REVIEW ARTICLE

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Cavernous Malformations of the Central Nervous System

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CME

Cerebral cavernous malformations (CCMs) are compact clusters of spongelike vascular spaces without intervening neural parenchyma that occur in the brain or spinal cord. At surgery, they appear as blebs or blood-filled bubbles, like a cluster of grapes (Fig. 1), with a characteristic appearance on magnetic resonance imaging (MRI), as described below. CCMs are found in approximately 0.5% of the general population.[1,2] In rare familial cases, the lesions also occur in the retina or skin. In the past, CCMs in the nervous system were called angiographically occult vascular malformations, because they typically cannot be detected on conventional angiography, and they have also been described as hemangiomas, cavernomas, and cavernous angiomas. Sporadic, single CCMs are most common, accounting for approximately 85% of cases; about 15% are familial, and CCMs induced by radiation are increasingly being identified.[1-4] The prevalence of CCMs, coupled with increased detection with the widespread availability of cerebral imaging, suggests that many physicians will see patients with these lesions.

Pathogenesis

Examination of pathological specimens shows that these lesions have a capillary structure predominantly made up of endothelial cells, with defective tight junctions and little or no neural tissue between vessels.[5,6] The vessels lack normal smooth muscle and elastic tissue, making their thin walls prone to distortion and rupture. Increasing evidence indicates that the three categories of CCMs (familial, sporadic, and radiation-induced) are genetically distinct. Advances in our understanding of the molecular mechanisms underlying the pathogenesis of CCMs have helped to explain some of the features of each type, as discussed below. (For further details, see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Familial CCMs

Familial CCMs are typically associated with autosomal dominant germline variants with incomplete penetrance; the most common pathogenic variants confer loss of function on *CCM1*, *CCM2*, or *CCM3* (Table 1).[7,8] These variants result in failure of endothelial cell–cell binding and attachment to the extracellular matrix, affecting numerous signaling pathways. This leads to endothelial-cell overgrowth and poor adhesion to adjacent cells, with the proliferation of blood-filled "bubbles" — abnormally dilated segments of capillaries.[1,2,5] The downstream effects of these variants on intracellular kinase (MEKK3) and actin–myosin polymerization regulated by RhoA–ROCK combine to increase proliferation of endothelial cells and angiogenesis, with excessive actin stress fibers that destabilize intercellular junctions. Unlike CCM1

KEY POINTS

Cerebral Cavernous Malformations

- CCMs are found in approximately 0.5% of the population and characteristically manifest with headache, seizure, or focal neurologic deficits.
- The majority of CCMs (approximately 85%) are single, sporadic lesions due to somatic variants, whereas multiple CCMs are typically associated with pathogenic germline variants (often in CCM1, CCM2, or CCM3) or prior cranial irradiation.
- MRI can be helpful for the detection and assessment of a CCM, particularly with susceptibility-weighted and T2-weighted imaging and sequences obtained after gadolinium administration.
- Treatment is evolving and varies according to the specific clinical scenario. Options include observation, surgical excision, and stereotactic irradiation, with growing, symptomatic lesions (including those associated with seizures) often considered for intervention.
- A recent understanding of the impact of specific CCM-associated mutations has helped to inform clinical practice, including screening, prognosis, and ongoing development of targeted therapies.

and CCM2, which are commonly found together in a protein complex, CCM3 is only rarely identified with the other two CCM proteins. CCM3 is more often identified in the striatin-interacting phosphatase and kinase (STRIPAK) signaling complex. An animal model has shown that loss of CCM3 perturbs both the CCM1–CCM2 signaling pathway and STRIPAK signaling, potentially impairing actin polymerization, Rho kinase, and PI3K (a phosphorylating enzyme with a major subunit encoded by *PIK3CA*).[9] This model suggests an explanation for the observation that patients with a pathogenic *CCM3* variant often have a more severe phenotype, as manifested by a larger number of lesions on MRI and a greater propensity for hemorrhage. Since CCM3 affects more cellular pathways than CCM1 and CCM2 do, it has been inferred that pathogenic *CCM3* variants result in worse clinical disease.

SPORADIC CCMS

Sporadic CCMs appear to be different from familial lesions, with greater genetic heterogeneity and a more common presentation as a single lesion. It has been hypothesized that individual CCMs develop through the "two-hit" mechanism: the function of one allele of *CCM* is lost as a result of a germline variant, followed by somatic loss of the remaining wild-type allele.[10,11] This hypothesis is supported by findings in persons with CCM and in animal models.

Sporadic CCMs may also have variants in other genes, including *MAP3K3*, *RASA1*, and *EPHB4*, and with any one of these, simultaneously harboring activating variants of *PIK3CA* (in approximately 40% of sporadic cases).[5,12] Sporadic CCMs may contain cells that undergo endothelial-to-mesenchymal transition, with cells derived from pericytes or arising from developmental venous anomaly progenitor cells that subsequently acquire additional somatic variants.[5,6,13,14] Ultimately, many sporadic CCMs exhibit up-regulation of MEKK3, which can result from biallelic loss-of-function variants in one of the CCM genes or from a primary activating variant in *MAP3K3*.[14,15] Thus, either loss of both copies of a CCM gene or gain of an activating somatic variant in *MAP3K3* has the same net effect, initiating a lesion, but sub-

Table 1. Genes and Corresponding Encoded Proteins Implicated in Cerebral Cavernous Malformations.

Gene	Protein
CCM1	KRIT1
CCM2	Malcavernin
CCM3	Programmed cell death 10 (PDCD10)
EPHB4	Ephrin type B receptor 4
MAP3K3	Mitogen-activated protein kinase kinase kinase 3 (MEKK3)
MTOR	Mammalian target of rapamycin (mTOR)
PIK3CA	Phosphatidylinositol 3-kinase (PI3K)
RASA1	RAS p21 protein activator 1 (RASA)
ROCK	Rho-associated coiled-coil–containing kinase (ROCK)

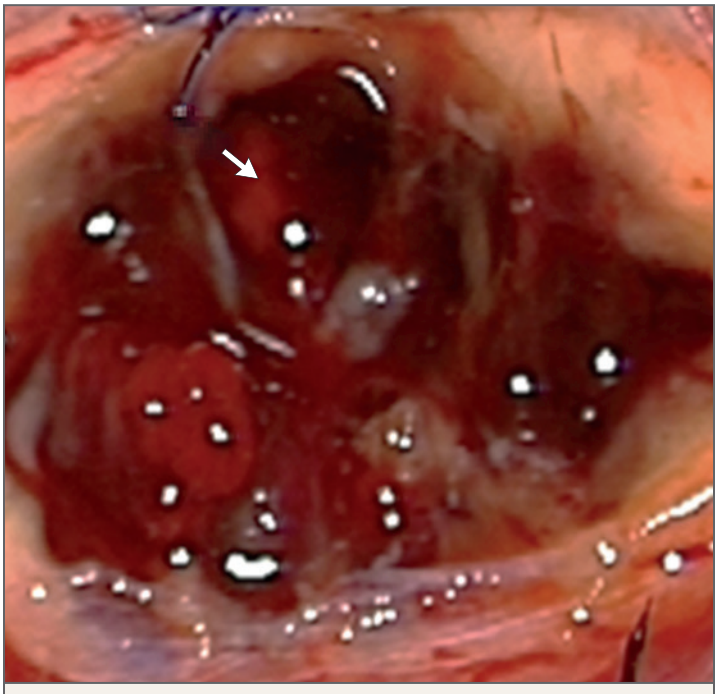

Figure 1. A Cerebral Cavernous Malformation (CMM) Seen during Surgery.
Characteristic blood-filled bubbles (white arrow) are visualized through the operating microscope.

sequent enlargement requires an additional growth signal.[16] Activating variants in *PIK3CA* can fuel proliferation of nascent CCMs by stimulating cell division. This breadth of genetic variability in sporadic CCMs may help explain the range of clinical presentations.

RADIATION-INDUCED CCMS

These lesions typically develop in the brain approximately 10 years after cranial radiation therapy and have been reported in approximately 8% of previously irradiated patients, with risk factors including treatment at less than 10 years of age and a radiation dose of more than 3000 cGy.[17] Limited observations suggest that radiation-induced CCMs may have a more indolent clinical course than other CCMs.[1] Histologic analysis suggests that these CCMs may represent two distinct entities, with some lesions resulting from radiation-induced fibrinoid vascular necrosis of normal vessels, and others having more typical histologic features. Although one report documented a loss-of-function *CCM1* variant in a surgical specimen, further study is needed to better characterize the genetic profile of these CCMs.[17-19]

POSSIBLE ENVIRONMENTAL INFLUENCES

Loss of function of PDCD10, which is part of the CCM signaling complex, affects both brain endothelium and gut epithelium through up-regulation of MEKK3. This increased activity impairs actin interactions with the cytoskeleton and connections to adjacent cells, resulting in ballooning of small vascular blebs and bleeding. Data from animal models suggest that *CCM3* variants may also impair gut epithelial function, resulting in failures in the gut barrier and potentially increasing circulating levels of lipopolysaccharide (LPS) produced by gram-negative bacteria in the gut microbiome.[5,20] LPS binds to the endothelial cell receptor TLR4 (Toll-like receptor 4), up-regulating MEKK3 activity through a separate pathway.[21] Current studies are assessing the hypothesis that the severe clinical course of patients with CCM3 caused by a pathogenic variant in *PDCD10* is at least partially caused by gut-mediated MEKK3 overactivity driven by bacterial LPS through the independent TLR4 pathway.[5,20,21]

CLINICAL PRESENTATION

Symptoms of CCMs are typically due to the accruing hemorrhage within and surrounding a lesion and to growth of the underlying malformation. The common presentations are focal seizures (in approximately 50% of cases) and focal neurologic deficits (in approximately 25%), both of which are concordant with the site of the lesion.[1,2,22] Sporadic CCMs are found in the cerebral hemispheres (in approximately 66% of cases), brain stem (in approximately 20%), cerebellum (in 6%), and basal ganglia or deep nuclei (in approximately 8%).[3,4] As compared with arterial-based cerebrovascular lesions such as true arteriovenous malformations or aneurysms, hemorrhage from CCM is less often fatal because of the limited volume of bleeding. Symptomatic CCMs are more common in the brain stem or eloquent cortex (e.g., the language areas) because of the limited volume of bleeding required to cause symptoms in these regions. However, 20 to 50% of CCMs are asymptomatic and are incidental

findings on imaging performed for various reasons such as headache.[1,2]

The risk of intracranial bleeding from nonfamilial CCMs is approximately 0.1 to 1% annually for patients with incidentally found lesions and approximately 3 to 10% for those who present with bleeding. The risk of subsequent hemorrhage in the first 1 to 5 years after an initial single hemorrhage is approximately 14 to 56%. Thus, the greatest risk factor for cerebral hemorrhage is a previous hemorrhage.[1-3] Patients with pathogenic *CCM3* germline variants have a higher risk of symptomatic bleeding and a larger number of lesions than do patients with sporadic CCMs.[1] Overall, the bleeding rate among patients with familial lesions is approximately 4% per year, with approximately 60% of patients having symptomatic hemorrhage and approximately 32 to 60% having seizures.[1,3,4] These data suggest that patients who present with a hemorrhage and those with familial CCMs warrant close follow-up, as do children (because of their expected long life span). Such follow-up is typically accomplished with MRI, particularly when there are new clinical symptoms. Some centers perform annual studies for approximately 5 years in these patients.[1,2]

IMAGING

CCMs typically have the appearance of what has been described as "popcorn" because of their multiloculated structure, especially on MRI scans obtained after the administration of contrast material and on T2-weighted sequences (Fig. 2A). The sporadic form is often associated with a developmental venous anomaly (Fig. 2B). A hemorrhagic CCM has hemosiderin rings, creating a "blooming artifact" — a halo of increased signal intensity on MRI caused by hemosiderin — which is prominent on susceptibility-weighted sequences (Fig. 2C). The use of imaging to determine whether a patient has a single CCM or multiple CCMs is important in identifying the cause. Most patients, as mentioned above, have a sporadic, single lesion, and these lesions are typically due to nonheritable somatic variants.[1,2] In contrast, multiple, noncontiguous CCMs are

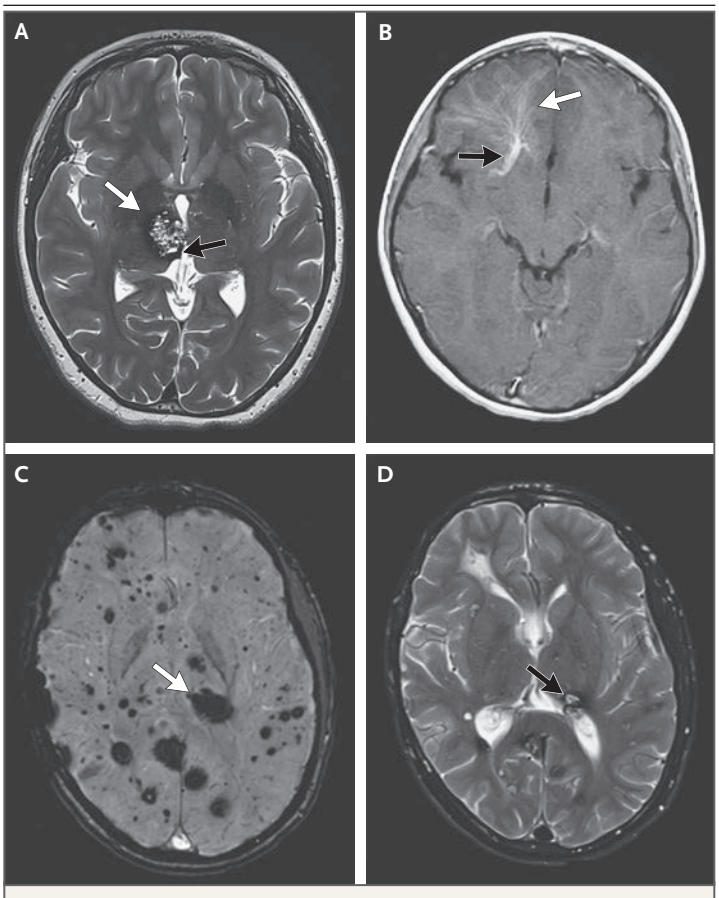

Figure 2. Characteristic Features of CCMs on MRI Studies.

A T2-weighted MRI sequence (Panel A) shows the typical "popcorn" lesion (which can also be seen on T1-weighted imaging after the administration of contrast material), with multiple lobules, often seen with a ring of hemosiderin staining around the malformation (white arrow). The dilated vascular spaces, with fluid–fluid levels comprising blood products and serum, are separated by density. The less-dense serum is suspended on top, and then settles as the patient lies flat in the MRI machine (black arrow, pointing to a "bubble" at the interface between the white plasma-based fluid on top and the black fluid level with denser cellular debris below). A T1-weighted MRI scan obtained after the administration of contrast material (Panel B) shows a developmental venous anomaly adjacent to the lesion (black arrow) and hydralike branches of the venous anomaly converging on the central draining vein (white arrow). A susceptibility-weighted image (Panel C) shows a typical "bloom" around a CCM, which is due to the hemosiderin (white arrow). This finding is particularly useful for detecting small lesions in familial cases that might not be readily visible on other MRI sequences; in contrast, T2-weighted images show greater detail of the CCM anatomy as shown by the clarity of the CCM and its relationship to the adjacent ventricle and parenchyma (Panel D, black arrow) as compared with the less distinct (but easier to see) characterization of the same CCM in the susceptibility-weighted image (Panel C, white arrow).

usually associated with either a germline variant or previous cranial radiation therapy. MRI with gadolinium infusion and T2-weighted images can be helpful in characterizing the anatomy of a CCM (Fig. 2D). Gadolinium is particularly helpful for characterization of developmental venous anomalies in association with CCM, and T2-weighted MRI sequences are helpful in visualizing regional anatomy because visualizing the lesion and distinguishing it from adjacent structures can be difficult on susceptibility-weighted MRI. T2-weighted MRI has less sensitivity than susceptibility-weighted MRI, so lesions that may be missed on T2-weighted MRI have a greater chance of being visualized on susceptibility-weighted MRI, owing to the blooming artifact that magnifies the signal of the CCM. Computed tomography is generally less sensitive than MRI for detecting a CCM but can identify bleeding and may show calcification of a long-standing lesion. The differential diagnosis based on imaging is limited, comprising hemorrhagic arteriovenous malformations, cerebral amyloid angiopathy, and tumors.

SCREENING

Genetic screening is not needed in most patients, because single CCMs, the most common type, are typically sporadic. Screening is indicated, however, for patients with multiple CCMs or a family history of CCM or related findings (brain hemorrhage, abnormal brain imaging suggestive of CCM, or in some cases, neurologic symptoms such as seizures in family members).[1,2] A susceptibility-weighted series on MRI is recommended to identify multiple CCMs, since this finding indicates approximately an 85% likelihood of a germline pathogenic variant.[1,2] Genetic testing for CCM identifies pathogenic variants in more than 75% of patients with multiple lesions.[5]

POSSIBLY MODIFIABLE RISK FACTORS

Patients with CCMs do not appear to have an increased risk of bleeding during routine exercise, amusement park rides, sports, or travel on airplanes, although activities that might result in concussion (e.g., tackle football or boxing) could theoretically increase the risk, and constraints on additional activities (e.g., driving or scuba diving) are warranted in patients with seizures.[1,2] Single-center studies have shown nonsignificant trends toward an association between bleeding and poorly controlled diabetes mellitus, nicotine use, or very low levels of vitamin D, findings that may stimulate further evaluation in larger cohorts.[1,23,24] Pregnancy and routine use of antithrombotic medications do not appear to increase the risk of CCM bleeding.[1,23-25]

TREATMENT

Surgical resection is usually recommended by multidisciplinary working groups as first-line therapy for most symptomatic CCMs given the extensive previous literature and clinical experience regarding successful curative excision, although this approach to treatment is based on retrospective and natural history studies and has not been evaluated in prospective clinical trials.[1] Primary indications for the treatment of CCMs typically include symptomatic or progressive growth or hemorrhage and seizures that are considered, on the basis of clinical findings or special studies, to originate in the region of a CCM. Some case series have shown seizure control in 80% of patients after resection, with lesion recurrence among approximately 1%, although this benefit comes with an approximately 4% risk of long-term neurologic deficits from surgery.[1,2] Early resection of CCMs associated with seizures, as compared with later resection, has been correlated with better long-term seizure control in some series.[1,26] CCMs that have not bled, are asymptomatic, or are located in high-risk areas for surgery, such as the brain stem or thalamus, require individualized risk–benefit assessments but are usually observed rather than surgically excised. Efforts are being made to better quantify the balance between the risks and benefits of intervention in such cases.[27]

Stereotactic radiation therapy is also useful for treating CCMs and has particular value for surgically inaccessible lesions such as those in the brain stem or in symptomatic patients with sporadic lesions who are poor candidates for surgery, with partial or complete responses in approximately 80% of patients and clinical improvement in approximately 56%.[28,29] Limited data on

advances in minimally invasive surgical techniques, such as laser interstitial thermal therapy, have expanded the scope of CCMs that are amenable to treatment, with the possibility of improved outcomes, although this treatment has not been compared with open resection in clinical trials.[23]

FUTURE DIRECTIONS

Opportunities exist for repurposing current medications, such as propranolol and statins, for the treatment of CCM. A phase 2 trial and a natural history study revealed a small but significant reduction in bleeding incidence but no change in hospitalizations with the use of antithrombotic agents.[25] None of these approaches are currently endorsed. The role of the microbiome in CCM bleeding offers another new area of investigation, but so far, it has not been systematically tested in a clinical setting.[20,21]

Most promising are the prospects of understanding the genetic drivers of these malformations.[5,7] Small-molecule therapeutics designed to exploit specific targets in the CCM1–CCM2–CCM3–MEKK3 pathways may reduce CCM growth, progression, and bleeding, offering the possibility of effective nonsurgical treatments for CCM.[5,7,30] A number of pharmacologic interventions for CCM are currently under evaluation in clinical trials, including Rho kinase–ROCK inhibitors, but with relatively short timelines for gaining insight into the possible efficacy of these therapies.[16,30]

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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