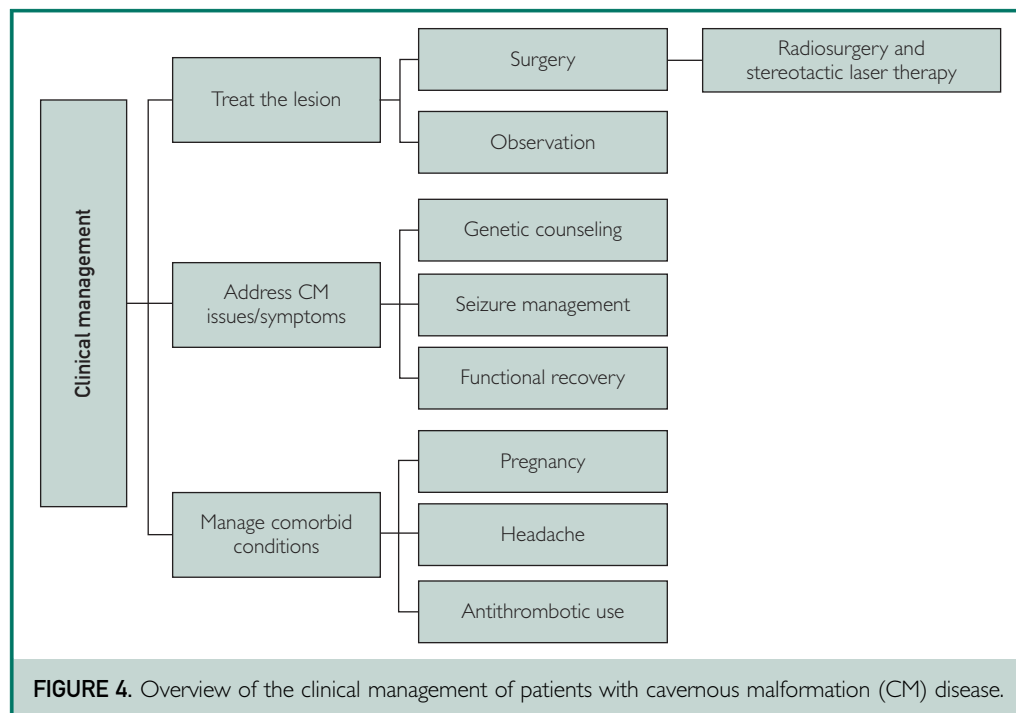


TABLE 3. Managing Clinical and Comorbid Conditions in Patients With CMs

Variable	Description
CM-related issues	
Genetic counseling	Patients with multiple CMs or a family history of CMs should be considered for genetic counseling and potential testing
	Genetic testing available for <i>CCM1</i> , <i>CCM2</i> , and <i>CCM3</i>
CM recovery from hemorrhage or focal deficit	Physical, occupational, and speech therapy as needed
Seizure disorder	Patients with facial nerve palsy or diplopia may benefit from surgery if recovery is partial
	No prophylactic medication if no seizure
	AED therapy is warranted for the first seizure in patients with CMs
	Avoid medications that may lower the seizure threshold, and avoid activities that may result in injury if a seizure occurs
	Surgery is considered in patients in whom the goal is to reduce future hemorrhage risk, patients intolerant or not responding to AED medication
Comorbid conditions in patients with CMs	
Antithrombotic medication	Weigh the risk of no antithrombotic drug therapy for the indicated condition if untreated vs the risk of CM hemorrhage
Headache management	If antithrombotics or anticoagulant required, monitor clinically for focal neurologic deficit or new headache
	Determine whether the headache is primary or secondary (due to bleeding)
	If primary headache, classify into appropriate subtype (eg, migraine, tension)
	There are no known contraindications to common oral migraine or tension headache prophylactic medications
	Regarding abortive medication, caution is recommended for use of NSAIDs in patients with recent hemorrhage
	No data exist for the safety of injectable calcitonin gene-related peptide inhibitors and CM
Lifestyle modification	Omnabotulinum toxin A injection for chronic migraine, occipital nerve blocks, and the Cefaly device may all be considered in appropriate patients with CMs and migraine if oral medications are not acceptable
	Patients with CMs and seizures should avoid activities that may reduce seizure threshold (eg, inadequate sleep) or potentially result in injury if a seizure occurs (eg, water activities)
	Very limited data may suggest that intense exercise or binge alcohol use may increase risk of hemorrhage; other data do not support limiting activity
Pregnancy	Provide prepregnancy counseling regarding genetic risk in familial form
	If the patient has a seizure disorder, consider the AED with the lowest teratogenic potential
	Advise folate supplementation if the patient is taking seizure medication during pregnancy
	MRI without contrast, if needed, during pregnancy or postpartum while breastfeeding
Nutrition/diet	Vaginal delivery is an acceptable mode of delivery unless recent hemorrhage or neurologic deficits preclude such
	Preclinical data suggest a possible role for vitamin D stabilizing the endothelium. No data exist as to whether supplementation is beneficial at this time
	Preclinical data suggest a role for healthy gut integrity to prevent gram-negative bacteria from migrating across the gut barrier. No data exist as to whether probiotics, prebiotics, or other supplementation is beneficial at this time

AED = antiepileptic drug; CM = cavernous malformation; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug.

controversial, and some argue that the highest risk of recurrent bleeding is from a brainstem CM; therefore, waiting for a second bleed may result in increased morbidity. Others argue that the favorable outcome after first bleed and the risk of surgery in certain brainstem regions may

favor conservative management after first hemorrhage.⁶²

A detailed discussion of the anatomical considerations in surgical resection of brainstem and deep-seated CMs is beyond the scope of this review.⁶³ In general, surgery is possible if a lesion approaches an

ependymal or pial surface, and the widespread application of intraoperative electrophysiologic neuromonitoring and frameless neuronavigation has improved the safety of surgery in areas once considered high risk.

Are There Options for Treatment Besides Open Surgery? Stereotactic radiosurgery (eg, gamma knife therapy or linear accelerator therapy) has been considered an alternative to open surgery in patients with surgically inaccessible lesions.^{64,65} However, it is not clear whether the benefit from radiosurgery is better than the natural history; many studies suggest that the risk of hemorrhage declines after 2.5 years similar to the natural history, and the radiosurgical studies have no control group. The Angioma Alliance guideline states that radiosurgery may be considered in a solitary CM with previous symptomatic hemorrhage if the surgical risk is unacceptably high.³³ The guidelines further state that radiosurgery is not recommended for asymptomatic or familial CM.³³ Because radiotherapy, including radiosurgery, has been associated with the development of CMs and patients with the familial form are susceptible to developing new lesions, radiosurgery is not advised in those patients due to concern of proliferation of further CMs.

Recently, a minimally invasive technique, MRI-guided stereotactic laser interstitial thermal therapy, has been used for the treatment of drug-resistant epilepsy, including a few patients with CMs.⁶⁶ The technique has the advantage of being minimally invasive and of allowing real-time visualization and monitoring of the treatment with MRI thermography. The experience in patients with CMs, although promising, is still too limited to make definitive conclusions and recommendations.

Managing Symptoms and Issues Related to CMs

Should I Obtain Genetic Testing in My Patient With CMs? Patients with multiple CMs or a family history of CMs should undergo genetic counseling and consider genetic

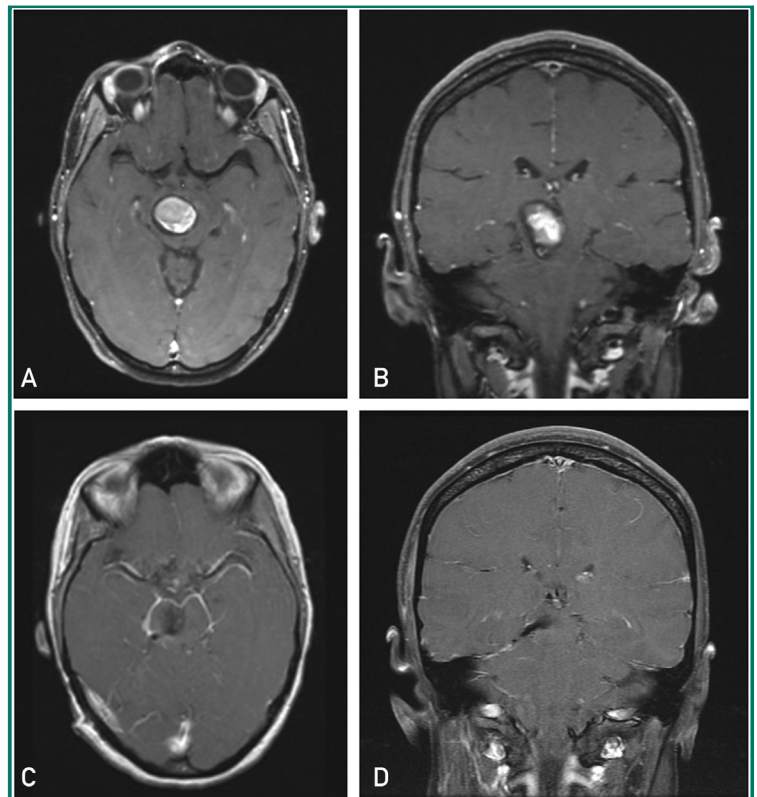


FIGURE 5. Axial (A) and coronal (B) T1-weighted magnetic resonance images (MRIs) with contrast of a 48-year-old woman with multiple bleeds from a midbrain cavernous malformation resulting in double vision, progressive left arm weakness, and tremor. The cavernous malformation, which extended superiorly in the posterior thalamus, was removed through a supracerebellar, infratentorial surgical trajectory. Although the lesion did not reach the surface, it could be safely removed through a small entry point at the level of the lateral mesencephalic sulcus. Postoperative T1-weighted MRI with contrast axial (C) and coronal (D) views confirms complete resection. On the axial postoperative view (C), one can appreciate the small entrance into the brainstem through the lateral mesencephalic sulcus. Postoperatively, the patient experienced improvement of her weakness but persistence of the other symptoms.

testing.³³ A 3-generation family history should be obtained. Sanger or next-generation sequencing analysis can be performed along with deletion/duplication analysis for the *CCM1*, *CCM2*, and *CCM3* genes.³³ Counseling should occur before testing to weigh the risks (including psychological consequences) and benefits, especially in asymptomatic individuals.

What Therapy Is Available for My Patient Who Had a Hemorrhage? Postsurgery patients or those with hemorrhage may require

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

Study	Location	Enrollment	Eligible patients	Study medication	Primary outcome
Permeability MRI in Cerebral Cavemous Malformations Type I in New Mexico: Effects of Statins NCT01764451	University of New Mexico	Closed	Familial CCM	Simvastatin	Effect of drug on permeability MRI
Atorvastatin Treatment of Cavemous Angiomas With Symptomatic Hemorrhage Exploratory Proof of Concept (AT CASH EPOC) Trial NCT02603328	University of Chicago	Recruiting	CM hemorrhage within 1 y	Atorvastatin	Mean change in lesional QSM MRI
Treat_CCM: Propranolol in Cerebral Cavemous Malformation NCT03589014	Italy	Recruiting	Familial CM	Propranolol	Lesion burden and clinical events
Effect of Oral Propranolol on mRNA Expression in Symptomatic CM NCT03474614	Barrow Neurologic Institute	Recruiting	Symptomatic CM	Propranolol	mRNA and miRNA expression

CCM = cerebral cavemous malformation; CM = cavemous malformation; miRNA = microRNA; MRI = magnetic resonance imaging; mRNA = messenger RNA; QSM = quantitative susceptibility mapping.

a combination of physical, occupational, and speech therapy depending on their neurologic deficits. Surgical treatments for diplopia and lower motor neuron facial weakness can be performed if patients do not improve over the course of 1 year.

Some patients develop delayed complications such as neuropathic pain, tremor, or hypertrophic olivary degeneration. Neuropathic pain medications or neuromodulation can be considered in patients with thalamic, medullary, and spinal cord pain syndromes. Rubral tremors can be a complication of midbrain hemorrhage or intervention. Although medications and, in some cases, deep brain stimulation are used, the results for this specific type of tremor are suboptimal.

My Patient With CMs Had a Seizure. What Should I Do?.

In patients with a single seizure, the risk of a recurrent seizure is as high as 94% over 5 years; thus, antiseizure medication for focal seizures is generally warranted.^{33,61,67} Early surgery may be considered in patients in whom the seizure was precipitated by a hemorrhage, and the goal is to reduce future hemorrhage as well as control seizure risk.⁶⁷ In addition, early surgery could be considered in patients poorly compliant with medication.⁶⁷ In patients with recurrent seizure despite adequate trials of 1 or 2 medications, surgery

should also be considered. Functional MRI, tractography, and other tools may help determine a patient's candidacy for safe surgery. Patients with a single lesion undergoing surgery have a high (approximately 70%-90%) likelihood of seizure freedom 2 years post-operatively.⁶⁷ Candidates with less than 2 years of seizures,^{67,68-71} CM size less than 1.5 cm,⁷² and focal seizures rather than secondary generalization have the best results,^{67,72} but studies vary. There is some debate whether lesionectomy alone vs lesionectomy with removal of hemosiderin affords a better outcome.⁶⁷ In general, we prefer lesionectomy with additional removal of surrounding gliotic and hemosiderin-stained brain only in non-eloquent areas. Patients who fail this strategy may be candidates for more specific seizure surgery.

How Often Should I Obtain Brain Imaging on My Patient With CMs?.

Because hemorrhagic CMs may lack the classic appearance on initial imaging and can sometimes be mistaken for metastases or other diseases, we recommend repeated MRI within 3 months after an initial hemorrhage to ensure typical evolution of the lesion.⁴⁹ We often repeat imaging 1 year after an initial hemorrhage as well.

In the absence of hemorrhage or new symptoms, the utility of repeated MRI of the

brain is unclear.³³ Once the diagnosis of CM is secure, gadolinium use is not necessary as any associated DVA is unlikely to change. However, if one is assessing for an alternative condition, gadolinium could be considered. In the future, repeated MRI may aid in determining the efficacy of candidate medications in reducing hemorrhage and lesion burden.

Managing Comorbid Conditions in a Patient With CMs

What If My Patient Requires Antithrombotic Therapy for Another Condition? Because CMs can bleed, there is justifiable concern about using concomitant antithrombotic agents (anticoagulation and antiplatelet). However, several single-center, non-randomized cohort studies and 1 meta-analysis suggest that the bleeding risk is lower in patients taking antithrombotic agents.^{11,27,73-75} There are plausible reasons why this might be the case. First, in patients with the sporadic form with an associated DVA, one theory is that 1 of the DVA radicles thromboses to cause outflow obstruction and increased pressure in the CM with subsequent hemorrhage, similar to what is observed with cerebral venous thrombosis.^{26,27} According to this hypothesis, the “protective” role of antithrombotic agents is its ability to reduce risk of thrombosis in the DVA. Second, the anti-inflammatory properties of aspirin may result in a lower bleed risk because CM leakiness may relate to inflammation.⁷⁶ Although these theories are attractive, these findings must be interpreted with caution. It is also possible that the findings are due to selection bias. That is, physicians selectively allow antithrombotic drug therapy in patients with CM who they feel are at lowest risk, and that clinical acumen is reflected in this cohort data on antithrombotic drugs in CM. Caution is recommended in interpreting these studies because they focused more on aspirin than on anticoagulants and more commonly involved the sporadic rather than the familial form. These studies at least indicate that the use of antithrombotic agents does not seem to precipitate hemorrhage.

Based on the current evidence, it is our opinion that antithrombotics should be

avoided if possible. In a patient in whom the bleeding risk from the CM is low and the morbidity from the condition requiring an antithrombotic agent is high, antithrombotic drugs should be used. Patients with a CM taking antithrombotics should be closely monitored for new symptoms potentially related to hemorrhage from the CM.

My Patient Wants to Become Pregnant. How Do I Counsel Her?

There are several considerations in a patient wanting to become pregnant or who is pregnant and has a CM. First, if she has the familial form of the disease, genetic counseling should be discussed. Second, if the patient has a seizure disorder, an assessment should be performed to determine whether a medication needs to be continued during pregnancy. If the patient does need antiepileptic medications, the safest drug and supplementation with folate should be considered to reduce teratogenicity. Finally, the risk of hemorrhage and the mode of delivery should be discussed. If neurologic symptoms occur during the pregnancy or postpartum while she is breastfeeding, an MRI without contrast can be considered.

There has been concern in the past that pregnancy increases the risk of hemorrhage from a CM due to a variety of case reports and case series published in the early 1990s. Subsequently, 2 large series of female patients have suggested that the risk of hemorrhage during pregnancy is no greater than in nonpregnant women of comparable age.^{77,78} There is no evidence to contraindicate pregnancy in a patient with a known CM. Similarly, unless specific contraindications (not related to the CM) exist, there is no reason to consider alternatives to a vaginal delivery.

My Patient With CM Has Chronic Headaches. What Is Safe to Use?

The first goal is to determine whether the patient has a primary or secondary headache. “Red flags” indicating a secondary headache (eg, hemorrhage or hydrocephalus) include thunderclap pain onset, associated focal neurologic deficit, worsening pain with straining, and new headache in a patient older than 50 years. If the patient has a primary headache, the headache should be

characterized and classified. Most commonly, patients with CMs have migraine or tension primary headaches.

There is very little literature addressing the issue of safety of medications used for headache in patients with CM. In terms of abortive therapy for tension and migraine headaches, some have raised a concern that nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of bleeding.¹⁴ However, data from a large, prospective cohort of mostly nonfamilial CMs have not supported NSAID use as a risk for hemorrhage.⁴⁴ In some cases, patients may bleed, causing a headache, and then take NSAIDs. The NSAIDs are, thus, an effect of the bleed rather than a cause. However, caution is recommended in the use of NSAIDs if a recent bleed has occurred until further data are known. Little data exist on the safety of triptan medications at this time.

Options to prevent headache include oral medications, injectable medications, and devices. There are no contraindications to standard migraine preventive medications in patients with CMs. In fact, due to case reports of potential benefit,⁷⁹⁻⁸³ propranolol is being evaluated to potentially reduce hemorrhage risk (see the "Research and Future Directions" section later herein). If a patient does not tolerate or cannot use oral prophylactic medications, Onabotulinumtoxin A may be considered for chronic migraine as well as occipital nerve block. No information exists on calcitonin gene-related peptide inhibitors and CM or other vascular pathology at this time. The Cefaly device (CEFALY US Inc) may be used in patients with migraine and CMs.

My Patient With CM Wants More Education and Coping Support. What Resources Exist? The Angioma Alliance is a patient-directed network whose mission is to educate and support patients with CMs and to support and drive research for a cure for the disease. Their website, <http://www.angioma.org>,⁸⁴ has patient information, research news, and information for professionals caring for patients with CMs.

RESEARCH AND FUTURE DIRECTIONS

What Insights Exist on Why or How CMs Form?

Patients who develop CMs typically have either a gene mutation or a DVA. But those 2 things alone do not necessarily result in CM formation. In addition, there is high variability in the familial disease, even among individuals with the same germline mutations. Other factors may play a role. Possible factors gleaned from detailed in vitro and animal data include oxidative stress, inflammation, and alterations in angiogenesis.^{76,85} Recent human data support these findings. Polymorphisms in inflammatory and immune-response pathways predicted CM lesion burden in patients with CCM type 1.⁸⁶ In another study, patients with sporadic CMs were more likely to have a chronic inflammatory disease compared with patients with a DVA without a CM.⁸⁷

Recently, investigators found a potential role for the gut microbiome in the genesis of CM. Researchers reported that gram-negative bacteria-containing lipopolysaccharide may penetrate the gut mucosa during inflammatory states or when the gut mucosal barrier thins.⁸⁸ Lipopolysaccharide can stimulate toll-like receptor 4 (TLR4) on the endothelial wall in mice with altered CM gene, resulting in CM lesion genesis. It was further found that antibiotics and blockade of TLR4 in the same mice prevent CM lesion formation. In 188 patients with CCM type 1, inflammatory and immune-related genes were assessed and compared with CM lesion burden.⁸⁶ Single nucleotide polymorphisms in 2 genes, *TLR4* and *CD14*, were associated with increased CM lesion number. Research on the influence of the gut microbiome in human CM disease is ongoing.

Are There Medications That Might Reduce the Risk of Bleeding?

With clearer understanding of the genetic mechanisms underlying the familial form of CM and new laboratory techniques to study repurposing medications, several identified candidate drugs may reduce hemorrhage risk and, for those with the familial form,

new lesion development.^{34,76,78,89,90} Preclinical animal and in vitro data have suggested potential roles for rapamycin,⁹¹ sorafenib,⁹² sulindac (NSAID),⁹³ TLR4-blocking agents,⁸⁸ fasudil,⁹⁴⁻⁹⁶ vitamin D,⁹⁰ tempol,⁹⁰ and simvastatin.⁹⁶ Positive effects of bevacizumab and propranolol⁷⁹⁻⁸³ have been reported in case reports. Several ongoing clinical trials are assessing the role of statins and propranolol on the clinical course and biomarkers of CM (Table 4).

Are There Advances in Biomarkers for CM Clinical Behavior?

Given the number of candidate medications and the low prevalence of symptomatic CM disease, clinical trials may prove difficult and may have type II statistical error if underpowered. Biomarkers may be necessary rather than clinical outcomes to increase power.

Quantitative susceptibility mapping (QSM) and dynamic contrast-enhanced quantitative perfusion are evolving techniques to aid in measuring the iron content and vascular permeability of CM lesions.⁹⁷⁻¹⁰⁰ In 1 study, a 6% threshold increase in iron content measured by QSM was found to reflect risk of future symptomatic hemorrhage. These studies may prove useful in studying the biologic effects of candidate medications.

Serum biomarkers are also being assessed to determine whether they reflect CM disease activity.^{101,102} Girard et al¹⁰² assessed the utility of plasma biomarkers that reflect angiogenesis, inflammation, and oxidative stress. They found that 4 plasma inflammatory cytokines (interleukin 2, interferon gamma, tumor necrosis factor, and interleukin 1 beta) helped stratify clinical behavior in patients with CM. Patients with a "high" inflammatory state as measured by the biomarker combination were associated with hemorrhage, seizure, and lesional growth during follow-up.

The Trial Readiness in Cavernous Angiomas With Symptomatic Hemorrhage (CASH) trial is a multicenter study currently underway to develop infrastructure for future clinical trials.¹⁰³ Standard imaging along with QSM and dynamic contrast-enhanced quantitative

perfusion imaging are being assessed as potential biomarker end points for future clinical trials. In addition, data are being gathered to determine potential knowledge gaps and assess the prevalence of the disease population at highest risk for repeated hemorrhage, that is, patients with a CM with hemorrhage in the past 1 year.

CONCLUSION

Cavernous malformations are low-flow, acquired, vascular malformations of the central nervous system. They may be sporadic, familial, or radiation induced. Cavernous malformations present to medical attention as an incidental finding on axial imaging studies or because of associated seizure, headache, or focal neurologic deficit (with or without concomitant hemorrhage). The natural history of the CM in each individual needs to be weighed against the risk of lesion treatment based on the age of the patient, symptoms, morphology of the lesion, and anatomical considerations. Treatment of comorbid conditions requires careful consideration of the risk, benefit, and knowledge of literature gaps. In the future treatment of CM, disease-modifying agents in addition to surgical options will become available for prevention of hemorrhage, treatment of seizures, and reduction of lesion burden.

Abbreviations and Acronyms: CCM = cerebral cavernous malformation; CM = cavernous malformation; DVA = developmental venous anomaly; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; QSM = quantitative susceptibility mapping; SWI = susceptibility-weighted imaging; TLR4 = toll-like receptor 4

Potential Competing Interests: Dr Lanzino is a board member for Superior Medical Editing. The other authors report no competing interests.

Correspondence: Address to Kelly D. Flemming, MD, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (Flemming.Kelly@mayo.edu).

REFERENCES

1. Gonzalez LF, Lekovic GP, Eschbacher J, Coons S, Porter RV, Spetzler RF. Are cavernous sinus hemangiomas and cavernous malformations different entities? *Neurosurg Focus*. 2006;21(1):e6.
2. Zabramski JM, Wascher TM, Spetzler RF, et al. The natural history of familial cavernous malformations: results of an ongoing study. *J Neurosurg*. 1994;80(3):422-432.

3. Kazawa N, Shibamoto Y. The MRI imaging of cerebral cavernous malformation with practical use of diffusion weighted image. *Int J Radiol*. 2015;2(1):24-28.
4. Rigamonti D, Drayer BP, Johnson PC, Hadley MN, Zabramski J, Spetzler RF. The MRI appearance of cavernous malformations (angiomas). *J Neurosurg*. 1987; 67(4):518-524.
5. Otten P, Pizzolato GP, Rilliet B, Bernay J. 131 cases of cavernous angioma (cavernomas) of the CNS, discovered by retrospective analysis of 24,535 autopsies. *Neurochirurgie*. 1989;35(2):128-131.
6. Courville CB. *Pathology of the Central Nervous System*. 3rd ed. Mountain View, CA: Pacific Press Publishing Association; 1950.
7. Al-Holou WN, O'Lynnner TM, Pandey AS, et al. Natural history and imaging prevalence of cavernous malformations in children and young adults. *J Neurosurg Pediatr*. 2012;9(2): 198-205.
8. Sage M, Brophy B, Sweeney C, et al. Cavernous haemangiomas (angiomas) of the brain: clinically significant lesions. *Australas Radiol*. 1993;37(2):147-155.
9. DelCurling O Jr, Kelly DL Jr, Elster AD, Craven TE. An analysis of the natural history of cavernous angiomas. *J Neurosurg*. 1991;75(5):702-708.
10. Flemming KD, Graff-Radford J, Aakre J, et al. Population-based prevalence of cerebral cavernous malformations in older adults: Mayo Clinic Study of Aging. *JAMA Neurol*. 2017;74(7): 801-805.
11. Al-Shahi Salman R, Hall JM, Home MA, et al. Untreated clinical course of cerebral cavernous malformations: a prospective, population-based cohort study. *Lancet Neurol*. 2012;11(3): 217-224.
12. Flemming KD. Clinical management of cavernous malformations. *Curr Cardiol Rep*. 2017;19(12):122.
13. Flemming KD, Link MJ, Christianson TJ, Brown RD Jr. The prospective hemorrhage risk of intracerebral cavernous malformations. *Neurology*. 2012;78(9):632-636.
14. Morrison L, Akers A. Cerebral cavernous malformation, familial. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. *GeneReviews*® [Internet]. Seattle, WA: University of Washington, Seattle; 1993–2017. <https://www.ncbi.nlm.nih.gov/books/NBK1293>. Accessed July 30, 2019.
15. Home MA, Flemming KD, Su IC, et al. Clinical course of untreated cerebral cavernous malformations: a meta-analysis of individual patient data. *Lancet Neurol*. 2016;15(2):166-173.
16. Flemming KD, Bovis GK, Meyer FB. Aggressive course of multiple de novo cavernous malformations. *J Neurosurg*. 2011; 115(6):1175-1178.
17. Cakir S. De novo formation of a cavernous malformation of the brain in the presence of a developmental venous anomaly. *Clin Radiol*. 2003;58(3):251-256.
18. Brinjikji W, Flemming KD, Lanzino G. De novo formation of a large cavernoma associated with a congenital torcular dural arteriovenous fistula: case report. *J Neurosurg Pediatr*. 2017; 19(5):567-570.
19. Chakravarthy H, Lin T-K, Chen Y-L, Wu Y-M, Yeh C-H, Wong H-F. De novo formation of cerebral cavernous malformation adjacent to existing developmental venous anomaly: an effect of change in venous pressure associated with management of a complex dural arterio-venous fistula. *Neuroradiol J*. 2016;29(6):458-464.
20. Campeau NG, Lane JL. De novo development of a lesion with the appearance of a cavernous malformation adjacent to an existing developmental venous anomaly. *AJNR Am J Neuroradiol*. 2005;26(1):156-159.
21. Nimjee SM, Powers CJ, Bulsara KR. Review of the literature on de novo formation of cavernous malformations of the central nervous system after radiation therapy. *Neurosurg Focus*. 2006; 21(1):e4.
22. Pozzati E, Acciarri N, Tognetti F, Mariani F, Giangaspero F. Growth, subsequent bleeding, and de novo appearance of cerebral cavernous angiomas. *Neurosurgery*. 1996;38(4):662-669.
23. Su I-C, Krishnan P, Rawal S, Krings T. Magnetic resonance evolution of de novo formation of a cavernoma in a thrombosed developmental venous anomaly: a case report. *Neurosurgery*. 2013;73(4):E739-E745.
24. Tekkok I, Ventureyra E. De novo familial cavernous malformation presenting with hemorrhage 12.5 years after the initial hemorrhagic ictus: natural history of an infantile form. *Pediatr Neurosurg*. 1996;25(3):151-155.
25. Brinjikji W, El-Masri AE, Wald JT, Flemming KD, Lanzino G. Prevalence of cerebral cavernous malformations associated with developmental venous anomalies increases with age. *Child Nerv Syst*. 2017;33(9):1539-1543.
26. Gross BA, Lin N, Du R, Day AL. The natural history of intracranial cavernous malformations. *Neurosurg Focus*. 2011;30(6):E24.
27. Schneble H, Soumare A, Herve D, et al. Antithrombotic therapy and bleeding risk in a prospective cohort of patients with cerebral cavernous malformation. *Stroke*. 2012;43(3):3196-3199.
28. Dammann P, Wrede KH, Maderwald S, et al. The venous angioarchitecture of sporadic cerebral cavernous malformations: a susceptibility weighted imaging study at 7 T MRI. *J Neurol Neurosurg Psychiatry*. 2013;84(2):194-200.
29. Dammann P, Wrede K, Zhu Y, et al. Correlation of the venous angioarchitecture of multiple cerebral cavernous malformations with familial or sporadic disease: a susceptibility-weighted imaging study with 7-Tesla MRI. *J Neurosurg*. 2017; 126(2):570-577.
30. Riant F, Bergametti F, Aygnac X, Boulday G, Tournier-Lasserre E. Recent insights into cerebral cavernous malformations: the molecular genetics of CCM. *FEBS J*. 2010;277(5): 1070-1075.
31. McDonald D, Shi C, Shenkar R. Lesions from patients with sporadic cavernous malformations harbor somatic mutations in the CCM genes: evidence for a common biochemical pathway for CCM pathogenesis. *Hum Mol Genet*. 2014; 23(16):4357-4370.
32. Akers A, Johnson E, Steinberg G, Zabramski J, Marchuk D. Biallelic somatic and germline mutations in cerebral cavernous malformations: evidence for a two-hit mechanism of CCM pathogenesis. *Hum Mol Genet*. 2009;18(5):919-930.
33. Akers A, Al-Shahi Salman R, Awad I, et al. Synopsis of guidelines for the clinical management of cerebral cavernous malformations: consensus recommendations based on systematic literature review by the Angioma Alliance Scientific Advisory Board Clinical Experts Panel. *Neurosurgery*. 2017; 80(5):665-680.
34. Zafar A, Quadri SA, Farooqui M, et al. Familial cerebral cavernous malformations. *Stroke*. 2019;50(5):1294-1301.
35. Eerola I, Plate KH, Spiegel R, Boon LM, Mulliken JB, Viskula M. *KRT11* is mutated in hyperkeratotic cutaneous capillary-venous malformation associated with cerebral capillary malformation. *Hum Mol Genet*. 2000;9(9):1351-1355.
36. Choquet H, Nelson J, Pawlikowska L, et al. Association of cardiovascular risk factors with disease severity in cerebral cavernous malformation type I subjects with the common Hispanic mutation. *Cerebrovasc Dis*. 2014;37(1):57-63.
37. Choquet H, Pawlikowska L, Lawton MT, Kim H. Genetics of cerebral cavernous malformations: current status and future prospects. *J Neurosurg Sci*. 2015;59(3):211-220.
38. Shenkar R, Peiper A, Pardo H, et al. Rho kinase inhibition blunts lesion development and hemorrhage in murine models of aggressive Pcd10/Ccm3 disease. *Stroke*. 2019;50(3):738-744.
39. Shenkar R, Shi C, Rebeiz T, et al. Exceptional aggressiveness of cerebral cavernous malformation disease associated with *PDCD10* mutations. *Genet Med*. 2015;17(3):188-196.
40. Wang K, Zhou J, Wang M. *CCM3* and cerebral cavernous malformation disease. *Stroke Vasc Neural*. 2019;4(2):67-70.

41. Cutsforth-Gregory JK, Lanzino G, Link MJ, Brown RD Jr, Flemming KD. Characterization of radiation-induced cavernous malformations and comparison with a nonradiation cavernous malformation cohort. *J Neurosurg*. 2015;122(5):1214-1222.
42. Salnan RA-S, Berg MJ, Morrison L, Awad I; Angioma Alliance Scientific Advisory Board. Hemorrhage from cavernous malformations of the brain: definition and reporting standards. *Stroke*. 2008;39(12):3129-3130.
43. Flemming KD, Kumar S, Brown RD Jr, Lanzino G. Predictors of initial presentation with hemorrhage in patients with cavernous malformations [published online October 9, 2019]. *World Neurosurg*. <https://doi.org/10.1016/j.wneu.2019.09.161>.
44. Agosti E, Flemming KD, Lanzino G. Symptomatic cavernous malformation presenting with seizure without hemorrhage: analysis of factors influencing clinical presentation. *World Neurosurg*. 2019;129:e387-e392.
45. Goyal A, Rinaldo L, Alkhatybeh R, et al. Clinical presentation, natural history and outcomes of intramedullary spinal cord cavernous malformations. *J Neurol Neurosurg Psychiatry*. 2019;90(6):695-703.
46. Labauge P, Bouly S, Parker F, et al. Outcome in 53 patients with spinal cord cavernomas. *Surgical Neurology*. 2008;70:176-181.
47. Lobato RD, Perez C, Rivas JJ, Cordobes F. Clinical, radiological, and pathological spectrum of angiographically occult intracranial vascular malformations: analysis of 21 cases and review of the literature. *J Neurosurg*. 1988;68(4):518-531.
48. Vaquero J, Leunda G, Martinez R, Bravo G. Cavernomas of the brain. *Neurosurgery*. 1983;12(2):208-210.
49. Flemming KD, Kumar S, Lanzino G, Brinjikji W. Baseline and evolutionary radiologic features in sporadic, hemorrhagic brain cavernous malformations. *AJNR Am J Neuroradiol*. 2019;40(6):967-972.
50. Gross BA, Du R. Hemorrhage from cerebral cavernous malformations: a systematic pooled analysis. *J Neurosurg*. 2017;126(4):1079-1087.
51. Taslimi S, Modabbernia A, Amin-Hanjani S, Barker FG, Macdonald RL. Natural history of cavernous malformation: systematic review and meta-analysis of 25 studies. *Neurology*. 2016;86(21):1984-1991.
52. Aiba T, Tanaka R, Koike T, Kameyama S, Takeda N, Komata T. Natural history of intracranial cavernous malformations. *J Neurosurg*. 1995;83(1):56-59.
53. Kim DS, Park YG, Choi JU, Chung SS, Lee KC. An analysis of the natural history of cavernous malformations. *Surg Neurol*. 1997;48(1):9-18.
54. Kondziolka D, Lunsford LD, Kestle JR. The natural history of cerebral cavernous malformations. *J Neurosurg*. 1995;83(5):820-824.
55. Labauge P, Brunereau L, Lévy C, Laberge S, Houtteville JP. The natural history of familial cerebral cavernomas: a retrospective MRI study of 40 patients. *Neuroradiology*. 2000;42(5):327-332.
56. Porter PJ, Willinsky RA, Harper W, Wallace MC. Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. *J Neurosurg*. 1997;87(2):190-197.
57. Barker FG, Amin-Hanjani S, Butler WE, et al. Temporal clustering of hemorrhages from untreated cavernous malformations of the central nervous system. *Neurosurgery*. 2001;49(1):15-25.
58. Duffau H, Capelle L, Sichez JP, et al. Early radiologically proven rebleeding from intracranial cavernous angiomas: report of 6 cases and review of the literature. *Acta Neurochir (Wien)*. 1997;139(10):914-922.
59. Moriarty J, Clatterbuck R, Rigamonti D. The natural history of cavernous malformations. *Neurosurg Clin N Am*. 1999;10(3):411-417.
60. Robinson JR, Awad IA, Little JR. Natural history of the cavernous angioma. *J Neurosurg*. 1991;75(5):709-714.
61. Josephson CB, Leach JP, Duncan R, Roberts RC, Counsell CE, Al-Shahi Salman R. Seizure risk from cavernous or arteriovenous malformations: prospective population-based study. *Neurology*. 2011;76(18):1548-1554.
62. Rinkel LA, Salnan RA-S, Rinkel GJ, Greving JP. Radiosurgical, neurosurgical or no intervention for cerebral cavernous malformations: a decision analysis [published online May 23, 2019]. *Int J Stroke*. <https://doi.org/10.1177/1747493019851290>.
63. Giliberto G, Lanzino DJ, Diehn FE, Factor D, Flemming KD, Lanzino G. Brainstem cavernous malformations: anatomical, clinical, and surgical considerations. *Neurosurg Focus*. 2010;29(3):E9.
64. Nagy G, Burkitt W, Stokes SS, et al. Contemporary radiosurgery of cerebral cavernous malformations, part 1: treatment outcome for critically located hemorrhagic lesions [published online July 27, 2018]. *J Neurosurg*. <https://doi.org/10.3171/2017.5.JNS17776>.
65. Nagy G, Stokes SS, Eross LG, et al. Contemporary radiosurgery of cerebral cavernous malformations, part 2: treatment outcome for hemispheric lesions [published online July 1, 2018]. *J Neurosurg*. <https://doi.org/10.3171/2018.2.JNS171267>.
66. Shimamoto S, Wu C, Sperling MR. Laser interstitial thermal therapy in drug-resistant epilepsy. *Curr Opin Neurol*. 2019;32(2):237-245.
67. Rosenow F, Alonso-Vanegas MA, Baumgartner C, et al. Cavernoma-related epilepsy: review and recommendations for management: report of the Surgical Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2013;54(12):2025-2035.
68. Moran NF, Fish DR, Kitchen N, Shorvon S, Kendall BE, Stevens JM. Supratentorial cavernous haemangiomas and epilepsy: a review of the literature and case series. *J Neurol Neurosurg Psychiatry*. 1999;66(5):561-568.
69. Cappabianca P, Alfieri A, Maiuri F, Mariniello G, Cirillo S, de Divitiis E. Supratentorial cavernous malformations and epilepsy: seizure outcome after lesionectomy on a series of 35 patients. *Clin Neurol Neurosurg*. 1997;99(3):179-183.
70. Yeon JY, Kim JS, Choi SJ, Seo DW, Hong SB, Hong SC. Supratentorial cavernous angiomas presenting with seizures: surgical outcomes in 60 consecutive patients. *Seizure*. 2009;18(1):14-20.
71. Hammen T, Romstock J, Dorfler A, Kerling F, Buchfelder M, Stefan H. Prediction of postoperative outcome with special respect to removal of hemosiderin fringe: a study in patients with cavernous haemangiomas associated with symptomatic epilepsy. *Seizure*. 2007;16(3):248-253.
72. Baumann CR, Acciani N, Bertalanffy H, et al. Seizure outcome after resection of supratentorial cavernous malformations: a study of 168 patients. *Epilepsia*. 2007;48(3):559-563.
73. Bervini D, Jaeggi C, Mordasini P, Schuch P, Raabe A. Antithrombotic medication and bleeding risk in patients with cerebral cavernous malformations: a cohort study [published online June 1, 2018]. *J Neurosurg*. <https://doi.org/10.3171/2018.1.JNS172547>.
74. Flemming KD, Link MJ, Christianson TJ, Brown RD Jr. Use of antithrombotic agents in patients with intracerebral cavernous malformations. *J Neurosurg*. 2013;118(1):43-46.
75. Zuurbier SM, Hickman CR, Tolias CS, et al. Long-term antithrombotic therapy and risk of intracranial haemorrhage from cerebral cavernous malformations: a population-based cohort study, systematic review, and meta-analysis. *Lancet Neurol*. 2019;18(10):935-941.
76. Retta SF, Glading AJ. Oxidative stress and inflammation in cerebral cavernous malformation disease pathogenesis: two sides of the same coin. *Int J Biochem Cell Biol*. 2016;81(pt B):254-270.
77. Kalani MY, Zabramski JM. Risk for symptomatic hemorrhage of cerebral cavernous malformations during pregnancy. *J Neurosurg*. 2013;118(1):50-55.

78. Witiw CD, Abou-Hamden A, Kulkarni AV, Silvaggio JA, Schneider C, Wallace MC. Cerebral cavernous malformations and pregnancy: hemorrhage risk and influence on obstetrical management. *Neurosurgery*. 2012;71(3):626-630; discussion 631.
79. Apra C, Dumot C, Bourdillon P, Pelissou-Guyotat I. Could propranolol be beneficial in adult cerebral cavernous malformations? *Neurosurg Rev*. 2019;42(2):403-408.
80. Berti I, Marchetti F, Skabar A, Zennaro F, Zanon D, Ventura A. Propranolol for cerebral cavernous angiomas: a magic bullet. *Clin Pediatr (Phila)*. 2014;53(2):189-190.
81. Goldberg J, Jaeggi C, Schoeni D, Mordasini P, Raabe A, Bervini D. Bleeding risk of cerebral cavernous malformations in patients on β -blocker medication: a cohort study [published online June 15, 2018]. *J Neurosurg*. <https://doi.org/10.3171/2017.12.JNS172404>.
82. Reinhard M, Schuchardt F, Meckel S, et al. Propranolol stops progressive multiple cerebral cavernoma in an adult patient. *J Neurol Sci*. 2016;367:15-17.
83. Zabramski JM, Kalani MY, Filippidis AS, Spetzler RF. Propranolol treatment of cavernous malformations with symptomatic hemorrhage. *World Neurosurg*. 2016;88:631-639.
84. Angioma Alliance website. <http://www.angioma.org>.
85. Fischer A, Zalvide J, Faurobert E, Albiges-Rizo C, Toumrier-Lasserve E. Cerebral cavernous malformations: from CCM genes to endothelial homeostasis. *Trends Mol Med*. 2013;19(5):302-308.
86. Choquet H, Pawlikowska L, Nelson J, et al. Polymorphisms in inflammatory and immune response genes associated with cerebral cavernous malformation type I severity. *Cerebrovasc Dis*. 2014;38(6):433-440.
87. Kumar S, Lanzino G, Brinjikji W, Hocquard KW, Flemming KD. Infratentorial developmental venous abnormalities and inflammation increase odds of sporadic cavernous malformation. *J Stroke Cerebrovasc Dis*. 2019;28(6):1662-1667.
88. Tang AT, Choi JP, Kahn ML. Endothelial TLR4 and the microbiome drive cerebral cavernous malformations. *Nature*. 2017;545(7654):305-310.
89. Chohan MO, Marchio S, Morrison LA, et al. Emerging pharmacologic targets in cerebral cavernous malformation and potential strategies to alter the natural history of a difficult disease: a review. *JAMA Neurol*. 2019;76(4):492-500.
90. Gibson CC, Zhu W, Davis CT, et al. Strategy for identifying repurposed drugs for the treatment of cerebral cavernous malformation. *Circulation*. 2015;131(3):289-299.
91. De Luca E, Pedone D, Moglianetti M, et al. Multifunctional platinum@BSA-rapamycin nanocarriers for the combinatorial therapy of cerebral cavernous malformation. *ACS Omega*. 2018;3(11):15389-15398.
92. Wustehube J, Bartol A, Liebler SS, et al. Cerebral cavernous malformation protein CCM1 inhibits sprouting angiogenesis by activating DELTA-NOTCH signaling. *Proc Natl Acad Sci U S A*. 2010;107(28):12640-12645.
93. Bravi L, Rudini N, Cuttano R, et al. Sulindac metabolites decrease cerebrovascular malformations in CCM3-knockout mice. *Proc Natl Acad Sci U S A*. 2015;112(27):8421-8426.
94. McDonald DA, Shi C, Shenkar R, et al. Fasudil decreases lesion burden in a murine model of cerebral cavernous malformation disease. *Stroke*. 2012;43(2):571-574.
95. Shenkar R, Shi C, Austin C, et al. RhoA kinase inhibition with fasudil versus simvastatin in murine models of cerebral cavernous malformations. *Stroke*. 2017;48(1):187-194.
96. Weiner GM, Ducruet AF. Fasudil slows development of cavernous malformations. *Neurosurgery*. 2017;80(5):N25-N27.
97. Girard R, Fam MD, Zeineddine HA, et al. Vascular permeability and iron deposition biomarkers in longitudinal follow-up of cerebral cavernous malformations. *J Neurosurg*. 2017;127(1):102-110.
98. Mikati AG, Khanna O, Zhang L, et al. Vascular permeability in cerebral cavernous malformations. *J Cereb Blood Flow Metab*. 2015;35(10):1632-1639.
99. Mikati A, Tan H, Shenkar R, et al. Dynamic permeability and quantitative susceptibility: related imaging biomarkers in cerebral cavernous malformations. *Stroke*. 2014;45(2):598-601.
100. Hart BL, Taheri S, Rosenberg GA, Morrison LA. Dynamic contrast-enhanced MRI evaluation of cerebral cavernous malformations. *Transl Stroke Res*. 2013;4(5):500-506.
101. Girard R, Khanna O, Shenkar R, et al. Peripheral plasma vitamin D and non-HDL cholesterol reflect the severity of cerebral cavernous malformation disease. *Biomark Med*. 2016;10(3):255-264.
102. Girard R, Zeineddine HA, Koskimaki J, et al. Plasma biomarkers of inflammation and angiogenesis predict cerebral cavernous malformation symptomatic hemorrhage or lesion growth. *Circ Res*. 2018;122(12):1716-1721.
103. Polster SP, Cao Y, Carroll T, et al. Trial Readiness in Cavernous Angiomas with Symptomatic Hemorrhage (CASH). *Neurosurgery*. 2019;84(4):954-964.