

# GIANT INFILTRATIVE CAVERNOUS MALFORMATION: CLINICAL PRESENTATION, INTERVENTION, AND GENETIC ANALYSIS: CASE REPORT

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**OBJECTIVE AND IMPORTANCE:** Cavernous malformations can present in children with a sporadic course of repeated hemorrhage and enlargement, but they are rarely aggressive, infiltrative, or multilobar. We present the case of a young boy with a complex cavernous malformation that evolved during the course of a decade to encompass the majority of his right cerebral hemisphere.

**CLINICAL PRESENTATION:** A 16-month-old boy presented with seizures, and radiographic studies demonstrated a large cavernous malformation in his right frontal pole. During the next 10 years, his seizures became intractable, and he developed progressive left hand weakness and atrophy. His malformation infiltrated his entire right frontal lobe as well as portions of his right parietal lobe, temporal lobe, and deep gray matter structures.

**INTERVENTION:** The patient underwent right hemispherectomy and near total resection of the lesion. Pathological analysis revealed dilated, thin-walled vessels separated by small amounts of intervening astroglial brain consistent with cavernous malformation. The patient recovered to his baseline neurological condition and has had no seizure or hemorrhage since his operation. Genetic testing did not reveal mutations in either the *CCM1* (*KRIT1*) or *CCM2* (malcavernin) genes.

**CONCLUSION:** This case may represent an atypical variant of cavernous malformation best termed *giant infiltrative cavernous malformation*. Despite its unusual size, multilobar location, and aggressive infiltration, it can be managed effectively with standard surgical resection.

**KEY WORDS:** Cavernoma, Cavernous angioma, Cavernous malformation, Giant, Pediatric, Seizure, Vascular malformation

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Cavernous malformations (CMs) are vascular anomalies with cavernous spaces lined by endothelial cells and collagen, devoid of smooth muscle or intervening neural tissue, and filled with blood at various stages of stasis, thrombosis, organization, and calcification. Most CMs are clinically silent, but when they are symptomatic, patients may present with seizures, hemorrhage, and focal signs from mass effect and neurological injury (2, 11, 30, 31, 48, 52, 63). Results from autopsy and magnetic resonance imaging (MRI) series suggest that the prevalence of CM is approximately 0.4% (6, 11, 16, 47, 56), although the true incidence of CM is difficult to establish because of overlapping pathological features among CM and other vascular malformations in the central nervous system (1, 4, 7, 9, 22, 23, 44, 49, 58, 63). CMs have been

reported in children (14, 15, 26, 42, 45, 57), and some CMs are considered acquired lesions that form in youth but remain dormant until adulthood. Most CMs occur sporadically as a solitary lesion, and suggested pathogenetic factors include radiation, anomalous venous drainage, associated venous angioma, outflow obstruction, or spontaneous mutations (27, 29, 34, 36, 38, 41, 44, 61). However, analysis of cohorts with the familial form of CM (multiple lesions and a positive family history) has elucidated the underlying genetics of this disease (18, 24, 39, 43, 59).

Familial forms of CM are inherited in an autosomal dominant manner, with loci identified on chromosomes 7q21.2 (*CCM1*) (12, 17, 24), 7p15-p13 (*CCM2*) (10), and 3q25.2-q27 (*CCM3*) (10). The disease gene responsible for *CCM1* encodes KRIT1 (KREV interaction

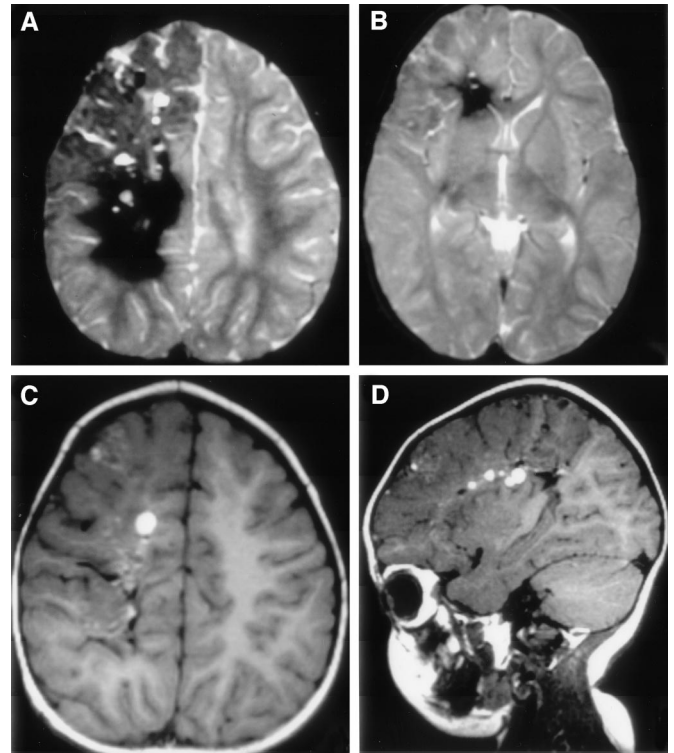
trapped 1) (32, 54), a protein of unknown function that contains four ankyrin domains and a C-terminal FERM domain (55). Although it is not yet understood how mutations in KRIT1 lead to the formation of CMs, integrin has been implicated in the pathogenesis, as KRIT1 has a binding affinity for integrin cytoplasmic domain-associated protein (ICAP1 $\alpha$ ) (65, 67), which contains a phosphotyrosine-binding domain also present in  $\beta$ 1 integrin (8, 66). Like CCM1, CCM2 has a responsible disease gene that exhibits eight different mutations in nine families with this form of the disease (35). The CCM2 gene encodes a protein called malcavernin that has a phosphotyrosine-binding domain similar to the KRIT1 binding partner, ICAP1 $\alpha$ . The pathogenetics of CCM3 are unknown currently. These findings suggest that CM pathogenesis may involve perturbations of the integrin signaling pathway and subsequent abnormalities in vascular morphogenesis in the brain.

CMs can enlarge, shrink, or remain unchanged over time. Growth is thought to be caused by hemorrhage and excavation of adjacent brain tissue by the new clot (37, 45). Actual infiltration of adjacent brain by CMs has not been reported. We present a unique case report of a giant infiltrative CM in a 13-year-old boy. To our knowledge, it is the largest CM reported in the literature, but it is of greater interest because of its progression from a multifocal lesion to a multilobar lesion occupying the majority of his right cerebral hemisphere during the course of a decade. Its unusual radiographic and histopathological features are presented, along with the surgical management and genetic analysis of the resected tissue.

## CASE REPORT

### Clinical Presentation

In 1990, at the age of 16 months, this right-handed boy experienced a generalized seizure. He had no significant medical history, previous radiation exposure, or family history of vascular malformations. At admission at another hospital, he was obtunded with left arm and leg weakness. A computed tomographic scan revealed two areas of hemorrhage in the right frontal lobe (not shown); in addition, the underlying brain in the right frontal lobe had unusual signal characteristics and some calcification. Administration of contrast revealed a large area of irregular contrast enhancement in the right frontal pole. MRI revealed that the majority of the right frontal lobe and a portion of the anterior parietal lobe were replaced by speckled areas of hyper- and hypointense signal on T1- and T2-weighted images (Fig. 1). Administration of gadolinium contrast revealed patchy and sometimes linear enhancement within or on the surface of the lesion. In addition, the right cerebral peduncle was much smaller than the left peduncle (not shown). The images were thought to be consistent with a large right frontal vascular malformation, most likely a CM, and an angiogram failed to reveal any arteriovenous shunting or any other abnormality except an

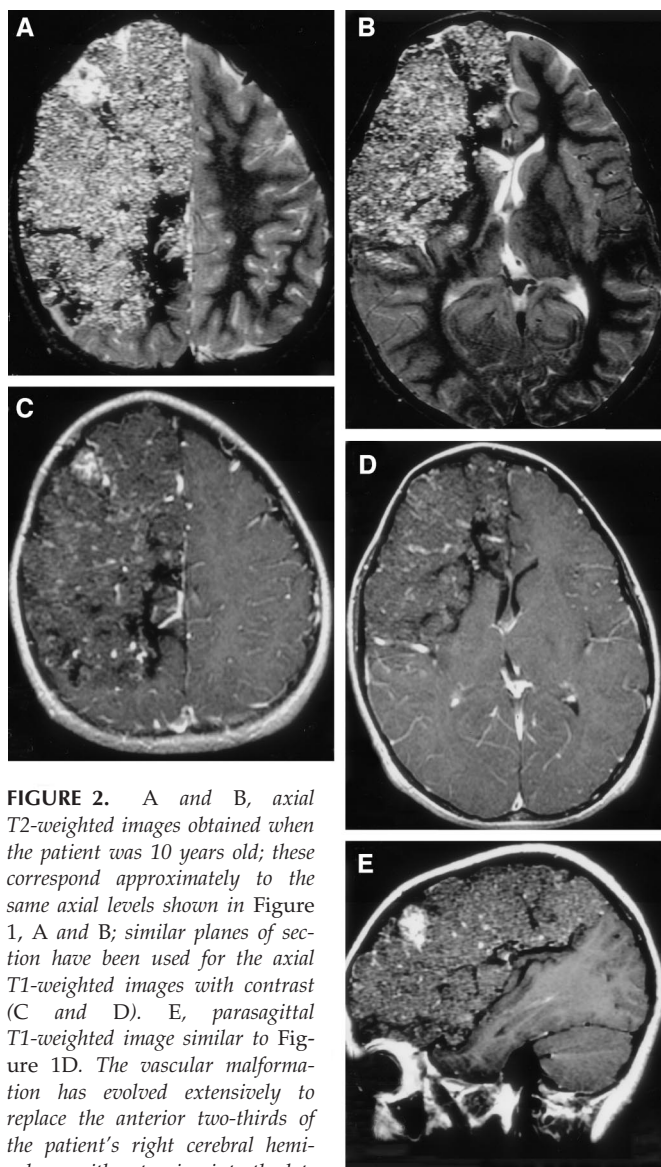


**FIGURE 1.** A and B, axial T2-weighted images obtained when the patient was 16 months old, showing signal abnormalities within the cortex and white matter of the right frontal lobe, including two large areas of decreased magnetic susceptibility consistent with subacute hemorrhage. C, axial T1-weighted image after contrast administration, with some linear areas of enhancement in the right frontal lobe. The latent signal of the right frontal lobe is abnormal compared with the left although not necessarily consistent with the boundaries of hemorrhage. D, this also can be observed in the parasagittal plane.

absent right A2 segment of the anterior cerebral artery (not shown).

The patient's seizures were controlled with Tegretol (Novartis Pharmaceutical Corp., East Hanover, NJ), and his weakness resolved spontaneously. Given the patient's complete and rapid recovery and his youth, he was followed-up without further intervention for many years. He achieved normal developmental milestones, although he had intermittent seizures that required adjustment of his medication. Neurobehavioral tests revealed delayed motor development in the left arm and hand.

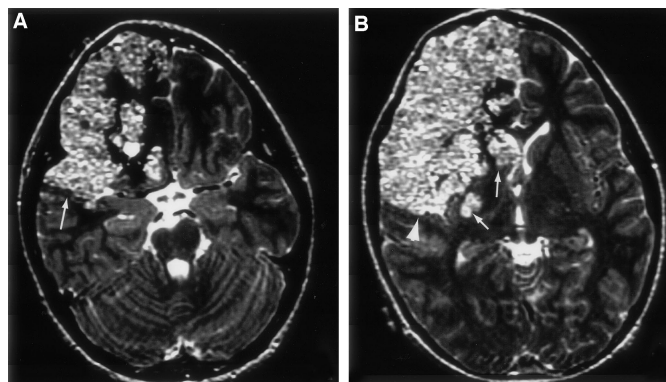
In 1998, at 10 years of age, the patient experienced another episode of left-sided weakness and headache. A computed tomographic scan revealed a new hemorrhage in the posterior frontoanterior parietal lobe, and MRI revealed that his CM had evolved extensively to replace the anterior two-thirds of his right cerebral hemisphere (Fig. 2), with extension into the lateral basal ganglia and the corpus callosum. In addition, the CM caused mass effect and had remodeled the inner table of the cranium. The patient recovered quickly after this setback,



**FIGURE 2.** A and B, axial T2-weighted images obtained when the patient was 10 years old; these correspond approximately to the same axial levels shown in Figure 1, A and B; similar planes of section have been used for the axial T1-weighted images with contrast (C and D). E, parasagittal T1-weighted image similar to Figure 1D. The vascular malformation has evolved extensively to replace the anterior two-thirds of the patient's right cerebral hemisphere, with extension into the lateral basal ganglia and the corpus callosum. For the most part, these areas correspond to the areas of abnormal brain signal evident in Figure 1. In addition, the CM exhibits mass effect and has remodeled the inner table of the cranium.

with only mild left hand weakness and clumsiness, and further treatment was not pursued.

In the fall of 1999, the patient's seizures became intractable, with oral auras and twitching at the left corner of his mouth. In addition, he had worsening left hand weakness and muscle atrophy. He was referred to the University of California, San Francisco, for consultation. Another MRI scan revealed continued evolution of the CM, which involved portions of the right anterior temporal lobe, had spread to include more of the right parietal lobe, and had further invaded the caudate head



**FIGURE 3.** A and B, axial T2-weighted MRI scans at two different planes of section, showing the extension of the vascular malformation into the anterior temporal tip and deep gray structures of the right hemisphere. The right cerebral peduncle is markedly smaller than the left peduncle (A); this level of asymmetry was evident on the patient's first MRI scan at 16 months of age (not shown).

(Fig. 3). Lesion dimensions at that time were 13 cm in the anteroposterior plane, 7 cm in the transverse plane, and 7 cm in the craniocaudal plane. The patient and his parents chose to pursue surgical resection.

### Surgical Intervention

In December 2000, the patient (then age 12 yr) underwent right hemispherotomy and resection of his vascular malformation. The right hemisphericum and dura were attenuated by the underlying lesion. The lesion was remarkably firm; it was purple and green in color and exhibited undulations resembling the gyral pattern of the brain (Fig. 4). The sylvian fissure was preserved, although the anteromedial portion of the temporal lobe was replaced by malformation. In an attempt to perform functional mapping of the patient's motor cortex, cortical and lesion stimulation failed to elicit responses on the left side of the body. The sylvian fissure was opened and the branches of the middle cerebral artery feeding normal parts of the posterior and lateral temporal lobe were preserved. The frontal pole was removed *en bloc*, but the rest of the lesion was so firm that further resection was performed piecemeal. Approximately 95% of the lesion was removed, leaving a thin rim of abnormal tissue posteriorly adjacent to presumed motor cortex and inferiorly adjacent to the basal ganglia. During the course of resection, portions of the lesion bled profusely with dark, venous blood, but this was controlled easily with electrocautery, hemostatic agents, and light pressure. At the end of the procedure, a ventricular catheter was inserted into the unroofed right lateral ventricle and the wound was closed.

Microscopic examination of the tissue from the portion of the anterior frontal lobe removed at the beginning of surgery revealed markedly dilated, thin-walled venous channels with a small amount of intervening, astroglitic brain (Fig. 5). The borders of the lesion were relatively discrete and exhibited

astrogliosis of adjacent brain parenchyma. Occasional lumina contained organizing thrombi. A Verhoeff elastic Van Gieson stain revealed no elastic lamina to suggest an arterial component within malformation vessels (Fig. 5). The pathological diagnosis was most consistent with CM.

Immediately after surgery, the patient was arousable and moving his right side spontaneously, but on the first day after surgery, he was obtunded and weak bilaterally. A computed tomographic scan revealed that the resection cavity had filled with CSF and air, but there was also an epidural hematoma over the left parietal lobe. We performed a left craniotomy and evacuation, but no arterial source for the bleeding was determined. The bone flap from this craniotomy was replaced with multiple dural tack-up sutures. Afterward, the patient made a good recovery and was discharged to a rehabilitation facility 17 days after surgery with moderate left hemiparesis, but with normal cognition, speech, and right side movement.

A follow-up MRI scan revealed almost no residual cavernous malformation except in the deepest regions of the resection cavity, adjacent to the deep gray matter, and no further extension of the CM into previously uninvolved brain (Fig. 6). In the 24 months since his operation, the patient has recovered with left hand weakness and clumsiness that is less pronounced than before his operation. He is able to run and jump on a trampoline, and he has returned to school. He has had no further seizures or hemorrhages, and his Tegretol dose is

being tapered slowly. He will be followed-up with serial MRI scans every 2 years.

The surgical specimen was frozen and stored at  $-80$  degrees. Deoxyribonucleic acid was extracted with a Puregene kit (Gentra Systems, Inc., Minneapolis, MN). Primers and amplification conditions for KRIT1 (53, 54) and malcavernin coding exons are available at <http://mgm.duke.edu/internal/faculty/marchuk/lab.htm>. Amplified products were directly sequenced on ABI3100 or ABI3730 instruments with BigDye chemistry (Applied Biosystems, Inc., Foster City, CA), according to the protocol recommended by the manufacturer.

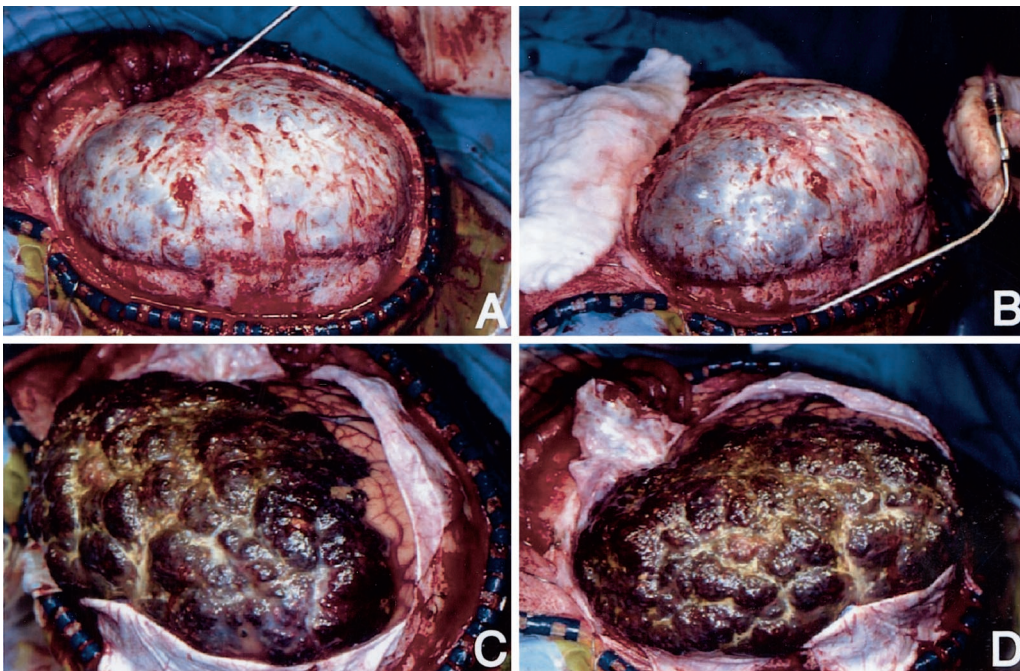
## RESULTS

Genetic analysis of CM tissue from the surgical specimen did not demonstrate mutations in either the *CCM1* (*KRIT1*) or *CCM2* (malcavernin) genes.

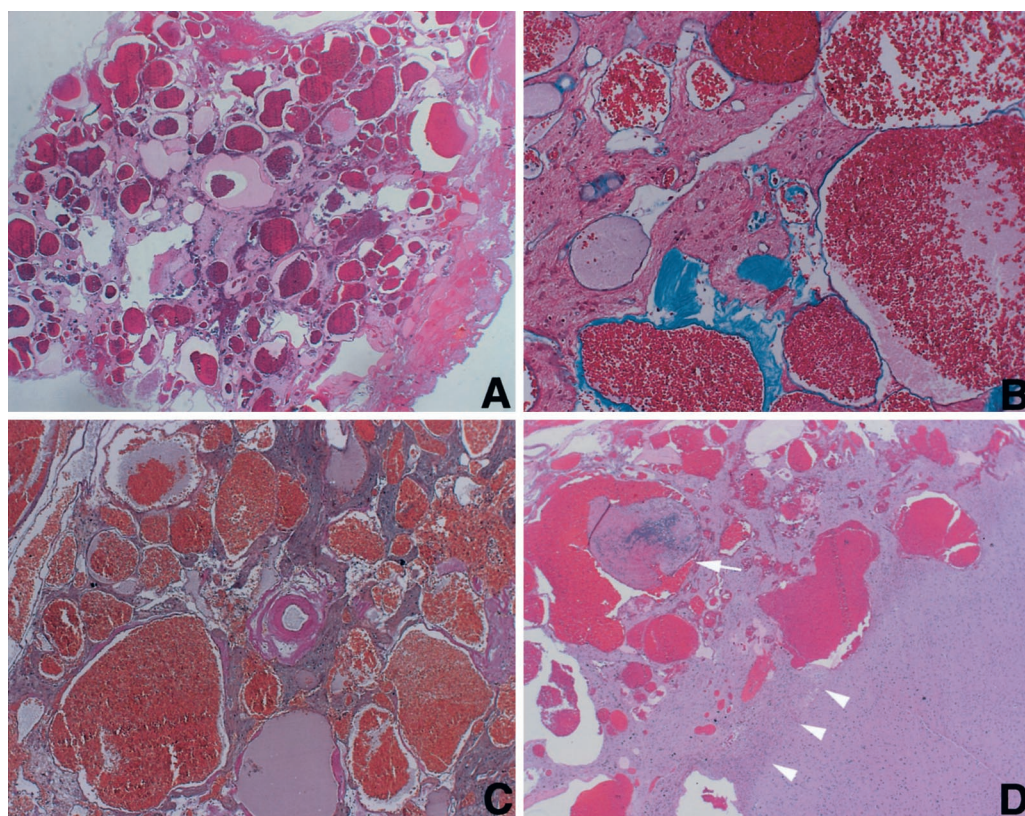
## DISCUSSION

The term *giant cavernous malformation* has crept into the literature without a precise definition (3, 14, 15, 26, 37, 42, 62). Unlike giant aneurysms that are defined as having a diameter of at least 25 mm, no threshold dimension has been accepted for giant CMs. CMs range in size from less than 1 mm to greater than 9 cm (37), and those at the high end of this

spectrum have loosely acquired the "giant" descriptor. It would be useful, albeit arbitrary, to define this term for future reporting with a threshold diameter of 6 cm. The CM presented in this case report belongs in this category of giant lesions. Previously, the largest giant CM was reported by Mottolese et al. (42) in a series of pediatric patients. One patient in the series had a CM 10 cm in diameter, and another patient was mentioned with a CM 11 cm in diameter. A review of the existing cases of CMs (MEDLINE, 1965–present) failed to reveal any case of a CM larger than the 13-cm CM harbored by our patient. Nonetheless, this case report is of interest not only because of its astonishing size, but also because of its unusual radiographic and histopathological appearance and its peculiar pattern of infiltration.



**FIGURE 4.** Intraoperative photographs. A and B, hemicraniotomy from two different perspectives before the dura is opened. The dura was attenuated and the lesion was evident by the dark purple discoloration visible through the dura. C and D, the extent of the lesion on the surface from two different perspectives. The surface of the lesion was indented in a pattern similar to the gyral indentations of the brain, but the texture of the lesion was firm, similar to tire rubber.



**FIGURE 5.** Photomicrographs. A, markedly dilated, thin-walled vessels with a small amount of intervening pink brain (hematoxylin and eosin; original magnification,  $\times 25$ ). B, interspersed astrogliotic brain. Vessels of the malformation are thin-walled and lack a muscular media (trichrome stain; original magnification,  $\times 250$ ). C, elastic lamina is not detected in vessels within the malformation, which indicates that there may be no significant arterial component (Verhoeff elastic Van Gieson stain; original magnification,  $\times 100$ ). D, although brain was present between vessels of the malformation, the malformation was relatively well circumscribed. A thin rim of astrogliosis surrounds the malformation (arrowheads). Organizing thrombus also is observed (arrow).

The MRI characteristics of giant CMs are like those observed with smaller CMs: well-demarcated, rounded, or lobulated lesions with large, cystic cavernous areas of mixed signal intensity representing blood and its breakdown products in various stages of evolution, surrounded by compressed, gliotic, hemosiderin-stained brain. Our patient had some of these features initially (Fig. 1), but his CM evolved into something atypical (Figs. 2 and 3). In later MRI scans, there were no large cavernous spaces; instead a speckled, heterogeneous pattern was revealed. At surgery (Fig. 4), the malformation lacked the classic mulberry appearance. It was solid and dense to the point of being difficult to retract with a standard retractor. The lesion had a gritty consistency and was devoid of cystic compartments. Only during microscopic examination were cavernous spaces appreciated within the lesion, and in some areas, these cavernous spaces were interspersed with areas of brain tissue.

The progressive clinical course of this lesion was as unusual as the radiographic and pathological findings. Serial MRI scans revealed evolution from scattered, multifocal lesions to a confluent, multilobar lesion involving the entire frontal lobe

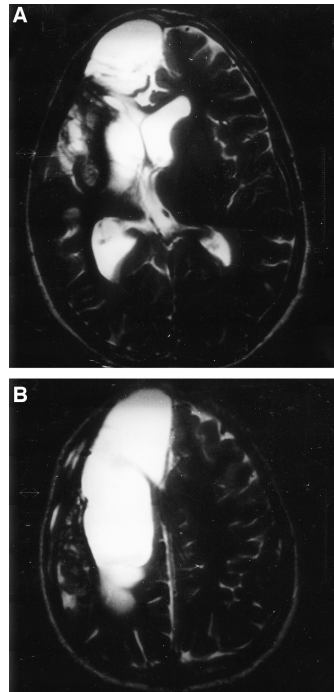
and portions of the temporal and parietal lobes. This infiltration into regions that were previously normal is atypical of CM. On the basis of imaging characteristics, pathological examination of surgical specimens, and recent studies of angiogenic factor expression, it has been suggested that CMs grow when friable vessels formed by abnormal angiogenesis cause repeated hemorrhages that excavate or push aside brain; subsequently, the intervening hematoma cavity becomes incorporated into the CM as an adjacent cyst without intervening brain parenchyma (5, 13, 18, 24, 28, 32, 33, 37, 39, 42, 45, 50, 51, 54, 60, 63, 64, 68). Our patient's course was punctuated by periodic hemorrhages, but serial MRI scans revealed a pattern of infiltrative growth invading adjacent brain regions without excavation by large hemorrhage.

This lesion's unusual radiographic and histopathological features, together with its infiltrative and aggressive behavior, raise the suspicion that it may represent

an atypical variant of CM that we would term *giant infiltrative cavernous malformation*. Such a lesion has not been described previously. The purpose of genetic testing for mutations in *CCM1* (*KRIT1*) and *CCM2* (*MGC4607*) was to link this atypical variant with the familial form of CM. Although the patient had a negative family history, his multifocal lesions initially suggested this disease form. Our negative findings suggest that this lesion has either a unique set of mutations distinct from familial CMs, or it has the genetics of sporadic CMs. The pathogenetics of sporadic CM are unknown, because current research has focused on the familial form, but they differ from those of familial CM. In an analysis of 72 sporadic CMs resected surgically, no somatic or germline mutations in *KRIT1* were demonstrated (46).

The genetics and pathogenesis of CMs are being elucidated; integrin plays a pivotal role. Integrin participates in communication between cells, both cell-to-cell and cell-to-extracellular matrix, and it is thought to modulate cellular migration and morphology. The identification of *KRIT1* as a binding partner of *ICAP1 $\alpha$*  (65, 67) suggests that *KRIT1* may

compete with  $\beta 1$  integrin for ICAP1 $\alpha$  binding, which may then interfere with normal integrin signaling (40). The presence of a phosphotyrosine-binding domain in malcavernin enables it to interact with KRIT1 and the cytoplasmic tail of  $\beta 1$  integrin, implicating it in competition for ICAP1 $\alpha$  binding and disruption of integrin signaling. A clear understanding of these mechanisms has yet to emerge, but they may be analogous to the abnormalities of cellular signaling identified in arteriovenous malformations (19–21, 25). Perhaps this variant, giant infiltrative CM, will be better characterized as these genetics unfold. In the absence of these data, we conclude that giant infiltrative CM is an extreme example of CM that can be managed effectively with standard surgical resection.



**FIGURE 6.** A and B, axial T2-weighted images showing the extent of resection 18 months after surgery; these panels correspond approximately to the same axial levels in Figures 1 and 2, A and B.

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## COMMENTS

Lawton et al. report the case of a young boy with a complex cavernous malformation that evolved over a decade to encompass most of his right cerebral hemisphere. Not only are rare clinical manifestations presented in this report, but also the results of genetic testing for CCM1 and CCM2. Genetic analysis of cavernous malformation tissue from the surgical

specimen did not demonstrate mutations in either the *CCM1* or *CCM2* gene. The authors concluded that “giant infiltrative cavernous malformation” is an extreme example of cavernous malformation that can be managed effectively with standard surgical resection.

**Yasushi Takagi**  
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The authors describe the clinical history of a 16-month-old boy who experienced seizures and displayed evidence of a large cavernous malformation involving the right frontal pole. During 10 years of follow-up, the lesion progressed, infiltrating most of the patient’s right cerebral hemisphere. The authors achieved near total resection of this lesion with excellent results.

This is an interesting and atypical case of an infiltrative cavernous malformation. The authors’ radiographic follow-up was excellent, as were the genetic studies performed. The latter did not detect the presence of genetic mutations differentiating this lesion from the familial form of cavernous malformations.

This case is an interesting addition to the literature. It also would be interesting to compare the genetic analysis of this lesion with those of other “giant infiltrative cavernous malformations.”

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Lawton et al. have presented a very interesting case of a giant pediatric cavernous malformation that seems to have invaded the brain over time. I agree with their belief that this lesion likely represents an atypical pathological variant, and thus I am not surprised that neither *CCM1* nor *CCM2* mutations were found. The authors achieved an excellent surgical outcome, especially the timely removal of the contralateral epidural hematoma. This complication has been described previously as being secondary to either rapid decompression or the use of head pins in the thin-cranium pediatric population (1, 2). In this case, the method of fixation was not mentioned, but one can easily postulate that the removal of a mass this size together with overdrainage of the “unroofed right lateral ventricle” might have been sufficient even if pins were used. As for the lesion itself, we can only hope that the authors will share additional radiological follow-up studies with us in the years to come. These undoubtedly will shed critical light on the proliferative potential of the residual malformation.

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2. Kirkpatrick PJ, Knibb AA, Downing HA: Rapid decompression of chronic hydrocephalus resulting in bilateral extradural hematomas: A general surgical complication. *J Pediatr Surg* 28:744–745, 1993.

The authors describe a patient who initially presented at the age of 16 months with seizures. Radiographic studies demonstrated a multifocal cavernous malformation in the right frontal pole. The patient’s seizures became worse over the ensuing 10 years, and when the child was 12 years old, radiographic studies demonstrated impressive involvement of the entire right frontal and parietal regions. The patient underwent surgery for almost complete resection of the lesion.

The authors nicely describe this patient and the difficult medical and surgical management. The curious feature of large and giant cavernous malformations is that they occur almost exclusively in children; in adults, it is unusual to find lesions that are larger than 2 or 3 cm that were not previously symptomatic and were not described during the patient’s childhood. An interesting feature of this particular case report is the radiographic documentation of the increase in size of the lesion. As the authors describe, there is general conjecture as to how cavernous malformations actually enlarge. The image documented by the authors in this publication shows that cavernous malformations can envelop an entire area of brain tissue. Previous descriptions of repeated hemorrhages with incorporation of angiogenic vessels around the areas of hemorrhage have been used to explain the situation in which cavernous malformations are described with varying ages of blood in isolated cystic areas, which most likely represent small areas of hemorrhage. In the present description, there seems to be true infiltration of the vessels, with an increase in the volume of the lesion based solely on the increase in the number of vessels, as opposed to small or multiple repeated hemorrhages.

The surgical attack on the lesion is interesting, because this is a formidable undertaking. The functionality of brain tissue near cavernous malformations makes it possible to excise these lesions in apparently eloquent areas, even with large lesions. This case also raises the issue of the plasticity of the nervous system in children. As the lesion enlarged, the functionality of adjacent brain almost certainly had to change in response to the enlargement and coalescence of the various cavernous malformation lesions into one giant lesion.

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