

Cerebral Cavernous Malformations Associated With Cutaneous Angiokeratomas and Hemangiomas

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PRACTICE POINTS

- Familial cerebral cavernous malformations (CCMs) are associated with extra-cerebral manifestations that include retinal cavernomas as well as a variety of cutaneous manifestations.
- Our patient presented with adult-onset eruptive angiokeratomas, cutaneous hemangiomas, and adult-onset seizures in the setting of numerous CCMs with confirmation of *CCM1* mutation.
- Dermatologists should be aware of the availability of genetic testing for CCM gene mutations and neurologic screening in patients presenting with multiple cutaneous vascular lesions, including eruptive angiokeratomas.

We report the case of a 66-year-old man with adult-onset seizures and multiple cerebral cavernous malformations who developed numerous eruptive cutaneous angiokeratomas on the legs, scrotum, abdomen, and back as well as lobular and cavernous hemangiomas on the arms. Genetic analysis demonstrated a mutation in the KRIT1, ankyrin repeat containing gene (also known as CCM1).

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Case Report

A 66-year-old non-Hispanic white man with a history of adult-onset seizures, renal cell carcinoma, and nephrolithiasis presented to the dermatology clinic with numerous dark red, dry, scaling lesions on the lower legs, abdomen, back, thighs, and scrotum that

bled easily. The lesions had developed 2 to 4 years prior to presentation. The patient also noted several dark blue lesions on the bilateral arms that had been present for several years.

Physical examination revealed multiple black, keratotic papules on the bilateral lower legs (Figure 1), with similar lesions on the lower abdomen and lower back. Numerous dark red, scaling papules were present on the thighs and scrotum, and firm, 1- to 3-cm, dark blue nodules were noted on the bilateral arms (Figure 2) and right side of the forehead. Biopsy of papules from the lower right leg and back demonstrated angiokeratomas on pathologic review (Figure 3). Four separate biopsies taken from the left forearm demonstrated lobular and cavernous hemangiomas (Figure 4).

The patient's medical history was remarkable for neurologic symptoms including adult-onset seizures at the age of 42 years. Recent magnetic resonance imaging of the head showed multiple areas of heterogeneous signal intensity with T2 hypointense rims consistent with cerebral cavernous malformations (CCMs) involving both cerebral hemispheres, the posterior cranial fossa, and the brainstem (Figure 5). Of note, the patient's mother had been diagnosed with epilepsy in her 40s, but no other family history of a clinically or radiographically diagnosed neurologic disorder was reported.

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Figure 1. Multiple black keratotic papules on the right lower leg.



Figure 2. Firm blue nodules noted on the left lateral forearm.

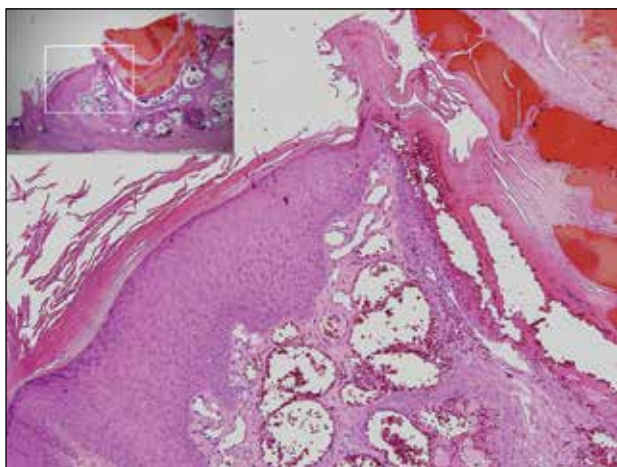


Figure 3. Histologic examination revealed dilated, blood-filled vessels in the papillary dermis with overlying acanthosis and hyperkeratosis consistent with an angio-keratoma (H&E, original magnification $\times 10$ [inset $\times 4$]).

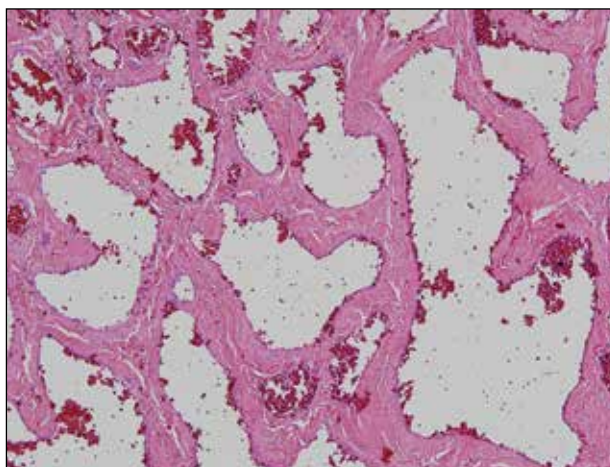


Figure 4. Histologic examination revealed a multilobular proliferation of numerous vascular spaces in the dermis demonstrating lobular and cavernous hemangiomas (H&E, original magnification $\times 10$).

This presentation of numerous CCMs and cutaneous vascular lesions prompted genetic testing for mutations in the 3 CCM genes. Bidirectional sequencing from a blood specimen confirmed a 1267C→T substitution resulting in an Arg423X nonsense mutation in the KRIT1, ankyrin repeat containing gene (also known as CCM1) on chromosome 7, which is a published mutation.¹ No treatment of the cutaneous lesions was administered. The patient continued to be treated by a neurologist for the seizure disorder after genetic testing and counseling was complete.

Comment

Cerebral cavernous malformations represent collections of dilated, capillarylike vessels without intervening brain parenchyma,² which can occur as a sporadic or autosomal-dominant condition with variable prevalence. Imaging and autopsy studies suggest CCMs may be present in 0.5% of the general population, with the incidence of clinically symptomatic disease being much lower.^{3,4} While sporadic cases are usually associated with the presence of a single CCM, hereditary cases generally display multiple CCMs⁵⁻⁷; studies indicate that most

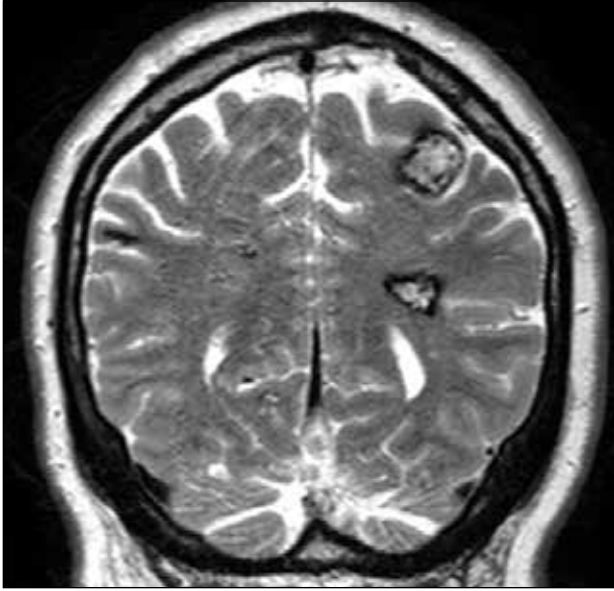


Figure 5. T2-weighted coronal magnetic resonance imaging study showing areas of heterogeneous signal intensity with T2 hypointense rims consistent with cerebral cavernous malformations.

patients who present with symptomatic CCMs are in the second to fifth decades of life.^{3,8-10} The most common clinical manifestations of CCMs are headaches, seizures, and focal neurologic deficits due to cerebral hemorrhages.¹¹

Three autosomal-dominant forms of familial CCMs are associated with several different heterozygous mutations in the *CCM1* gene, which encodes Krev interaction trapped protein 1; the cerebral cavernous malformation 2 gene (*CCM2*), which encodes the protein malcavernin; and the programmed cell death 10 gene (*PDCD10*) (also known as *CCM3*), which encodes the *PDCD10* protein.¹²⁻¹⁴ Although the precise pathophysiologic mechanisms linking these mutations with the resultant clinical phenotypes have yet to be fully elucidated, these genes are thought to play roles in angiogenesis as well as vascular maintenance and remodeling.¹¹ Among non-Hispanic white kindreds with familial CCMs, 40% to 72% of kindreds were linked to mutations in *CCM1*, 20% were linked to mutations in *CCM2*, and 8% to 40% were linked to mutations in *CCM3*, depending on the series.^{13,15} The prevalence of symptomatic disease among gene carriers for kindreds linked to *CCM1*, *CCM2*, and *CCM3* was 88%, 100%, and 63%, respectively.¹³ A specific founder mutation in *CCM1* is thought to be responsible for virtually all cases of familial CCMs in Hispanic American individuals¹⁶ and up to 50% of this patient population are thought to

have the familial form of the condition.⁵ As more is learned about the role of CCM gene mutations in the pathogenesis of CCMs, understanding how different mutations with different degrees of prevalence affect different patient populations will be important to help guide testing and perhaps treatment in the future.

Extracerebral manifestations of familial CCMs include retinal and cutaneous involvement. The incidence of retinal cavernomas has been estimated at 5% in familial CCM patients.¹⁷ The most commonly reported cutaneous finding (with an incidence of 3% to 5% reported in large case series) is hyperkeratotic cutaneous capillary-venous malformations (HCCVMs), which are composed of dilated capillaries and blood-filled, venouslike channels extending into the dermis and hypodermis with an overlying hyperkeratotic epidermis.^{7,18-20} Although the prevalence for *CCM1*-associated CCMs is reported to be higher than that for the HCCVMs in families affected by both cerebral and cutaneous lesions, all patients manifesting HCCVMs also have CCMs.¹⁸⁻²⁰ Perhaps the cutaneous lesions may serve as markers of neurologic involvement in affected families. Other reports have shown an association between CCMs and cutaneous cavernous hemangiomas,²¹ capillary malformations,²⁰ venous malformations,^{20,22} and cherry angiomas,^{21,23} although the relevance of cherry angiomas is unclear given their high prevalence in the general population.

There are few reports of patients with CCMs having angiokeratomas, including a 77-year-old Hispanic man with a solitary angiokeratoma, cutaneous venous malformations, multiple CCMs, and demonstration of the 2105C→T *CCM1* founder mutation, which is commonly found in Hispanic patients²⁴; a Chinese man with a *CCM1* mutation and purple-black, raised, angiomalike skin lesions (similar to those seen in our patient) that which were not biopsied²⁵; and a patient with multiple eruptive angiokeratomas who was found to have numerous CCMs before the availability of genetic testing.²⁶ In our patient, the presentation of eruptive angiokeratomas prompted consideration of genetic testing and subsequent confirmation of a *CCM1* mutation. Knowledge of the association between familial CCMs and cutaneous vascular lesions may be used to identify patients with clinically silent, undetected CCMs who may be at risk of developing future neurologic disorders or who may benefit from appropriate genetic counseling.

Conclusion

Familial CCMs are associated with extracerebral manifestations that include retinal cavernomas

along with a variety of cutaneous manifestations. We present a case of a patient with adult-onset seizures, eruptive angiokeratomas, and cutaneous hemangiomas in the setting of numerous CCMs with confirmation of *CCM1* mutation on genetic testing. We hope to raise awareness of the cutaneous findings associated with CCMs and the availability of genetic testing for CCM gene mutations so that patients with multiple cutaneous vascular lesions, including eruptive angiokeratomas, can be screened and tested for genetic mutations and neurologic involvement when appropriate.

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