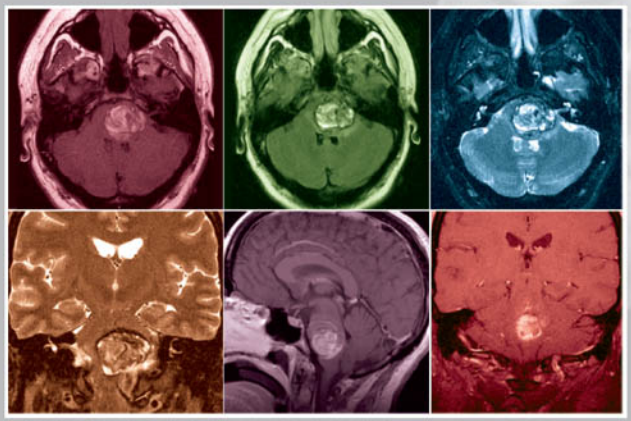
Cavernous Malformations of the Brain and Spinal Cord

Giuseppe Lanzino
Robert F. Spetzler



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Dedication

This book is dedicated to my parents Franco and Matilde and to my wife Desiree.

—Giuseppe Lanzino

To my wife Nancy, whose grace delights me, whose strength supports me, and whose courage humbles me.

—Robert F. Spetzler

Contents

Preface

Considered uncommon lesions before the introduction of magnetic resonance imaging (MRI), cavernous malformations (CMs) of the central nervous system (CNS) are frequently encountered in clinical practice. In the past two decades, we have gained a wealth of knowledge about their pathogenesis, natural history, and treatment. However, several aspects remain controversial.

It is now accepted that CMs in the CNS occur in a sporadic and in a familial form. The familial form is characterized by a dominant heterozygotic mode of transmission and has been linked to various mutations of genes coding for different proteins. Further understanding of the molecular biology and genetic bases of CMs will shed more light on their formation, evolution, and clinical behaviour.

The natural history of CMs is still a matter of controversy. It appears that supratentorial, superficial lesions have a fairly benign natural history, especially if discovered incidentally, with a very low-risk of hemorrhage. Cavernous malformations located in highly eloquent areas such as the brain stem seem to have a more aggressive clinical course. Whether this is related to a true higher tendency to bleed or to the eloquence of the areas involved (with minimal volumetric expansion becoming symptomatic) is still a matter of debate. Similarly to other vascular lesions in the CNS, the risk of hemorrhage is higher during the first few months after a bleeding episode and tends to stabilize thereafter. Better definition of the natural history of CMs of the brain and spinal cord is complicated by the now well-established dynamic nature of these lesions. Some CMs grow in size even in the absence of clinical symptoms while others appear de novo. Definitively, large-scale, well-designed prospective studies are necessary to further clarify some of these issues.

Intriguing and a topic of further study is the relationship between CMs and other vascular anomalies particularly developmental venous anomalies (DVAs). Developmental venous anomalies are observed on MRI studies in a high percentage of patients with CMs. More recently, development of a de novo CM adjacent to a DVA has also been documented. Further understanding of this mutual relationship will clarify the etiopathogenesis of CMs.

Hemorrhage and seizures are the two most common clinical presentations of CMs of the brain and spinal cord. Hemorrhage usually occurs within the boundaries of the CM. Given the low pressure of the blood flowing through the small vessels feeding the CM, catastrophic bleeding is very unusual. It is well accepted that surgical excision is indicated in patients with symptomatic hemorrhage especially if the CM is easily accessible. Improvements in intraoperative neuronavigation and microsurgery have allowed for safe resection of lesions in highly eloquent areas such as the thalamus, brain stem, and spinal cord. Surgery is also indicated for accessible lesions causing seizures. The outcome of seizures after surgical excision of a CM is dependent upon the interval from symptom onset and the number of seizures suffered. Patients operated on early after their first on seizure having better outcomes. Controversy surrounds the issue of whether lesionectomy alone or resection of the CM along with portions of the surrounding brain is best to achieve seizure control.

These and other controversial issues are elaborated in the following chapters. In a multiauthored book, duplications are almost unavoidable and we apologize to the reader. Although a separate clinical entity, we have included a chapter on cavernous angiomas of the cavernous sinus. By doing so, we have tried to stress their different nature despite their histopathological similarities with CMs in other areas of the CNS.

This book is intended to summarize the current knowledge on CMs of the brain and spinal cord while providing a platform for further studies. Like any other effort in the medical field, this text is the result of team work. We are particularly indebted to Brigitta Bradenburg and Ivy Ip from Thieme; Shelley Kick, Judy Wilson, and Jamie Canales from the editorial office at the Barrow Neurological Institute; Joanna Gass and Chris Shepler from the Illinois Neurological Institute; and to Rosa McDonald from the University of Illinois College of Medicine at Peoria. This text would not have been possible without their dedication and hard work.

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Section I

General Aspects

1

Natural History of Cavernous Malformations of the Central Nervous System

Iman Feiz-Erfan, Joseph M. Zabramski, Louis J. Kim, and Jeffrey D. Klopfenstein

Cavernous malformations are focal vascular abnormalities that affect the blood vessels supplying the brain. Although cavernous malformations make up only 5 to 10% of all cerebrovascular malformations, they are increasingly recognized as a cause of seizures and focal neurologic deficits.[1–4] The introduction of magnetic resonance imaging (MRI) allowed cavernous malformations to be diagnosed without the need for pathologic confirmation, which, in turn, has greatly enhanced our understanding of the natural history of these lesions. The growing availability of MRI has encouraged clinical interest in these lesions, and recognition that a large number of these cases have a familial component has stimulated research into the genetic basis of this disease, which is reviewed elsewhere in this text.

A logical approach to the management of these lesions requires that neurosurgeons understand the epidemiology and natural history of cavernous malformations. The purpose of this chapter is to provide readers with an in-depth review of the available literature on these topics and to examine the implications related to the treatment of these patients.

♦ Epidemiology

Before the introduction of modern imaging technology, cavernous malformations were considered rare lesions. In 1976, Voigt and Yasargil[5] described their clinical experience with one case and thoroughly reviewed the world literature; they found only 126 reported cases. Soon after the publication of this article, computed tomography (CT) became widely available. Although CT was a significant advance in neuroimaging, it lacked both sensitivity and specificity for the diagnosis and imaging of cavernous malformations. The subsequent introduction of MRI in the mid-1980s revolutionized our understanding of these lesions. The imaging characteristics of cavernous malformations are sufficiently unique to allow most lesions to be diagnosed on the basis of MR findings alone **(Fig. 1–1)**.[6–10]

Cavernous malformations are more common than is generally suspected. Postmortem studies performed in the 1980s demonstrated that cavernous malformations affect 0.37 to 0.5% of the population.[2,11] Remarkably similar results were reported by two groups reviewing more than 22,000 MR examinations, with incidence rates of 0.4 to 0.5%.[12,13] Based on these studies, it is estimated that 18 to 22 million people are affected by cavernous malformations worldwide.

Cavernous malformations occur in two forms: spontaneous and familial. The spontaneous form occurs as an isolated case, most commonly with a single lesion, whereas the familial form is characterized by multiple lesions and an autosomal dominant mode of inheritance.[14–17] The presence of three or more lesions and a family history of seizures are pathognomonic for the familial form of this disease.

♦ Clinical Manifestations

Cavernous malformations have been reported in infants and children, but most patients become symptomatic between their second and fifth decades.[12,13,16] Not all patients with cavernous malformations are clinically symptomatic. Fifteen to 20% of lesions are incidental findings discovered during a workup for headache.[12,13] In the authors' experience, as many as 40% of patients with the familial form of the disease remain asymptomatic despite the presence of multiple lesions.[16]

Seizures are the most common manifestation of supratentorial cavernous malformations, accounting for 40 to 80% of the presenting symptoms.[1,12,13,15,16,18] A few studies have focused on the future risk of seizure activity in patients harboring asymptomatic cavernous malformations. The rate of new onset of seizures in this group ranges between 1.5 and 2.4% per patient-year.[13,19,20] The exact mechanism that leads to seizure activity in these lesions is unknown, but it appears to be related to the deposition of iron in hemosiderin. Iron is a well-known epileptogenic material and has been used to induce seizures in laboratory models of epilepsy.[21,22] Focal neurologic deficits are rarely associated with supratentorial lesions.

In contrast, the sudden onset of focal neurologic deficits is the most frequent presentation of patients with cavernous malformations involving the brain stem.[23–26] Porter et al.[26] reported 100 surgical cases of brain-stem cavernous malformations. In their series, 97% of patients presented with focal neurologic deficits from hemorrhage. In the brain stem where lesions may be adjacent to critical tracts

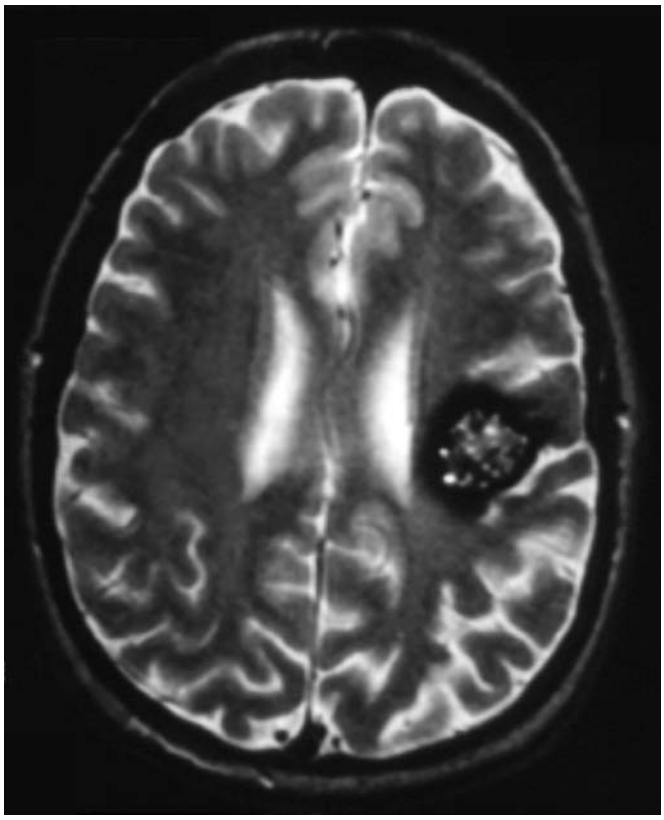


Figure 1–1 T2-weighted magnetic resonance image demonstrating the classic appearance of a cavernous malformation. Note the reticulated "salt and pepper" core surrounded by a hypointense rim.

and nuclei, even small focal hemorrhages may be poorly tolerated. Symptoms are characteristically maximal at onset. Symptoms from the initial episode tend to resolve as the hemorrhage is organized and absorbed. Often, patients have recovered completely by the time they are seen in neurosurgical consultation. Recurrent episodes of hemorrhage, however, are associated with progressively more severe deficits and an increased risk of permanent neurologic impairment. Death is rare without a history of multiple previous episodes of symptomatic hemorrhage.

♦ Natural History

Numerous studies have been published on the natural history of cavernous malformations (**Table 1–1**). Most of the data are derived from patients referred to neurosurgical centers and are therefore subject to bias that is likely to inflate hemorrhage rates. On the other hand, calculations that assume that these lesions are present from birth may significantly underestimate the risk of hemorrhage. The congenital nature of cavernous malformations has been recently challenged by well-documented reports of de novo formation of lesions in both sporadic and familial forms of the disease.[16,17,27–36] These uncertainties emphasize the need to rely on prospective natural history data in this population.

Another confounding factor is the dynamic nature of these lesions. Zabramski et al. classified cavernous malformations into four types based on imaging characteristics

Table 1–1 Summary of Literature on the Natural History of Cavernous Malformations of the Central Nervous System

Reference	Rate of Hemorrhage	New Onset Seizure per Person-Year (%)	Study Design	Statistically Significant Clinical Demographic Findings
Del Curling et al. (1991)[13]	0.1% per lesion per year 0.25% per person-year	1.51	Retrospective	NA
Robinson et al. (1991)[12]	0.7% per lesion per year	NA	Retrospective	Females had highest risk of bleeding
Canavero et al. (1994)[46]	1.6% per person-year*	NA	Literature review Only spinal cord lesions	 NA
Fritschi et al. (1994)[24]	2.7% per lesion per year† 21% per lesion per year‡	NA	Literature review Only brain-stem lesions	NA
Zabramski et al. (1994)[16]	1.1% per lesion per year† 6.5% per person-year† 2% per lesion per year 13% per person-year*	NA	Prospective Only familial form of disease	NA
Aiba et al. (1995)[39]	22.9% per lesion per year‡	NA	Prospective	Younger age, females, and previous bleed correlated with higher risk of hemorrhage No correlation between lesion location and risk of bleed
Kondziolka et al. (1995)[19]	1.3–2.63% per person-year 4.5% per person-year‡	1.5	Retrospective Prospective	Prior hemorrhage correlated with higher risk of bleed No correlation with sex, lesion number, seizure, or headache
Kim et al. (1997)[50]	1.4–2.6% per lesion per year 2.3–3.8% per person-year	NA	Retrospective	NA

Porter et al. (1997)[40]	4.2% events per person-year§ 1.5% hemorrhage per person-year	NA	Prospective	Deep or infratentorial lesion location correlated with bleed No correlation with prior bleed, sex, or number of lesions
Moriarity et al. (1999)[20]	3.1% per person-year	2.4	Prospective	Females had highest risk of bleed No correlation with lesion location, prior bleed, or form of disease (familial vs. sporadic)
Porter et al. (1999)[26]	5% per person-year 30% per person-year‡	NA	Retrospective Only brain-stem lesions	NA
Zevgaridis et al. (1999)[45]	1.4% per lesion per year	NA	Literature review Only spinal cord lesions	NA
Labauge et al. (2000)[38]	2.5% per lesion per year 11% per person-year	NA	Retrospective Only familial form of disease	NA
Steinberg et al. (2000)[51]	6.6% per person-year†	NA	Retrospective Only deep-seated lesions	NA
Barker et al. (2001)[42]	15% per person-year‡	NA	Retrospective	Temporal clustering of hemorrhages Higher re-hemorrhage rates in younger patients No sex predilection
Kupersmith et al. (2001)[52]	2.46% per person-year	NA	Retrospective Only brain-stem lesions	Reduced bleed rate if older than 34 years No correlation with sex or location
Labauge et al. (2001)[37]	0.7% per lesion per year 4.3% per person-year	NA	Prospective Only asymptomatic familial form of disease	NA
Kim et al. (2002)[53]	35.5% per person-year‡	NA	Retrospective	NA
Sandalcioglu et al. (2002)[54]	6.8% per person-year† 1.9% per person-year‡	NA	Retrospective Only brain-stem lesions	NA
Hsu et al. (2003)[48]	3.2% events per person-year§	NA	Retrospective Only spinal cord lesions	NA
Mathiesen et al. (2003)[41]	2% per person-year in incidental lesions 7% per person-year in symptomatic lesions	NA	Prospectively collected data retrospectively reviewed Only deep-seated lesions	NA
Sandalcioglu et al. (2003)[47]	4.5% per person-year† 66% per person-year‡	NA	Retrospective Only spinal cord lesions	NA
Wang et al. (2003)[55]	6% per person-year† 60% per person-year‡	NA	Retrospective Only brain-stem lesions	Rebleed rate increased with duration of clinical history

Source: Adapted from Feiz-Erfan I, Zabramski JM, Lanzino G, and Porter RW. Natural history of cavernous malformations of the brain. Operative Techniques in Neurosurgery 2002;5(3):171–175. Reprinted with permission.

*All hemorrhages.

†Symptomatic hemorrhages.

‡Represents rate of hemorrhage in lesions that previously bled.

§Event is defined as a subjective acute worsening of neurologic symptoms accompanied by objectively worse neurologic findings with or without radiologic proof of hemorrhage.

Abbreviations: NA, not applicable.

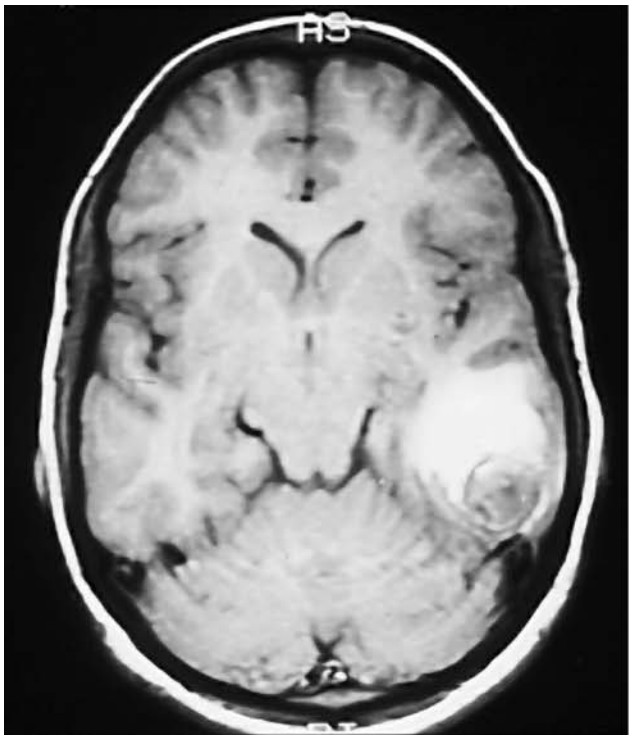
Table 1–2 Magnetic Resonance Imaging Classification for Cavernous Malformation

Lesion Type	MRI Signal Characteristic	Pathologic Characteristics
Type I_A	T1: hyperintense focus of hemorrhage T2: hyper- or hypointense focus of hemorrhage extending through at least one wall of the hypointense rim that surrounds the lesion. Focal edema* may be present. **(Figs. 1–2 and 1–3)**	"Overt" subacute focus of hemorrhage extending outside the lesion capsule of hemosiderin-stained gliotic brain
Type I_B	T1: hyperintense focus of hemorrhage T2: hyper- or hypointense focus of hemorrhage surrounded by a hypointense rim **(Fig. 1–4)**	Subacute focus of hemorrhage surrounded by a rim of hemosiderin-stained macrophages and gliotic brain
Type II	T1: reticulated mixed signal core T2: reticulated mixed signal core surrounded by a hypointense rim **(Fig. 1–1)**	Loculated areas of hemorrhage and thrombosis of varying age surrounded by gliotic, hemosiderin-stained brain; in large lesions, areas of calcification may be seen
Type III	T1: iso- or hypointense T2: hypointense with a hypointense rim that magnifies size of lesion GE: hypointense with greater magnification than T2	Chronic resolved hemorrhage with hemosiderin staining within and around the lesion
Type IV	T1: poorly seen or not visualized at all T2: poorly seen or not visualized at all GE: punctate hypointense lesions	Two lesions in the category have been pathologically documented to be telangiectasias

Source: Adapted from Zabramski JM, Wascher TM, Spetzler RF, et al. The natural history of familiar cavernous malformations: results of an ongoing study. J Neurosurg 1994;80:422–432. Reprinted with permission.

*Focal edema may surround the extralesional portion of hemorrhage in type IA lesions but raises diagnostic concerns in other lesion types.

Abbreviations: GE, gradient-echo sequences; MRI, magnetic resonance imaging; T1, T1-weighted MRI; T2, T2-weighted MRI.



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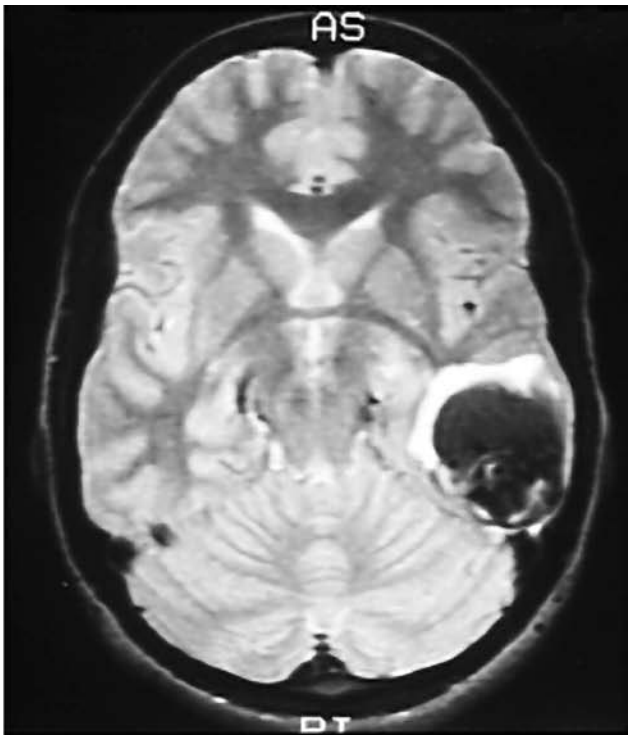

B

Figure 1–2 Example of a large "overt" hemorrhage (type I_A; **Table 1–2**). **(A)** T1-weighted and **(B)** T2-weighted magnetic resonance images demonstrating subacute, extralesional hemorrhage from a pathologically proven posterior temporal lobe cavernous malformation. The signal characteristics of the blood on these images are consistent with early subacute hemorrhage (within 1 week).

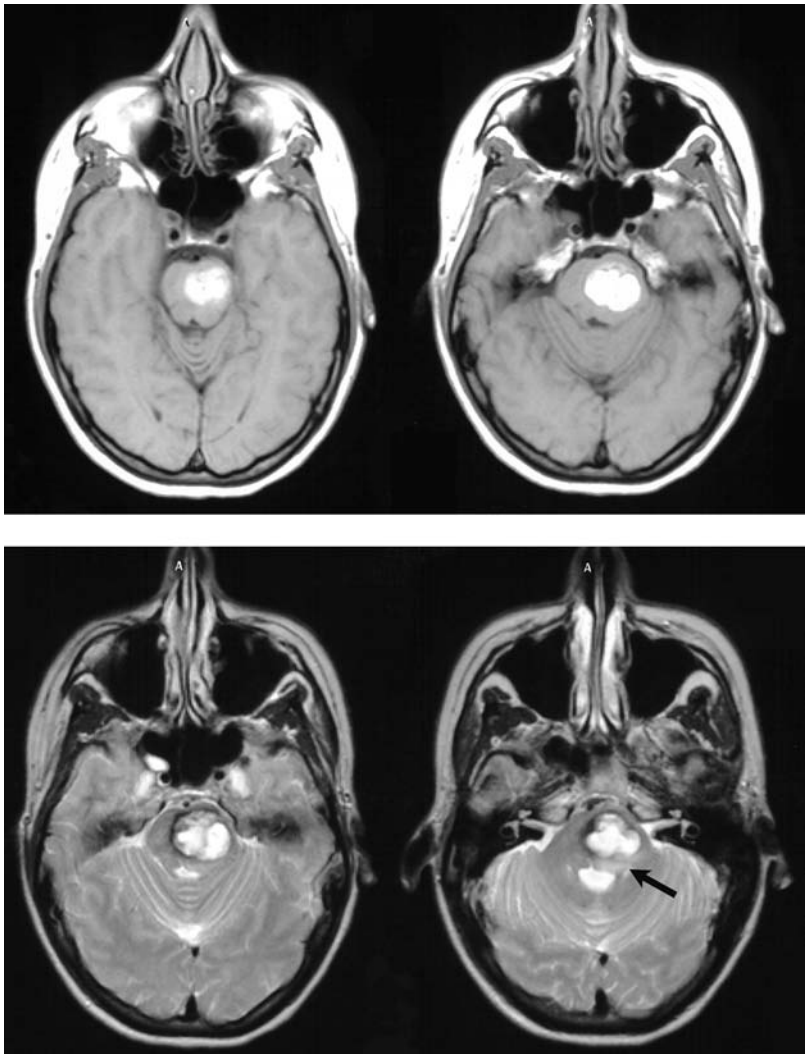

Figure 1–3 (A) T1-weighted and **(B)** T2-weighted magnetic resonance images demonstrating a subacute "overt" hemorrhage (type I_A; **Table 1–2**) from a brain-stem cavernous malformation. Note the displacement of the fourth ventricle secondary to mass effect, and the focal edema (**B**, *arrow*) adjacent to the area of hemorrhage that extends outside the hypointense rim (capsule) that surrounds the remainder of the lesion on the T2-weighted image.

(Table 1–2; Figs. 1–1 to 1–4).[16] These authors and others have found that the risk of hemorrhage appears greatest for type I and type II lesions, both of which are more likely to be associated with symptoms.[37,38] Most clinical studies are heavily biased to these two lesion types, which are most readily identified on MRI and do not require gradient-echo sequences for visualization.

Most studies of the natural history of cavernous malformations have tended to include patients with both the spontaneous and familial forms of the disease. Del Curling et al.[13] reviewed 8131 MRI studies performed at their institution over 3 years and identified 32 patients with 76 lesions. Six of these patients had four or more lesions (range, 4 to 19), consistent with a familial etiology. Sixteen patients presented with seizures. Assuming all lesions had been present from birth, they estimated that the risk of seizure development was 1.56% per person-year (1.34% for 26 patients with a single lesion and 2.48% per person-year for the 6 patients with multiple lesions). An additional problem, which is well illustrated in this study, is the lack of a widely accepted definition of hemorrhage. The authors report that only three patients exhibited "clinically significant, radiographically identifiable hemorrhages" and calculated a hemorrhage rate for their cohort of 0.25% per person-year. Yet they note that 7 of 32 patients had focal neurologic deficits attributable to their cavernous malformation at the time of diagnosis and that three patients had a history of prior transient deficits. Of the entire population, only six patients were asymptomatic. Assuming that the onset of seizures and neurologic deficits (whether temporary or permanent) follows at least one episode of hemorrhage, the risk of symptomatic hemorrhage in this cohort would be a minimum of 2.18% per person-year or 0.9% per lesion-year.

In another review of serial MRI studies, Robinson et al.[12] identified 66 patients with 76 lesions from 14,035 scans. They prospectively followed 57 patients with 66 lesions for an average of 26 months and found a risk of symptomatic hemorrhage of 0.7% per lesion-year. This rate compares favorably to the adjusted risk of symptomatic hemorrhage of 0.9% per lesion-year for the patients in study by Del Curling et al. and to the risk of symptomatic hemorrhage of 1.2% per lesion-year reported by Zabramski et al.[16] in a group of patients with familial cavernous malformations.

Kondziolka et al.[19] reported a slightly higher hemorrhage rate of 2.6% per year but noted that the risk of hemorrhage was strongly related to clinical presentation. They followed 122 patients with cavernous malformations for a mean of 34 months. The hemorrhage rate was significantly lower in

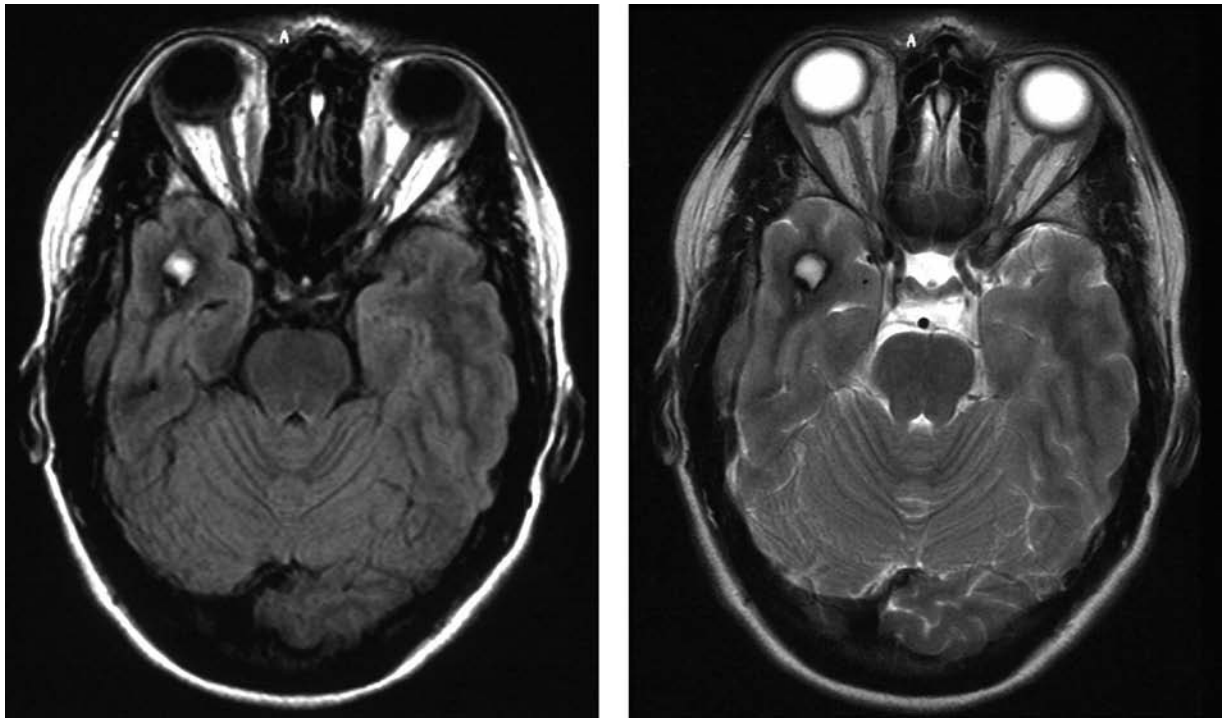

Figure 1–4 Example of type I_B (**Table 1–2**) hemorrhage. **(A)** T1-weighted and **(B)** T2-weighted magnetic resonance images showing a focal area of subacute hemorrhage within a small temporal lobe cavernous malformation. There is no evidence of hemorrhage outside the hypointense lesion capsule.

patients who presented with incidental lesions: 0.6% per year ($n = 61$) compared with 4.5% per year in those with a history of previous symptomatic hemorrhage ($n = 61$). Aiba et al.[39] noted a similar low risk of hemorrhage in asymptomatic patients. They followed 23 patients with incidental cavernous malformations for a mean of 2.4 years and reported a 0% hemorrhage rate for patients with incidental lesions and rate of 0.4% per year in those with seizures.

Porter et al.[40] reported a slightly higher annual event rate of 4.2%. This group defined an event as any neurologic worsening of symptoms with or without radiologically proven hemorrhage. The authors followed 110 patients with cavernous malformations for an average of 46 months, yielding 427 years of observation. In this study, location was the most important factor for predicting future events. Event rates were significantly higher for deeply located (10.6% per year) than for superficially located lesions (0% per year). Radiographically proven interval hemorrhages occurred in seven patients, for an annual risk of 1.6% per patient-year. Six of these seven patients presented with a history of hemorrhage.

Mathiesen et al.[41] also noted an increased risk of hemorrhage associated with deep-seated and brain-stem cavernous malformations. The authors followed 11 patients with asymptomatic lesions for an average of 4 years. The symptomatic hemorrhage rate was 2% per patient-year in this group, compared with a hemorrhage rate of 7% per patient-year in 23 patients with symptomatic lesions.

Hemorrhage rates appear to be particularly high in patients who present after bleeding episodes that violate the lesion capsule, producing a so-called overt extralesional hemorrhage (type I_A) into the surrounding brain **(Figs. 1–2 and 1–3)**. Aiba et al.[39] followed 62 such patients for a mean of 3.12 years. Their risk of recurrent symptomatic hemorrhage was 22.3% per lesion-year. Barker and colleagues[42] reported a similar experience with 141 patients selected for intervention who presented with "overt" hemorrhages. In this series, 63 patients experienced a second hemorrhage before treatment. Hemorrhages clustered around the initial event; the re-hemorrhage rate was 25.2% per year for the first 28 months. After this 28-month cutoff, the risk of rebleeding decreased to 9.6% per year. Comparable rates of rebleeding have been reported after incomplete resection of cavernous malformations that interrupt the lesion capsule, stressing the importance of complete resection if surgery is contemplated.[24,41,43,44]

Spinal Cord Cavernous Malformations

Cavernous malformations of the spinal cord are rarely diagnosed before symptom onset. Data on the natural history of these lesions are sparse. Based on lifetime risk analysis (assuming lesions are present from birth), hemorrhage rates range from 1.4 to 4.5% per patient-year.[45–48] Once lesions have become symptomatic, patients tend to experience progressive neurologic deterioration, with prospective re-hemorrhage rates as high as 66% per patient-year.[47,48]

Familial Cavernous Malformations

Familial cavernous malformations are inherited as an autosomal dominant disorder. At least three distinct genetic loci have been identified with this form of the disease. A detailed review of the genetics of familial cavernous malformations is beyond the scope of this chapter but is provided elsewhere in this book. The hallmark of familial cavernous malformations is the presence of multiple lesions and a

strong family history of seizures. In a recent series of 132 patients with familial cavernous malformations, Denier and coworkers reported that 80% had multiple lesions on T2-weighted MR images and 90% had multiple lesions on gradient-echo images. The average was five lesions per patient on T2-weighted images and 20 lesions per patient on gradient-echo sequences.[49]

The natural history of the familial form of cavernous malformations parallels that of their spontaneous counterparts. Lesions occur throughout the central nervous system in rough proportion to the tissue volume of the various compartments (80% supratentorial, 15% posterior fossa, and 5% spinal cord). Clinical penetrance is highly variable with 40 to 60% of patients reported as symptom free.[16,37,38] The most common presentations are seizures and headaches for supratentorial lesions and focal neurologic deficits for those involving the brain stem and basal ganglia.

Several prospective studies have examined the natural history of this population. Zabramski et al.[16] prospectively followed 59 members of six families with the familial form of cavernous malformations. From this cohort, 21 patients harboring a total of 128 lesions (mean, 6.5 lesions per patient) were followed a mean of 2.2 years. Serial MRI studies were performed at 6- to 12-month intervals. Clinically silent hemorrhages were common. MR evidence of hemorrhage (defined as signal changes consistent with acute/subacute hemorrhage) occurred in 28% of patients, but only half of these episodes were associated with symptoms. The reported symptomatic hemorrhage rates were 1.1% per lesion-year and 6.5% per patient-year. This report also documented the ongoing development of new lesions. During the follow-up period, 29% of the patients developed new lesions: Altogether, 17 de novo lesions were identified for a rate of 0.4 new lesions per patient-year.

The findings of Zabramski et al.[16] were confirmed by Labauge et al.[38] who identified 264 patients with familial cavernous malformations in 51 families. Forty of these patients, who had 232 lesions (mean, 5.9 lesions/patient), underwent at least two clinical and MRI studies. The mean follow-up was 3.2 years. New lesions were noted in 27% of patients, for a rate of 0.2 new lesions per patient-year. MR evidence of hemorrhage was present in 21 lesions (9%) in 14 patients (35%), but only seven patients were symptomatic. Therefore, the symptomatic hemorrhage rate was 0.8% per lesion-year and 5.5% per patient-year. Hemorrhage was most common in type I and type II lesions (**Table 1–2**): 32% of type I and 14% of type II lesions demonstrated evidence of hemorrhage on follow-up MRI. In contrast, only 2.8% of type III lesions and 0% of type IV lesions showed evidence of hemorrhage.

In a subsequent study, Labauge and colleagues prospectively followed 33 asymptomatic patients with familial cavernous malformations with serial clinical and MR examinations, including gradient-echo sequences, for a mean of 2.1 years.[37] On initial evaluation, 234 lesions were identified for a mean of 7.1 lesions per patient. The lesions, which were classified according to Zabramski et al. (**Table 1–2**), included 46 (19.6%) type II, 34 (14.5%) type III, and 154 (65.8%) type IV lesions. There were no type I lesions in this population of asymptomatic patients. During follow-up, new lesions occurred in 30% of the patients for an average rate of 0.4 new lesions per patient-year. MR evidence of hemorrhage was noted in three patients (9%), but only one (3%) patient was symptomatic. Therefore, the symptomatic hemorrhage rate was 0.2% per lesion-year and 1.4% per patient-year. Hemorrhage was noted only in type II lesions.

♦ Conclusion

Cavernous malformations are relatively common lesions that affect 0.4 to 0.5% of the population. They occur in two forms: a sporadic form characterized by a single lesion and a familial form characterized by multiple lesions and an autosomal dominant mode of inheritance. Cavernous malformations are found throughout the central nervous system in rough proportion to tissue volume: 80% supratentorial, 15% posterior fossa, and 5% spinal cord. The lesions are composed of dilated capillary vessels with a propensity for focal hemorrhage and hemosiderin deposition, which are hallmarks for their diagnosis on MRI. Supratentorial cavernous malformations cause symptoms when recurrent episodes of hemorrhage lead to seizure activity. Lesions located in the brain stem and basal ganglia can cause focal neurologic deficits.

The natural history of cavernous malformations is related to their clinical presentation, imaging characteristics, and location. Incidental lesions and those diagnosed during evaluation for nonspecific symptoms such as headache have a low risk of symptomatic hemorrhage (0.2 to 2% per patient-year). The risk of recurrent symptomatic hemorrhage is higher in patients with symptomatic lesions and varies with the type of hemorrhage. The recurrent hemorrhage rate approaches 25% per year in patients with "overt" hemorrhages that disrupt the lesion capsule (type I_A; **Table 1–2**). In patients with symptomatic type I_B or type II lesions, the intermediate risk of recurrent symptomatic hemorrhage ranges from 4 to 7% per patient-year.

Symptomatic hemorrhage rates are higher for cavernous malformations in the brain stem and basal ganglia. Hemorrhages in these eloquent locations are more likely to cause focal neurologic symptoms than those in subcortical locations. Patients presenting with symptomatic, "overt" hemorrhage from a brain-stem cavernous malformation are at greatest risk of disability and death from rebleeding.

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2

Molecular Biology of Cerebral Cavernous Malformations

Pascal M. Jabbour, Judith Gault, Robert Shenkar, and Issam A. Awad

Cerebral cavernous malformations (CCMs) are proliferative hemorrhagic lesions consisting of clusters of sinusoidal caverns lined by endothelium and filled with thrombus at various stages of organization.[1] The lesions are compact and surrounded by gliosis and blood degradation products. Their prevalence in the general population is estimated to range from 0.1 to 0.9%.[1–8] Depending on their size and location, the lesions can be clinically silent or manifest symptoms ranging from headaches and focal neurologic deficits to seizures and severe intracranial hemorrhage.[2–9] Ultrastructural analysis suggests abnormalities of the interendothelial tight junctions and subendothelial layer of the blood-brain barrier.[10–12] Typically, lesions are confined to the central nervous system, occurring in a volume distribution,[5] but they rarely involve the epidural space and other locations including the skin, liver, and orbit.[13–15]

The CCMs occur in a sporadic or autosomal dominant inherited form. Familial cases are characterized by the multiplicity of lesions, whereas sporadic cases harbor usually a single overt CCM.[16–18] The frequency of the familial form has been estimated to be as high as 50% in Hispanic-American patients[17,19] and 20 to 30% in other patients.[19] Three CCM loci have been identified: CCM1 on 7q, CCM2 on 7p, and CCM3 on 3q.[16, 20–22] The disease gene responsible for CCM1 encodes the Krev interaction trapped 1 (KRIT1) protein,[16,23,24] and recently the CCM2 gene, *MG4607,* has been identified.[25]

♦ Characterization of Cerebral Cavernous Malformations

Types of Vascular Malformations in the Central Nervous System

Current lesion nomenclature of cerebral vascular malformations is based on classic histologic descriptions by Russell and Rubinstein.[26–29] The arteriovenous malformations (AVMs) exhibit mature vessel wall elements with direct communications between arteries and veins and a high-flow profile predisposing to vascular recruitment, arterialization of venous structures, and gliosis of intervening and adjacent brain tissue. They have three major components: arterial feeders, nidus, and venous outflow. The AVMs are prone to apoplectic hemorrhage by rupture of nidal vessels or associated aneurysms or by venous outflow obstruction.[26,29,30]

In contrast, the CCMs appear to grow by a process of vascular cavern proliferation, in the setting of repetitive lesional hemorrhages. The CCMs exhibit brittle vascular morphology devoid of mature vessel wall elements.[31,32] They do not exhibit the high-flow features of AVMs and are less commonly associated with apoplectic hemorrhage.[5,7,33,34]

A third and the most common form of cerebral vascular malformation is the venous malformation (VM), also known as venous angioma or venous developmental anomaly, a lesion that rarely manifests clinical sequelae except when associated with a CCM lesion.[35,36] It is composed of abnormally enlarged vessels of venous structure separated by normal neural parenchyma.[8,37] These vessels are arranged in a radial pattern extending from a dilated central venous trunk, which itself drains into either a deep or superficial venous sinus.[37,38] Large VMs often reflect regional venous dysmorphism and serve as sole or major channels of venous drainage of adjacent brain.

Mixed vascular malformations, exhibiting features of more than one lesion type, have been described.[39] Nonfamilial CCMs are often associated with a VM in the same region of the brain, whereas this association is rare in familial cases.[35] The CCM lesions are often associated with adjacent nonhemorrhagic capillary telangiectasia (mixed CCM-capillary malformations), and components of CCM lesions may exhibit maturation of vessel wall, akin to true AVMs.

Early biologic studies and genetic investigations have largely considered and compared pure AVMs and CCMs and avoided the mixed lesions. Future studies will need to explore and compare the mixed vascular malformations in comparison with the pure forms, as their pathobiology will likely shed critical light on the nature of individual lesion types and their pathogenesis and evolution. Other vascular malformations including the dural AVMs, with arteriovenous shunting within the dural leaflet, are also important clinically, and there has been new information on their pathobiology. However, consideration of these lesions is beyond the scope of this review.

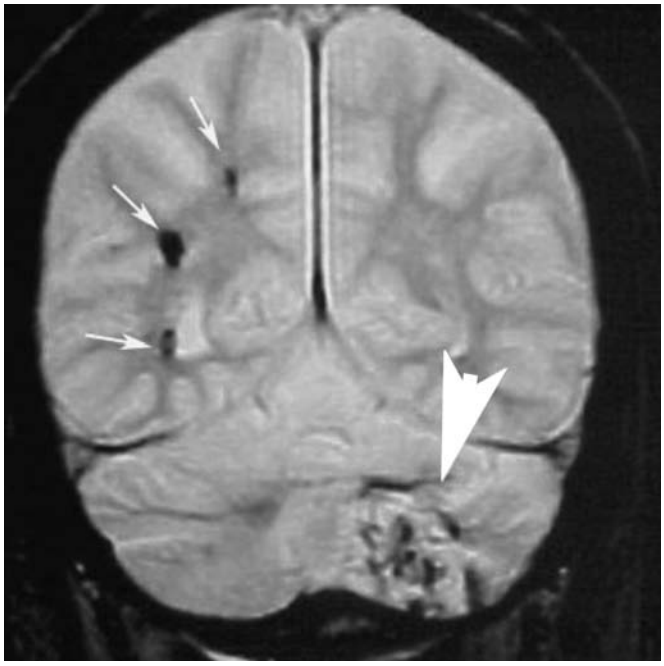

Figure 2–1 Brain magnetic resonance imaging (MRI): Gradient-echo–weighted image showing multiple cerebral cavernous malformations (CCMs). Only the larger symptomatic infratentorial lesion (*large arrowhead*) was visible on conventional MR sequences (T1, T2, and FLAIR [fast fluid-attenuated inversion-recovery]), whereas the multiple supratentorial "baby lesions" (*small arrows*) were only seen on gradient-echo imaging.

Magnetic resonance imaging (MRI) is considered the gold standard for the diagnosis of CCMs,[5,40–48] with typical features of mixed signal intensity within the lesion and a rim of surrounding hypointensity reflecting hemosiderin.[49,50] Gradient-echo MRI can detect small areas of chronic hemorrhage not seen on conventional spin-echo techniques, including multiple minute lesions in familial cases thought to represent precursors of larger and more symptomatic lesions **(Fig. 2–1).** MRI with contrast is also important to detect any venous malformation associated with the CCM.

Clinical Variants of Cerebral Cavernous Malformations

The clinical manifestations of CCMs include incidentally discovered lesions, those presenting with headache or nonspecific symptoms, seizures, hemorrhage, and focal neurologic deficits. Severity of disease is mostly defined in relation to the frequency of clinically overt hemorrhagic episodes. Other indices of disease severity include clinical penetrance in familial cases (frequency of affected kindreds), age at clinical presentation, prevalence of clinical disability, and the need for surgical interventions.[9,14]

Most clinical series include 14 to 19% of cases with asymptomatic lesions incidentally discovered on MRI.[5,51,52] The prevalence of overt hemorrhage ranges between 6% and 30% of cases.[5,51,53–56] The risk of overt hemorrhage is estimated to range between 0.25% and 0.7% per lesion per year,[57–61] with infratentorial lesions significantly more likely to cause clinically significant and disabling bleeds.[62]

Solitary lesions are most common in the sporadic form of the disease, occurring in 60 to 80% of cases. Multiple lesions are the hallmark of familial cases, occurring in increasing frequency with age and more likely detected by gradient-echo MRI.[6,63–70] De novo CCMs appear commonly in familial cases,[71] with a rate of new CCM formation on MRI of 0.4 to 1 lesions per patient-year.[63] De novo formation of CCMs has also been documented in the setting of preexisting VM and after cranial radiation therapy to treat an unrelated lesion and in the absence of any other apparent causative factors.[72–75]

Cerebral Cavernous Malformations and Mixed Vascular Malformations

Mixed lesions (mixed VM-CCM, mixed AVM-CCM, and mixed VM-AVM) have been described, which include features of more than one lesion type. It is not clear if these develop as mixed or transitional lesions or instead evolve mixed features from preexisting malformations. The mixed VM-CCM has been well described[19,32,76] in 20 to 30% of CCMs. Familial CCMs are rarely associated with VM. The AVM-CCM association has largely been reported in pathologic specimens of lesions presenting as angiographically occult vascular malformation, indistinguishable clinically and radiographically from pure CCMs. One possible explanation is that microhemorrhage from a cryptic AVM results in reactive angiogenesis and ultimately the formation of a CCM.[33] Another possibility is that some CCMs include portions with attempted vessel maturation, with features of mature vessel wall elements mimicking AVM.[77] The mixed VM-AVM is the least common.[78,79] One proposed explanation is that the VM may be a potential precursor of AVMs with fistulization of arteriovenous bed draining into a VM.[78]

♦ Histopathology and Ultrastructure of Normal Vasculature

Blood vessels within central nervous system parenchyma are composed of a tunica intima, media, and a specialized outer layer intimate with surrounding astrocytic milieu.[80] The tunica intima maintains a competent blood-brain barrier and consists of a layer of endothelial cells connected by specialized tight junctions, resting on a basal lamina including pericytes and specialized matrix proteins fibronectin, laminin, and collagen IV, that provide structural support and anchor endothelial cells[32,81] **(Fig. 2–2)**. Astrocytic foot processes provide additional structural integrity and unique signaling opportunities. Generally, immature vessels early in angiogenesis consist of nonadherent proliferating endothelium in a fibronectin-rich matrix, whereas more mature vessels have an adherent nonproliferating endothelium and express laminin more uniformly with a paucity of fibronectin in the matrix.[81] Collagen IV is abundant within the basal lamina and important in maintaining structural integrity of the vessel wall.[80]

The tunica media consists chiefly of concentric layers of helically arranged smooth muscle cells; interposed among smooth muscle cells are variable amounts of elastic and reticular fibers, in addition to proteoglycans.[80] The tunica media layer is rich in extracellular matrix protein, collagen III, expressed at all stages of angiogenesis, and various vascular smooth muscle cell proteins including, α-smooth muscle actin, myosin heavy chain, and smoothelin (SMTN) are expressed in this layer.[32,82] In arteries, the media is separated from the intima by an internal elastic lamina, a layer largely

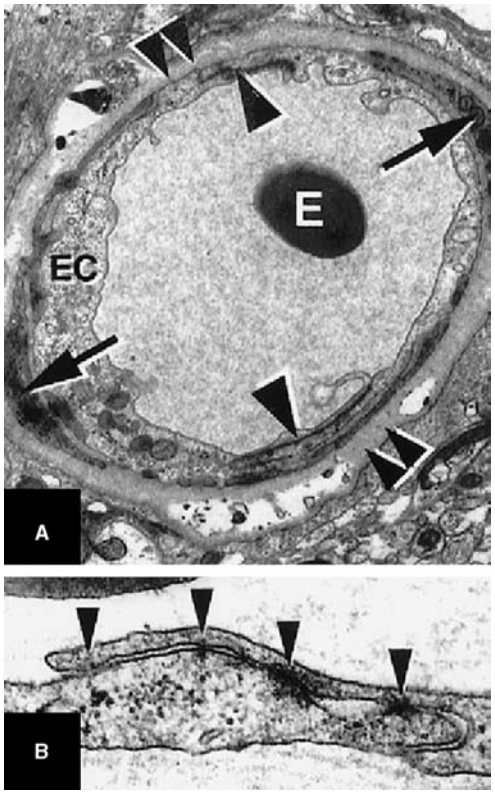

Figure 2–2 Transmission electron micrographs of normal cerebral capillary. **(A)** Pericytes (*arrows*) within the basal lamina (*double arrowheads*); EC, endothelial cell; arrowheads, tight junctions; E, erythrocyte (original magnification, × 8100). **(B)** Normal endothelial cells. Arrowheads, tight junctions (original magnification, × 42,000). (From Wong JH, Awad IA, Kim JH. Ultrastructural pathological features of cerebrovascular malformations: a preliminary report. Neurosurgery 2000;46(6):1454–1459. Reprinted with permission.)

composed of elastin protein. Larger arteries possess a thinner external elastic lamina that separates the media from the outer tunica adventitia. In capillaries and postcapillary venules, the media is represented by pericytes.

Vascular smooth muscle cells are integral to vascular repair and provide structure to the tunica media and vessel wall. Of the two vascular smooth muscle phenotypes, synthetic and contractile, the latter is more common in the adult population. α-Smooth muscle actin is a contractile protein found earliest in smooth muscle cell differentiation; it is the most abundant contractile protein in vascular smooth muscle cells. Actin appears to be expressed in all layers of arteries and in the subendothelium (intima) of veins. Myosin heavy chains (MYHCs) are ubiquitous actin-based motor proteins that convert the chemical energy (ATP) into mechanical force involved in cytokinesis, vesicular transport, and cellular locomotion. In eukaryotic cells, myosin heavy chains (MYH1 and MYH2) are present at a later stage of smooth muscle differentiation than actin and are expressed in all layers of arteries but not in veins. SMTN is a cytoskeletal protein that is different from other smooth muscle–specific proteins, which are expressed in both synthetic and contractile smooth muscle cells; SMTN is specific for contractile cells and serves as a marker for these cells. SMTN is expressed in the media of some arteries but not in veins.[32,80,81,83]

♦ Angioarchitecture of Cerebral Cavernous Malformations

Ultrastructure of Cerebral Cavernous Malformations

CCMs are characterized by caverns that are filled with blood or thrombus, lined by a single layer of endothelial cells, and separated by an amorphous connective tissue matrix (collagen).[11] The lining of caverns in CCM lesions lacks interendothelial cell tight junctions and subendothelial support[11,12] **(Fig. 2–3)**. Endothelial tight junctions are a component of the blood-brain barrier, and their disruption is consistent with an underlying abnormality in cytoskeletal structure. The CCM subendothelium, at the level of the basal lamina (extracellular matrix), expresses fibronectin to a greater extent than normal brain vessels and AVMs. In

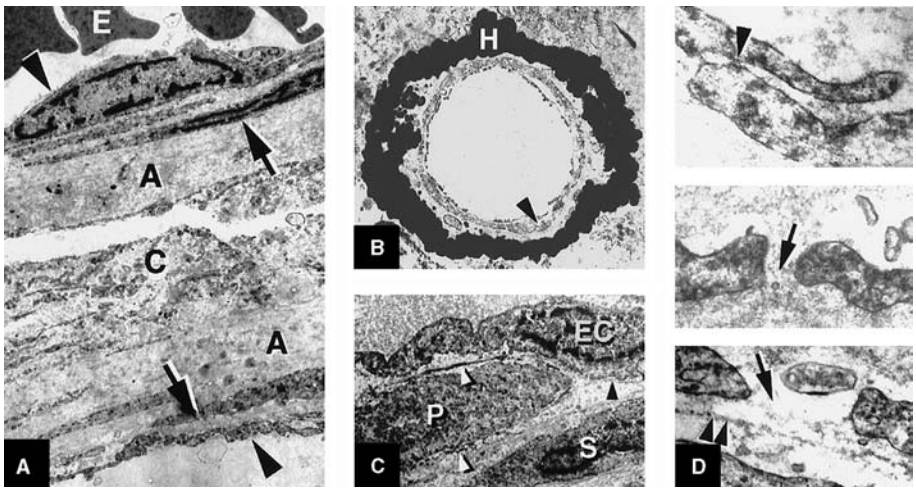

Figure 2–3 Transmission electron micrographs of CM. **(A)** Fibrous septa separating caverns at top and bottom; E, erythrocyte; arrowheads, endothelial cells; arrows, subendothelial cells; A, amorphous connective tissue; CM, cavern wall; C, collagen bundles (original magnification, × 4700). **(B)** Peripheral capillary showing electron-dense hemosiderin (H) ring with tight junction (*arrowhead*) (original magnification, × 7600). **(C)** CM, cavern wall; EC, endothelial cell; P, pericyte; S, subendothelial cells; arrowheads, basal lamina (original magnification, × 5100). **(D)** Lack of normal interendothelial cell junctions (*arrows*); double arrowheads, basal lamina. *Top*, original magnification, × 100,000; *middle*, original magnification, × 84,000; *bottom*, original magnification, × 69,000. (From Wong JH, Awad IA, Kim JH. Ultrastructural pathological features of cerebrovascular malformations: a preliminary report. Neurosurgery 2000;46(6):1454–1459. Reprinted with permission.)

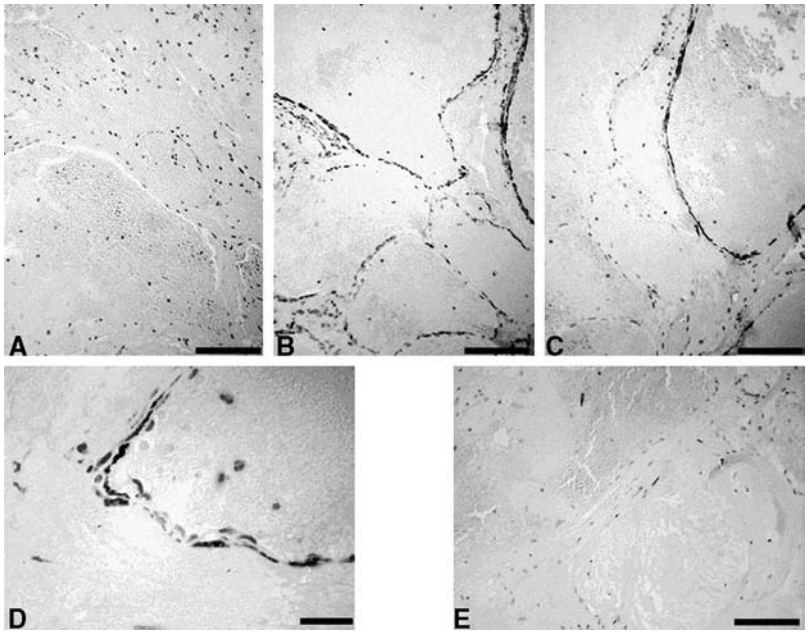

Figure 2–4 Immunohistochemistry of [α]-SMA, myosin heavy chain (MYHC), and smoothelin (SMTN) in cerebral cavernous malformations (CCMs). **(A)** Negative control (original magnification, × 100). **(B)** Immunostaining for [α]-SMA showing confined delineation of walls of the caverns. The staining involved the subendothelial cell layer and rare scattered cells in intercavernous connective tissue (original magnification, × 100). **(C, D)** Immunostaining for MYHC showing immunoexpression in the thin subendothelial layer of some but not all caverns. Note many caverns devoid of MYHC expression in their walls. **(D)** MYHC expression was localized in the subendothelial layer (original magnification, × 400). **(E)** Immunostaining for SMTN showing no expression in any caverns (original magnification, × 100). (From Uranishi R, Baeu NI, Kim JH, et al. Vascular smooth muscle cell differentiation in human cerebralvascular malformations. Neurosurgery 2001;49(3):671–680. Reprinted with permission.)

contrast, laminin is underexpressed in the subendothelial layer of CCMs compared with AVMs and normal vessels. The CCMs express collagen IV within the subendothelial layer and collagen III only focally in the perivascular tissue.

Smooth muscle maturation in CCMs has recently been studied[82] **(Fig. 2–4)**. Most caverns in CCMs express actin in the subendothelial layer. Only 20% of large caverns express MYHC in the subendothelial layer, and most small caverns do not express MYHC. Actin and myosin expression in CCMs is largely limited to the subendothelial layer, with scant expression within the intercavernous matrix. The CCM lesions do not exhibit recognized muscularis layers as in normal vessels and AVMs. SMTN expression, characteristic of contractile smooth muscle cells, is absent in CCMs.[82] The CCMs have characteristic hemosiderin deposits near the basal lamina and lack astrocytic foot processes; the processes stop at the border of the lesion.[11,12]

Angiogenesis Activity in Cerebral Cavernous Malformations

Normal adult cerebral vasculature generally does not express angiogenesis factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF2). VEGF, FGF2, and TGFB1 expression in cerebral vascular malformations is possibly induced by proliferation of new vessels, hemodynamic stress, ischemia, and/or hemorrhage.[32,84] VEGF is predominately expressed in the subendothelial layer and media of AVM vessels and in the intercavernous matrix and subendothelial layer in CCM lesions[32] **(Fig. 2–5)**. FGF2 is expressed in the media of AVM vessels and in both the subendothelial layer and the intercavernous matrix of CCMs.[32] The proportion of fms-related tyrosine kinase 1 (FLT1) and kinase insert domain receptor (KDR) immunopositive vessels is significantly greater in AVMs and in CCMs compared with control brain ($P < 0.05$).[85] Increased tyrosine kinase receptors (TEK) are detected in AVMs and CCMs compared with control brain (not statistically significant), and tyrosine kinase with immunoglobulin (TIE) was detected in rare vessels of all lesion types and brain.[85]

Compared with CCMs and AVMs, VMs rarely hemorrhage and are variants of normal venous drainage. Kilic et al.

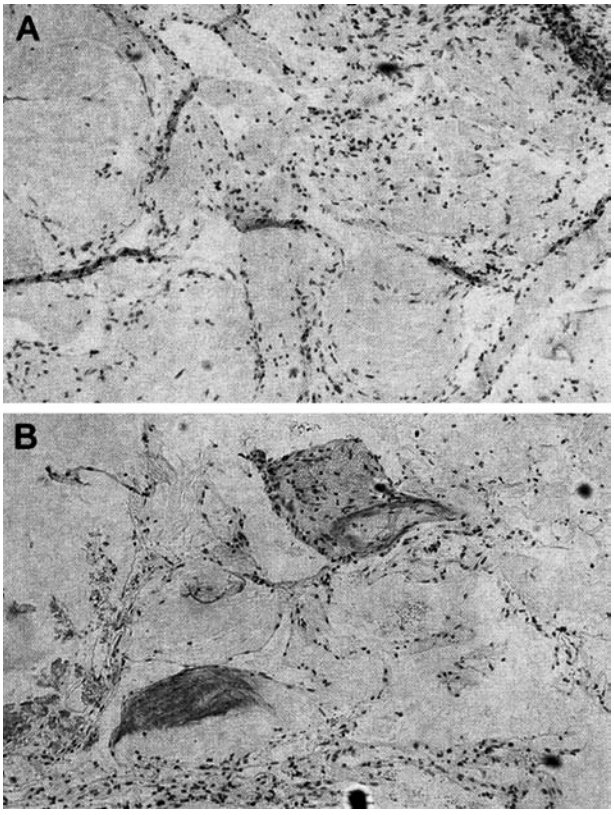

Figure 2–5 CM, VEGF expression. **(A)** control; **(B)** anti-VEGF. Note the staining of the intercavernous matrix and the endothelium. (From Rothbart D, Awad IA, Lee J, et al. Expression of angiogenic factors and structural proteins in central nervous system vascular malformations. Neurosurgery 1996;38(5):915–925. Reprinted with permission.)

described two VMs with negligible expression of angiogenic factors VEGF, FGF2, and TGFB suggesting they are angiogenically dormant.[84]

♦ Genetics of Cerebral Cavernous Malformations

Genetic Substrate of Familial Cerebral Cavernous Malformations

Families with CCM exhibit Mendelian inheritance at three chromosomal gene loci (CCM1, CCM2, CCM3). The *CCM1* gene was positionally cloned by linkage, haplotype, and mutation analyses mainly in CCM families with a Hispanic-American ancestral disease haplotype[24,86] in the 7q11.2-q21 region and a common mutation in *CCM1* that encodes the KRIT1 (Krev interaction trapped 1) protein.[21, 24,87,88] The *CCM1* gene consists of 20 exons spanning 45,799 base pairs (bp) and maps to the 7q11.2-q21 region. The start of translation appears to be in exon 5, and more than 88 different germline mutations distributed throughout the *CCM1* gene have been described in association with CCM in many different races.[13,23,24,89–91] Mutations in *CCM1* described to date all presumably result in CCM1 protein truncation. Germ-line *CCM1* mutations have been identified in apparently sporadic CCM cases with multiple lesions that were due to unrecognized familiality or spontaneous germ-line mutations.[86,92]

A novel gene, *MGC4607,* exhibiting eight different mutations was recently identified in nine families with linkage to the CCM2 locus.[16,25]

The Two-Hit Hypothesis of Lesion Genesis

Two different somatic mutations in *CCM1* were identified in DNA isolated from a lesion surgically excised from a patient without a family history of the disease and harboring a single CCM, supporting a two-hit hypothesis of lesion genesis.[93,94] Another study performed by Reich et al.[95] failed to identify CCM1 somatic mutation in 72 paraffin-embedded CCM lesions suggesting the role of somatic mutation requires further investigation. In the two-hit model, a vascular cell with two mutations (either germ line or somatic), resulting in complete loss of functional CCM1 protein, clonally expands to form a CCM lesion. Presumably, the multiple CCM lesions found in familial cases result from the same germ-line mutation found in every cell plus a different somatic mutation. Multiple lesions would not be the result of metastasis. Familial CCM exhibits an autosomal dominant mode of inheritance but is likely recessive at the cellular level, and lesion genesis may require two hits to the same gene.

Cerebral Cavernous Malformation Gene Functions

Since the identification of the *CCM1* gene, investigations have been focused on functional characterization of the CCM1 protein. Three functional domains have been predicted based on sequence homology with known proteins and protein-protein analysis using yeast two-hybrid screening. The two-hybrid system is set up to detect transcription of a reporter gene either by colormetric tests or selection for growth. Reporter gene transcription depends upon association of a DNA-binding domain, fused to a gene of interest, and a transcriptional activation domain fused to many different genes that may interact with the gene of interest. Protein-protein interactions are identified when a yeast colony grows or turns blue indicating the fusion protein containing the gene of interest is interacting with one of the fusion proteins containing the activation domain and allowing transcription of the reporter gene. The NPXY motif, in the amino terminal of CCM1, apparently binds integrin cytoplasmic domain-associated protein (ICAP1), suggesting CCM1 is part of the integrin signaling pathway (specifically with β_1-integrin complexes) and cell adhesion to other cells as well as to the extracellular matrix.[87,96,97] At least 8 of 22 integrin heterodimers are expressed on angiogenic and quiescent vascular endothelial cells including five with β_1-integrin components.[98] Integrins are activated by VEGF and FGF2 signaling in angiogenesis.[98,99] Ankyrin repeats, in the middle of the CCM1 protein, are thought to be involved in protein-protein interaction. The FERM domain found in exons 14 to 18 of *CCM1* has been found in proteins that link cytoplasmic proteins to transmembrane proteins. The carboxy-terminal of CCM1 interacts with Ras-related protein 1A (RAP1A) (alias Krev-1/Rap1a), a member if the Ras-family of GTPases, using a yeast two-hybrid screen suggesting a tie to the tumor suppression pathway possibly at the point where Ras becomes part of the integrin pathway.[87,97,100] The *CCM1* gene has an alternately spliced form missing the region required for Rap1a.[2] The *CCM1* gene is transcribed as a 3.5-kb message in brain and additional tissues not known to be affected in CCM patients (heart and muscle).[87,94,101] Recently, published data from Guzeloglu-Kayisli et al.[10] demonstrated that KRIT1 is expressed in a broad variety of human organs, where it localizes to the vascular endothelium of capillaries and arterioles of each organ. KRIT1 antibodies stained intensely where endothelial cells tend to adhere to one another like the blood-brain barrier, suggesting that additional cell type contributes to the pathophysiology of CCMs. Using CCM1 antibodies, CCM1 colocalizes with β-tubulin in endothelial cells in culture and is thought to interact with the cytoskeleton to determine cell shape through cell-cell and cell-matrix interactions.[102]

Whitehead et al. demonstrated using murine gene targeting that CCM1 is required for vascular development, and KRIT1-associated vascular defects are not secondary to disrupted neural patterning but secondary to disrupted genetic pathway important in establishing arterial identity.[103]

The *CCM2* gene encodes a protein with a phosphotyrosine-binding domain, similar to ICAP, and may lead to the formation of CCM by a similar mechanism involving altered regulation of integrin-mediated intercellular tight junctions.[16,25]

Sporadic versus Familial Cases of Cerebral Cavernous Malformations

The majority of patients (50 to 80%) with CCM are apparently sporadic without a known family history of CCM.[7,11] Single CCM lesions may be found in roughly 75% of sporadic cases and 8 to 19% of familial cases.[11,19,104,105] Examination of 202 cases with CCM1 mutations found 13% of cases with a single CCM lesion and 2.5% with no detectable lesion

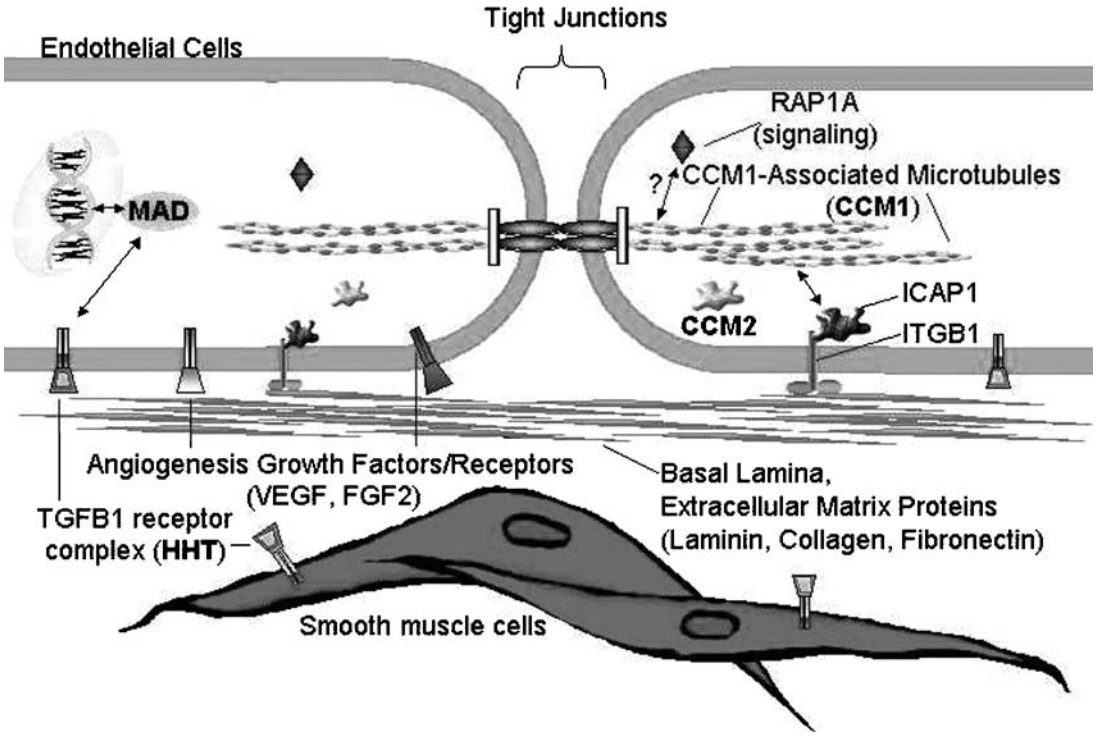

Figure 2–6 Depiction of some of the key molecular components implicated in vascular malformations. Cerebral cavernous malformation (CCM) protein (CCM1) interacts with Ras-related protein 1A (RAP1A), integrin cytoplasmic domain-associated protein (ICAP1), and microtubules. ICAP1 interacts with the integrin β_1 (ITGB1). CCM2, like ICAP1, has a phosphotyrosine-binding domain. Hereditary hemorrhagic telangiectasia proteins (HHT), endoglin (ENG), and activin receptor-like kinase (ACVR1) are part of the TGFB receptor complex and regulate transcription through mothers against decapentaplegic homologue proteins (MAD, alias SMAD). Epithelial-specific protein receptor tyrosine kinase (TEK; alias TIE2) mutations result in multiple cutaneous and mucosal venous malformations (VMCM).

using T2-weighted MRI.[19] The presence of multifocal lesions is indicative of familial forms of CCM. Conversely, solitary lesions and lesions associated with VM are less likely associated with familial disease.

Familial CCMs have been associated with gene defects likely impacting on endothelial cell cytoskeleton, and this presumably causes defects in interendothelial cell adhesions **(Fig. 2–6)** and defective maturation of proliferating capillaries in response to ongoing hemorrhage.

It is likely that sporadic lesions reflect a disruption involving the same respective genes within the lesions themselves (somatic mutations) or disruption of the same molecular pathways resulting in similar alteration of signaling and ultimately the same lesion phenotype as in familial cases. Hence, the genetic story of familial cases can hold the key to revealing molecular pathways for the genesis of familial *and* sporadic lesions.

♦ Genetic Modifiers and Multiple Gene Interaction

Genotype-Phenotype Correlations

Substantial intrafamilial heterogeneity is found in CCM1, supporting the hypothesis that clinical penetrance and severity of disease are dependent on additional factors both genetic and environmental. The clinical course for individuals with CCM lesions is quite variable and highly unpredictable even within families. One mutation, a C to T transition at position 1363 in exon 14 of *CCM1*, is common in the individuals with Hispanic-American ethnicity due to a *founder effect.* Initial estimates of CCM1 gene clinical penetrance are lower in the Mexican-American families than in Caucasian families suggesting the type of mutation may influence clinical manifestation.[22, 24,86] However, if the *CCM1* mutations all lead to a loss of functional KRIT1, different mutations would not be expected to contribute to clinical penetrance or symptoms. Forty-six percent of 72 Mexican-American subjects studied with the ancestral disease haplotype were clinically asymptomatic. Other factors including age[86] and sex[9] contribute to clinical manifestation. It is likely that part of the clinical variability may be due to differences in genes involved in the same CCM disease pathways or other genes involved in the development or maintenance of cerebral vessels. The additional genetic determinants of clinical phenotype may include mutations that obviously disrupt a gene's function or polymorphisms that are not sufficient to cause disease themselves. Obvious candidates for genetic modification are the genes implicated in heritable forms of cerebral vascular malformation disease. Genetic changes in the *CCM1* gene may affect disease caused by either the *CCM2* or *CCM3* genes. Characterization of the pathways involved in angiogenesis and maintenance will identify additional candidates that may modify cerebral vascular malformation disease phenotypes. In addition to genes modulating lesions genesis, there may be other genes causing or predisposing to lesion growth, hemorrhage, or associated epilepsy. Identification of disease

genes and modifiers of disease phenotypes will allow the integration of molecular genetics into more accurate prediction of disease manifestations and outcome.

Lesion Genesis versus Progression

Although a limited number of genes involved in lesion genesis have been identified, it is likely that many factors affect the ultimate manifestation of disease, including the modification of gene expression and the interaction of a myriad of other genes in association with disease severity or particular clinical manifestations.

Several components of the molecular pathways involved in causing and maintaining familial forms of cerebral vascular malformations have been identified. However, complex interactions are expected between proteins and other molecules that define the CCM lesions, necessitating the concurrent examination of pathways in more detail. Genes involved in angiogenesis and vasculogenesis are among those that may be involved in the genesis of vascular malformation lesions. Other genes, such as those involved in inflammation and immune responses, may contribute to lesion progression (i.e., subsequent development of the lesion after its formation), and other groups of genes may reflect lesion behavior (i.e., hemorrhage, epileptogenicity, etc.).

The application of differential gene expression technologies offers promise in identifying molecular signatures of clinical behavior and in defining mechanistic elements interacting in lesion pathogenesis.[106] Significant advances, including the prediction of some disease outcomes and the identification of new therapeutic strategies, have been made with the use of microarray technology.[107–110] Comparison of gene expression between two or more tissues allows identification of expression that is unique to a particular disease state. Differential gene expression may be related to genesis of disease or modifiers of disease manifestation. The expression profile of a disease state includes genes that may be targets for therapy.

♦ Differentially Expressed Vasculogenesis/ Angiogenesis Genes

Technology and Data Processing

Differential gene expression can be measured at the level of transcription (mRNAs) or protein and used for both confirmation and discovery of gene involvement in disease. Gene transcription is quantitated on cDNA or oligo arrays allowing simultaneous assessment of expression levels of thousands of genes. cDNA arrays are generally more sensitive for measuring less abundant mRNAs, and oligo arrays are generally more gene specific due to less cross-hybridization. Gene-specific cDNAs or oligos are attached to quartz wafers, glass slides, or nylon membranes and hybridized with cDNAs reverse transcribed from mRNAs isolated from the tissues of interest. Hybridization can be separate, one chip per isolated mRNAs, or combined with one color for each cDNA set. Gene expression array results should provide confirmation that the known disease genes may actually be differentially expressed and implicate previously unsuspected genes including genes with unknown functions.

Results from gene expression array experiments must be verified independently using Northern blot analysis, quantitative RT-PCR to confirm gene expression differences, and follow-up with in situ hybridization using gene-specific probes and hybridizing to tissue sections is necessary to characterize tissue-specific gene expression. Confirmed differential gene expression does not necessarily mean that the protein is at higher levels, and promising findings should be extended to include quantitation of protein expression. Identifying differential protein expression is more labor intensive and dependent on optimal separation of proteins. Proteomics allows the identification of hundreds of proteins, and mass spectrometric and other methods are available now for reliable and rapid quantification and identification of differentially expressed proteins in biologic tissues. When antibodies are available for specific proteins, immunoprecipitation, Western blots, and immunohistochemistry methods can verify protein quantification and determine tissue-specific expression. Proteomic studies in general would corroborate only a subset of the differential gene expression results (only proteins in sufficient quantities that can be resolved by 2D gel), and gene transcription levels do not always correlate with protein levels.[111]

Gene and protein expression data are compiled and analyzed with computer programs and using statistical analyses that take into account multiple (thousands) of comparisons. Normalization of expression levels per unit of tissue or mRNA, appropriate controls for differential expression, and the problem of tissue heterogeneity must each be considered in analyzing and interpreting the data. Advanced bioinformatics methods are being developed; including complex statistical approaches factoring groups of functionally related genes and proteins (such as those involving related pathways), rather than assuming independent expressions of each gene/protein.

The expectation that some vasculogenesis, angiogenesis, and disease-related genes are differentially expressed in cerebral vascular malformations has in part been confirmed[106] **(Fig. 2–7)**. Preliminary gene expression results identified 310 upregulated and 558 downregulated genes in both AVM and CCM compared with superficial temporal arteries (STAs) ($P = 0.012$) including differences in genes involved in growth factor signaling (decreased *ANGPT1,* increased *VEGF* [a trend], and increased *ENG* [endoglin, a TGFB receptor component]), decreases in a cell adhesion gene (*PECAM1,* alias CD31), decreases in an endothelium-specific gap junction (*GJA4*), and decreases in extracellular matrix genes (*LAMA3*, laminin; *SMTN*, smoothelin).[106] Increased protein expression measured by immunohistochemistry of *VEGF*[32,81,82,85] and decreased expression of *LAMA3* and *SMTN*[82] in both AVM and CCM compared with STAs is consistent with results of transcript quantitation.

In addition, CCMs showed unique decreased expression of a VEGF receptor (*KDR*), cell adhesion molecules involved in integrin signaling (*ITGB3*, integrin β3; *ROCK1*) when compared with AVMs and STAs. The AVMs showed specific differential gene expression of growth factor signaling molecules (increased *FLT1*, a VEGF receptor; decreased *TIE* and *TEK*, angiopoietin receptors), decreased integrin signaling molecules (*ITGB5*, integrin β_5; *ITGA6*, integrin β_6; *CTNNA1*, α catenin), and decreased *CCM1* gene expression.[106]

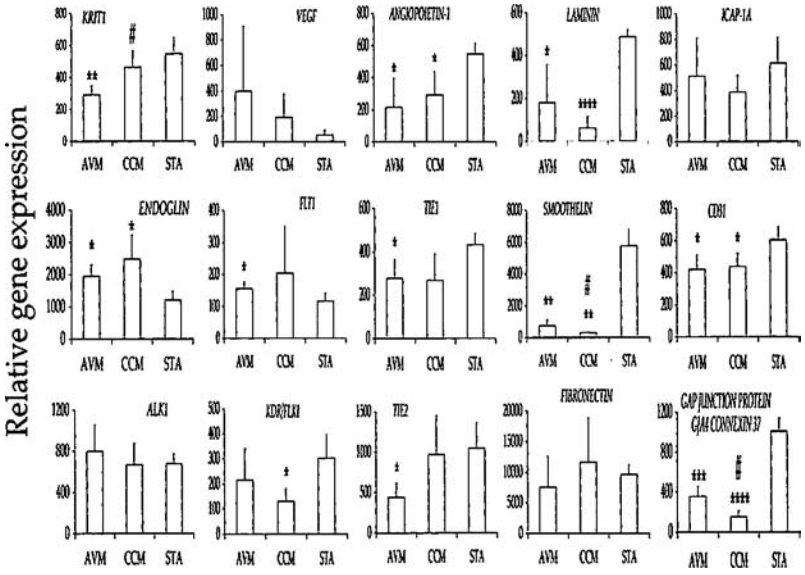

Figure 2–7 Bar graphs illustrating the differential mRNA expression of 15 relevant proteins identified by immunohistochemistry in arteriovenous malformations (AVMs), cerebral cavernous malformations (CCMs), and superficial temporal arteries (STAs). Expression is derived by averaging the fluorescence intensity for each gene after scaling chips to an average intensity of 500. $^{*}P < 0.05$ versus *STA*; $^{**}P < 0.01$ versus *STA*; $^{***}P < 0.001$ versus *STA*; $^{****}P < 0.0001$ versus *STA*; $\#P < 0.05$ versus *AVM*. (From Shenkar R, Elliott JP, Diener K, et al. Differential gene expression in human cerebral vascular malformations. Neurosurgery 2003;52(2): 465–478 . Reprinted with permission.)

Differential Gene Expression and Novel Discoveries

Additional expression profiles indicative of disease stage and prognosis might allow integration of molecular data into clinical decision-making. The preliminary results of differential gene expression have revealed possible evidence of a unique immune response within the CCM lesions. Thirteen immunoglobulin genes and a unique allele of the major histocompatibility complex were upregulated in CCMs compared with AVMs and STAs. Progression of CCMs may be caused by inflammation resulting from an immune response or hosts may have a unique immune predisposition.

In summary, genes involved in the growth, integrity, and maintenance of blood vessels and immune response may be important disease modifiers in CCMs. These modifiers may affect the severity of the disease, including lesion size and age at clinical presentation, or may be associated with specific clinical manifestations, including hemorrhage or epilepsy. These candidate genetic modifiers should be examined systematically, as individual genes and in related mechanistic and functional pathways, in relation to specific categories of lesion genotype, phenotype, and clinical manifestations.

♦ Future Research Directions

Enhanced Disease Classification

The field of cerebral vascular malformations has come a long way since the early classification schemes based solely on descriptive pathoanatomy and empiric clinical observations. Imaging advances, notably MR techniques and rigorous histopathologic features, have allowed the definition of distinct phenotypes and also endophenotypes representing clinically relevant disease states.[35,39,105] Terms such as *cryptic vascular malformations, angiographically occult vascular malformations, angiomas,* and *telangiectasias* have been replaced by more precise lesion nomenclature with biologic underpinning and clinical relevance. Familial CCMs are now correlated with specific gene loci. Imaging studies allow sensitive and specific lesion recognition and surveillance of disease progression (lesion genesis, progression, and clinical behavior). Special imaging sequences allow the recognition of mixed vascular malformations (including mixed CCM and venous malformations) and the occult precursors of clinically relevant lesions (gradient-echo imaging of baby CCMs).

Specific molecular markers are emerging for more sensitive and specific disease classification, as in CCM 1, 2, or 3. These may carry clinical or prognostic significance, as with Hispanic Americans of Mexican descent likely carrying CCM1 disease. Most sporadic CCMs still elude specific molecular classification, but it is clear that these lesions form by mechanisms affecting the same pathways as familial lesions, as in the recent discovery of somatic *CCM1* mutations in a case of solitary CCM with unaffected parents (no germ-line mutation).[94] The future holds much promise of classification of most lesions for more accurate diagnosis and prognosis.

Genetic Counseling

These advances have already affected practical clinical management. Multifocal CCM now calls for a thorough family history, and this in turn can uncover affected patients, previously unrecognized or misdiagnosed. Cases with myelopathy of unknown cause and others misdiagnosed as multiple sclerosis have now been clearly shown to represent unrecognized CCMs because of familial clustering. The management of epilepsy in the setting of CCM is vastly different if lesions are solitary or multiple on gradient-echo MRI.[113] The presence of associated venous anomaly calls for special surgical considerations, aimed at preserving the venous angioma.[35] The *CCM1* and *CCM2* genes can be directly screened for mutation in asymptomatic relatives of individuals with a familial form of CCM. Approximately 2.5% of cases with CCM1 mutations may not have CCM lesions on MRI and 37% may not manifest clinical symptoms.[19]

The epigenetics of CCM disease is starting to take shape. Genetic and environmental contributions to the likelihood

of de novo lesion genesis or of lesion progression are current considerations. Preexisting lesions has imposed rational surveillance strategies to accompany symptomatic follow-up. The counseling of women of childbearing age about pregnancy with CCM, options of management before and during gestation, and screening regarding possibly affected offspring has removed much fear and replaced anxiety with truly informed decisions.

More Accurate Prediction of Disease Progression

With more accurate molecular classification, careful correlation of genotype and phenotype will emerge, as well as the significance of surrogate endophenotypes in predicting disease behavior. Not all forms of disease will carry the same clinical associations or prognosis. The behavior of CCMs remains highly unpredictable, and it is clear that host, environmental, and gene susceptibility factors affect disease severity and specific clinical manifestations. The definition of these factors will allow better screening for patients harboring a particular lesion who are more likely to bleed or to develop intractable epilepsy, or there may be specific factors predicting individual lesion progression, and clinicians will learn to seek these factors in individual patients.

Molecular Modification of Disease

The modification of clinical phenotype is the ultimate goal of molecular medicine, and this is also true of vascular malformations. Gene or molecular therapy may soon be guided to the host with the aim of preventing lesion genesis or more likely to the lesions to make them less vulnerable to bleed, more sensitive to radiotherapy, less epileptogenic, or even to promote lesion involution altogether. Therapeutic vectors have been developed altering gene expression in endothelial cells,[114,115] and these could be delivered to lesions by endovascular or stereotactic routes.

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3

Pathology of Cerebral Cavernous Malformations

Huan Wang and Meena Gujrati

Cavernous malformations are one of the distinct and common clinicopathologic categories of vascular malformations, characteristically seen as a well-circumscribed lesion, consisting of enlarged vascular channels with no intervening parenchyma. They were first described by Luschka in 1853,[1] and Virchow[2] gave a detailed description in 1863. Until recently, there has been considerable confusion regarding the nomenclature. Cavernous malformations have previously been variably referred to as cavernous hemangiomas, cavernous angiomas, and cavernomas, all of which imply a neoplastic process, but these lesions are considered hamartomas and, therefore, cavernous malformation is the preferred and accepted term. They have also been included in the descriptions of angiographically cryptic or occult vascular malformations because cavernous malformations cannot be routinely detected on angiography. They were frequently mislabeled as arteriovenous malformations, especially when mixed features of vascular malformations were not recognized.[3] The neurosurgical importance of cavernous malformations has been increasingly emphasized, and computed tomography (CT) scanning and magnetic resonance imaging (MRI) have revolutionized their diagnosis.

♦ Incidence of Cavernous Malformations

In large autopsy series, cavernous malformations were estimated to range from 0.02 to 0.13% of the general population.[4,5] However, with the introduction of MRI, these lesions were found to be more common than previously thought, ranging from 0.2 to 0.4%.[6,7] Cavernous malformations appear to occur in every age group (range, 4 months to 84 years; mean, 34.6 years) with an approximately equal male-to-female ratio.[5,6] Most occur sporadically, but ~10 to 30% are part of a familial syndrome inherited as an autosomal dominant pattern with variable penetrance.[5,8] A gene responsible for familial cases has been mapped to chromosome 7q using linkage analysis.[9] A higher incidence of the familial form has been reported in a patient population of Mexican descent.[10]

♦ Prevalence by Anatomic Location

The majority (80%) of cavernous malformations are reported to be located supratentorially, but up to 15% occurred infratentorially, and 5% occurred in the spinal cord.[5,8,11] These frequencies are proportional to the volume of the CNS tissue in these different regions. In the cerebrum, the majority of cavernous malformations are cortical or subcortical with characteristic locations around the Rolandic fissure, but they can also occur in the basal ganglia, the periventricular white matter, corpus callosum, internal capsule, and lateral and third ventricles.[5] The most usual site in the posterior fossa is the brain stem, particularly the pons.[5] Cavernous malformations form 5 to 16% of all spinal vascular malformations. Most of these lesions involve vertebral bodies or epidural space; in contrast, intramedullary lesions are rare and tend to be distributed evenly throughout.[11–15] An association of spinal cord cavernous malformation with multiple malformations in the neuraxis has been well described.[16] Multiple lesions are common, ranging from 26 to 50% of patients.[10] The familial form of the disease is more typically characterized by the presence of multiple lesions.[10]

In rare cases, cavernous malformations have been reported to involve cranial nerve nuclei or cranial nerves, commonly in the optic nerve and chiasma, III, VII, and VIII nerves.[17] Intracranial extracerebral cavernous malformations are also very rare and have been reported in the cavernous sinus and in the region of cerebellopontine angle.[17–19] Dura-based cavernous malformations also occur and are usually seen in the middle cranial fossa.[17]

♦ Etiology

The precise mechanisms by which cavernous malformations develop remain elusive. Some are genetically transmitted through autosomal dominant patterns, but most appear to be sporadic in nature. Cavernous malformations have traditionally been presumed to be congenital lesions,[20] and reported cases of cavernous malformations in neonates support a congenital origin.[21,22] It is well documented that

lesions may increase in size with time due to small repeated hemorrhages, gradual thrombosis, or thickening and hyalinization of the walls of the vascular channels.[23,24]

Recently, de novo development of cavernous malformations has been observed in both sporadic and familial cases by serial MRI.[25] De novo cavernous malformations have also been reported after radiation therapy, surgical biopsy, and chemotherapy.[25–28] Spontaneous lesions have also been reported in association with pregnancy and were presumed to be hormone-related, but hormone receptors could not be demonstrated in the tissue by immunohistochemistry.[29]

Infection with the polyoma virus has been shown to induce the formation of multiple cavernous malformations in nude mice.[30] Thus, viral infections that cause hemorrhages followed by reactive angiogenesis resulting in the formation of cavernous malformations may explain their apparent de novo origins in some patients. Capillary telangiectases have also been suggested as precursors of cavernous malformations.[31]

♦ Clinical Presentation

Cavernous malformations are not benign entities as previously thought. The rate of hemorrhage has been reported as 13% per patient per year or 2% per lesion per year,[32] and only ~11 to 20% of cases may be truly asymptomatic.[33] Clinical presentation depends on anatomic location. Seizures, headaches, and progressive neurologic deficits are the three most common presentations.[32,33] Infratentorial lesions present more commonly with progressive neurologic deficits because of the space constraints.[5]

♦ Macroscopic Features

Cavernous malformations are well-circumscribed "mulberry-like" masses **(Fig. 3–1A)**. They may range in size from a few millimeters to several centimeters.[5] Examination of sections of the lesions typically shows a honeycombed lattice of multilobulated spaces filled with blood and thrombi in various stages of organization **(Fig. 3–1B)**. The thin-walled vascular spaces are interlaced with fine fibrous strands. The surrounding brain is gliotic in appearance and is characteristically stained yellow or brown by hemosiderin. Calcification and even bone formations may occur near the center of some large lesions.[4,34] Cavernous malformations are notoriously associated with developmental venous anomalies, which may or may not be appreciated on imaging studies but are frequently observed at surgery.[35]

♦ Histology

Histologically, cavernous malformations are characterized by a complex of vascular spaces of varying sizes without any abnormally large arteries, arterialized veins, or large venous outflow vessels **(Fig. 3–2)**. In contrast with normal capillaries, the vascular channels are lined with a single

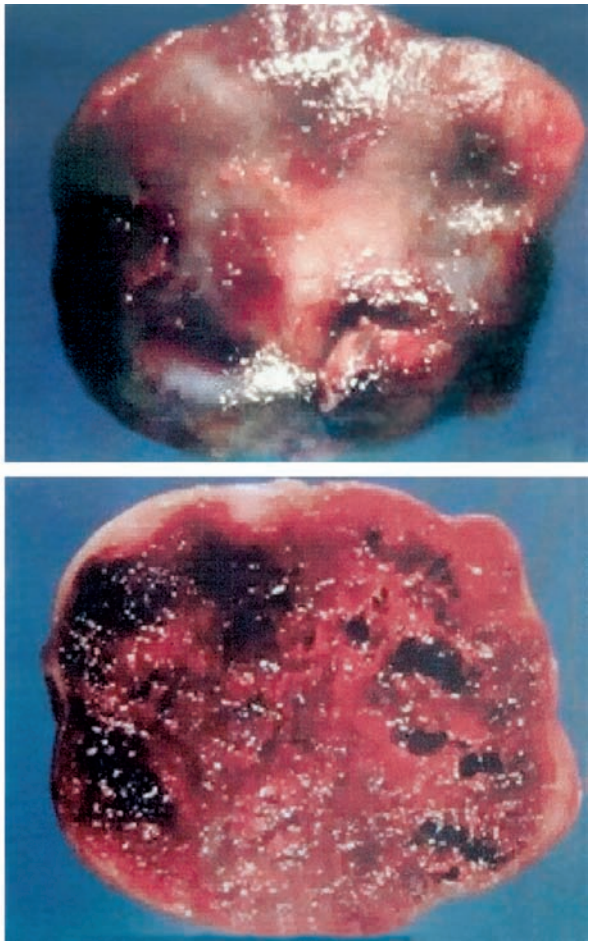

Figure 3–1 (A) Cavernous malformations are well-circumscribed, "mulberry-like" masses. **(B)** Cross sections typically show a honeycombed lattice of multilobulated spaces filled with blood and thrombi in various stages of organization.

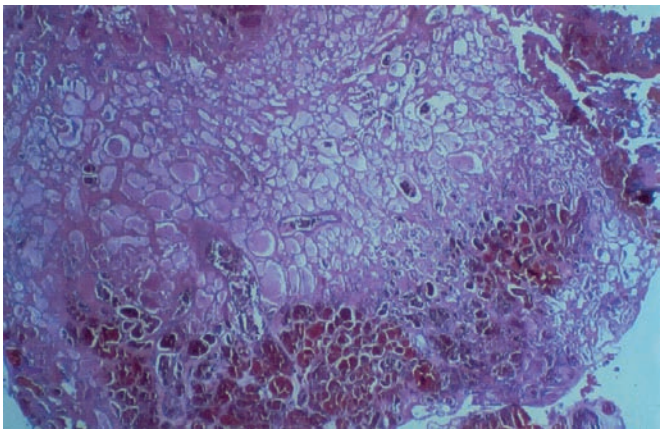

Figure 3–2 Histologically, cavernous malformations are characterized by a complex of vascular spaces of varying sizes with no intervening parenchyma (hematoxylin and eosin stain; magnification, × 20).

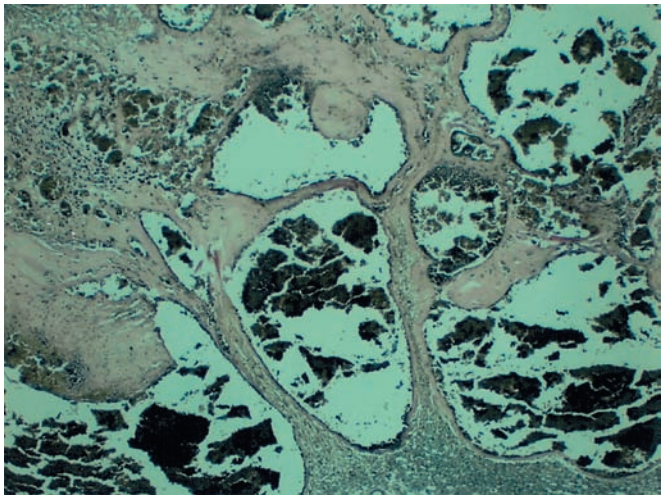

Figure 3–3 Micrograph showing thin- and thick-walled vascular spaces lacking elastin and smooth muscle fibers (EVG [elastase von Gieson] stain; magnification, × 40).

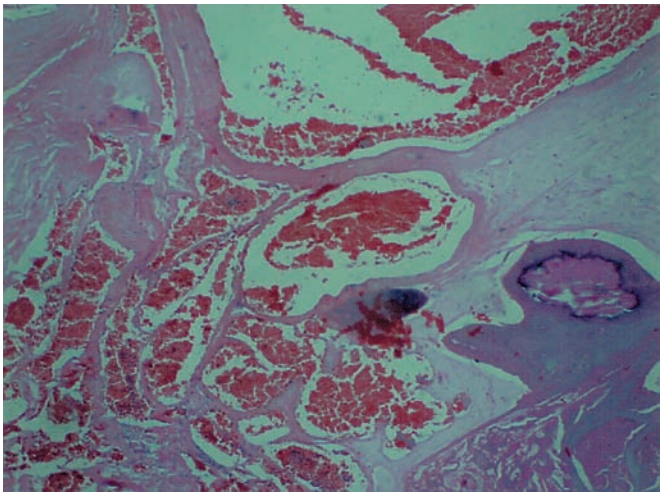

Figure 3–4 Micrograph showing focally thickened and hyalinized walls of vascular channels with a focus of calcification (hematoxylin and eosin stain; magnification, × 40).

layer of endothelial cells with no associated basement membrane. They do not contain elastin or smooth muscle **(Fig. 3–3)** but can show collagenous thickening as well as calcification **(Fig. 3–4)** and ossification. Although dense fibrillary neuroglial tissue may penetrate the mass, in general the vascular channels are arranged in a back-to-back pattern with little or no intervening brain parenchyma. Thus, cavernous malformations are distinguished from the classic capillary telangiectases in which neural tissue intervenes throughout the lesion.[36] There is often a peripheral margin of gliotic tissue containing hemosiderin-laden macrophages **(Fig. 3–5)**. Thrombi of varying age and degree of organization are usually present and cholesterol clefts, as evidence of previous hemorrhage, can also be seen. Endothelialized membranes within organizing thrombi may also be present.

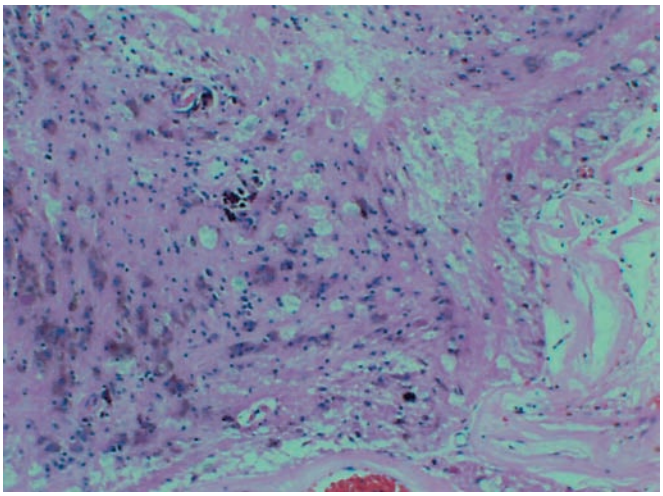

Figure 3–5 Micrograph showing the peripheral margin of gliotic tissue containing hemosiderin-laden macrophages (hematoxylin and eosin stain; magnification, × 100).

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4

Genetics of Cerebral Cavernous Malformations

E. W. Johnson and Joseph M. Zabramski

Cerebral cavernous malformations (CCMs) are vascular anomalies of the central nervous system (CNS) that affect 0.4 to 0.5% of the population.[1,2] CCMs occur in two distinct forms: a sporadic form and a familial, or inherited, form. Patients with the sporadic form usually have a single isolated lesion and no family history of neurologic illness. In contrast, the familial form is characterized by multiple lesions and a strong family history of seizures.[3] Indeed, the presence of multiple CCMs on magnetic resonance imaging (MRI) studies is almost pathognomonic for the familial form of this disease.[4]

In the recent MRI study of 132 confirmed carriers of the *CCM1*/*KRIT1* mutation, Denier and coworkers[5] reported that 80% of patients had multiple lesions on T2-weighted MR images and 90% had multiple lesions on gradient-echo images. The mean number of lesions per subject was 4.9 ± 7.2 on T2-weighted images and 19.9 ± 33.2 on gradient-echo sequences. Even in this highly selective population, 10% of confirmed *CCM1* carriers had only one lesion on gradient-echo MR images. Eight patients (all asymptomatic carriers) had no lesions identified on T2-weighted images, emphasizing the importance of gradient-echo imaging and a careful family history in diagnosing the familial nature of CCMs in some patients.

The first suggestion that CCMs might be a hereditary disease appeared in the German medical literature in 1928.[6] Sporadic reports of the familial occurrence of CCMs followed, but studies were hampered by the lack of a reliable screening tool to identify affected individuals.[7–9] In 1982, Hayman and colleagues convincingly demonstrated that the familial form of CCM was inherited as an autosomal dominant disorder.[10] Their report emphasized the variable clinical penetrance of this disorder as well as the limitations of computed tomography (CT) for the detection of these lesions.

By the mid-1980s, the MRI characteristics of CCMs were well established, for the first time making it possible to screen patients accurately for this disease.[11–15] In 1988, Mason and coworkers[16] and Rigamonti and colleagues[3] published reports confirming the autosomal dominant inheritance of CCMs in Hispanic families. In 1994, Kurth et al.[17] used linkage analysis on genetic material collected from patients in the latter study to map the affected gene, designated *CCM1*, to the long arm of chromosome 7. Subsequent work by this group and others rapidly confirmed linkage of *CCM1* to the same region of 7q and identified a founder effect in Hispanics of Mexican-American heritage: More than 70% of documented CCMs and almost all familial CCMs in this group can be attributed to mutations at *CCM1* from one common ancestor.[15,18–22]

Linkage to *CCM1* was also identified in non-Hispanic families. Within these studies, however, were reports of many families with either weak or no clear linkage to the *CCM1* locus. In 1998, Craig and coworkers[23] reported linkage to two additional loci: *CCM2* on the short arm of chromosome 7 (7p13-15) and *CCM3* on the long arm of chromosome 3 (3q25.2-27). Within the general population, 40% of families with familial CCM link to *CCM1*, 20% link to *CCM2*, and 40% link to *CCM3* or to other yet unidentified CCM loci.[23,24] This chapter reviews the available information on these loci, including the gene products and their potential role in the pathophysiology of CCM.

♦ CCM1

In 1994, collaborators at the Center for Medical Genetics in Marshfield, Wisconsin, and at the Barrow Neurological Institute in Phoenix, Arizona, linked the first gene for familial CCM, designated *CCM1*, to chromosome 7q in a large Hispanic family.[17,22] Subsequent work by these investigators and others led to identification of the *CCM1* gene at 7q21 as *Krev-1 interaction trapped 1* (*KRIT1*).[25,26] More than 100 mutations have been identified at the *KRIT1* locus.[24–39] All mutations identified to date are putative, loss-of-function mutations, including frameshifts, nonsense, and invariant splice site mutations.

As its name implies, *KRIT1* was initially identified because of an interaction with Krev-1/Rap1a, a member of the Ras family of guanosine triphosphatase (GTPases) with tumor-suppressor activity for Ras oncogenes.[40] Thus, initial hypotheses for mechanisms of CCM1 pathogenesis focused on KRIT1 as a regulator of Rap1a-dependent cell proliferation. Extending this theme, Rap1a functions as a Ras antagonist. Loss of *KRIT1* in CCM1 patients was hypothesized to perturb this molecular relationship.[41] In this model, *KRIT1* acts as a tumor-suppressor gene.

In support of this hypothesis, the Krev-1/Rap1a pathway is known to be altered in type 2 tuberous sclerosis (TSC2), an autosomal dominant condition characterized by benign neurocutaneous tumors.[42,43] The TSC2 gene product, tuberin, functions as a tumor-suppressor protein for Krev-1/Rap1a. Somatic inactivation or loss of heterozygosity of the wild-type tuberin allele in TSC2-associated tumors leads to unregulated growth.[43,44] A two-hit model, with a central tumor-suppressor function for KRIT1 in CCM1, would be similar to the mechanism of tuberin inactivation in TSC2. In this model, mutations in *CCM1* would lead to unregulated endothelial proliferation. Although a possible mechanism, the dilated capillaries observed pathologically in these lesions appear to reflect a defect in organization or adhesion more than in proliferation.

Since the initial identification of *KRIT1* by its association with Rap1a, the *KRIT1* sequence has been verified to encode for an additional 207 amino acids at the 5′ end of the cDNA.[37,45] Importantly, this additional segment has been shown to harbor multiple *CCM1* mutations.[24,33,36,37,46] Two groups have subsequently identified integrin cytoplasmic domain-associated protein α (ICAP-1α) as a KRIT1-binding partner for this extended protein.[47,48] ICAP-1 α is a modulator of β_1 integrin signal transduction, a means whereby mammalian cells sense and respond to the extracellular matrix as well as to other cells.

In a vascular context, integrins are crucial in the regulation of cell adhesion and migration during angiogenesis.[49] Antibodies to β_1 integrin block the formation of capillaries, and β_1 null cells fail to form blood vessels when tumors are implanted in mice.[50–52] Maturation of blood vessels in the CNS is accompanied by marked upregulation of β_1 integrin expression, suggesting that integrins are also important in maintaining endothelial function in the adult CNS.[53]

Using in situ hybridization, Denier et al.[54] have demonstrated that KRIT1 is expressed preferentially in neural and epithelial tissues in both the embryonic and adult mouse. Immunohistochemical staining with antibodies to KRIT1 protein demonstrated a similar distribution in human tissues.[55] KRIT1 localizes to the vascular endothelium of capillaries and arterioles in a broad variety of human organs. In the brain, expression was identified in both the endothelial cells of the capillaries and in the astrocytic foot processes that make up the blood-brain barrier. These findings suggest that perturbation of integrin-mediated cell adhesion via the KRIT1/ICAP-1α pathway may result in impaired formation or maintenance of capillaries.

To explore the role of CCM1 in development, Whitehead and colleagues[56] generated a *CCM1* mutant allele in the mouse. Heterozygous mutant mice ($CCM1^{+/-}$) were phenotypically normal and indistinguishable from wild-type embryos; however, homozygous mutant embryos ($CCM1^{-/-}$) suffered from generalized developmental arrest in midgestation and were disintegrating by E10. Defective development in $CCM1^{-/-}$ embryos was first observed in the vascular system in the vessels of the cephalic mesenchyme. These vessels are destined to invade the neural tube and begin formation of the intracranial vasculature at E10.0, a stage of development that the homozygous mutant embryos fail to reach. The precursor vessels become progressively dilated, reminiscent of the dilated endothelial sacs observed in the lesions of patients with CCM1.

Using in situ hybridization Whitehead et al.[56] demonstrated that the vascular defects in CCM1 mice are associated with the loss of arterial endothelial markers and subsequent failure of smooth muscle recruitment to the developing arteries. They found that the expression of the arterial-specific mammalian NOTCH genes (*DLL4* and *NOTCH4*) was significantly downregulated in $CCM1^{-/-}$ embryos before the gross appearance of the mutant phenotype. Given the observed similarities between the enlarged vessels in $CCM1^{-/-}$ embryos and human CCMs, the authors speculated that a similar disruption of arterial identity might underlie the pathology of cavernous malformations in patients with CCM1. Using antibodies against human NOTCH4, they examined previously excised cavernous malformations from three patients with familial CCM1. They were unable to detect NOTCH4 expression in the cavernous malformations. NOTCH4 expression was also reduced markedly in the arteries of the brain tissue adjacent to the vascular malformation. Control preparations from unaffected individuals showed prominent expression of NOTCH4 in arterial endothelium and smooth muscle cells.

Because CCM1 is an autosomal dominant disease in humans, it was expected that heterozygous knockout mice would be an appropriate model for the disease. However, careful screening over multiple generations revealed no vascular abnormalities in the brains of $CCM1^{+/-}$ animals. As mentioned, complete loss of *CCM1* ($CCM1^{-/-}$) from a defect in arterial morphogenesis is lethal in midgestation. These findings have led to speculation that the formation of cavernous malformations requires a somatic loss of the wild-type allele. In sporadic cases of CCM, two independent somatic mutations would be required in the same cell, whereas in the familial form only one somatic mutation would be required. This two-hit model would explain the focal, randomly scattered nature of the lesions in patients with the familial form of the disease.

In support of this hypothesis, Plummer et al.[57] have recently reported that loss of the tumor suppressor gene *p53* sensitized mice with the *CCM1* mutation to form cerebral vascular malformations. The authors crossed mice that were heterozygous for *CCM1* and homozygous for loss of the tumor suppressor gene *p53*, which has been shown to increase the rate of somatic mutations. They found cerebral vascular malformations that were double mutants ($CCM1^{+/-}$ $p53^{-/-}$) in 55% of animals, but not in other genotypes. Pathologically, the vascular lesions had many of the characteristics of cavernous malformations. Importantly, loss of *p53* alone ($CCM1^{+/+}$ $p53^{-/-}$) was not associated with development of vascular malformations.

♦ CCM2

In nature, a single phenotype may arise from mutations of multiple genes that converge on a common cellular pathway. Hereditary hemorrhagic telangiectasia (HHT) is a well-documented example of a vascular disease in which mutations involving three separate genes produce a common phenotype by three coded proteins that form a heteromeric complex in the same signal transduction pathway.[58] Likewise, multiple genetic loci have been identified in families with CCMs and are suspected to converge on a common signaling pathway. In 2003, Liquori et al.[59] identified

the *CCM2* gene at 7p13 as *MGC4607*, a known gene of unknown function, and named it *malcavernin*. Eight mutations were identified in nine families with one shared mutation. The mutations, which map throughout the *MGC4607* gene, include five frameshift, one nonsense, and two splicing mutations, each of which would result in a truncated protein. *MGC4607* was selected as a potential candidate for mutation sequencing because its translated protein product encoded a phosphotyrosine-binding (PTB) domain. This same domain is found in ICAP-1α, a binding partner of the CCM1 gene product KRIT1. Subsequent work by Denier et al.[60] confirmed identification of *MGC4607* as the *CCM2* gene in an additional 10 families. In this second study, mutations in the *MGC4607* gene included two large deletions and eight additional point mutations.

The *MGC4607* gene has been reported in several genome databases, but little is known about its function. It extends over 76 kb and includes 10 coding exons. The coding portion of the cDNA is 1323 bp long and encodes for a 444-amino-acid predicted protein. MGC4607 is highly expressed in skeletal muscle, heart, liver, and brain. The presence of a PTB domain in MGC4607 predicts a possible interaction with the CCM1 protein, KRIT1, or with β_1-integrin. MGC4607 may complete with ICAP-1α to regulate β_1-integrin signaling.

♦ CCM3

Bergametti et al.[61] recently identified the *CCM3* gene at 3q26.1 as *PDCD10* (*programmed cell death 10*). Seven distinct deleterious mutations were identified in seven families. There were three nonsense mutations, three splicing mutations, and one large deletion. *PDCD10*, also known as *TRAF15*, was initially identified by screening for genes differentially expressed during the induction of apoptosis in the TF-1 premyeloid cell line. This gene is upregulated in a fibroblast cell line exposed to specific apoptosis inducers.[62] Its cDNA extends over 50 kb and includes seven coding exons and three 5′ noncoding exons. Three alternative transcripts encoding the same protein, differing only in their 5′ untranslated regions (UTRs), have been identified for this gene. The coding portion of the cDNA is 636 bp long and encodes a 212-amino-acid predicted protein. Searches of the protein databases with the coding sequence of *Homo sapiens PDCD10* failed to reveal any known transmembrane or functional domains. Northern blot analysis of human tissues using the entire cDNA as a probe revealed ubiquitous expression in all tissues except colon.[61]

These preliminary data suggest that this gene, which is highly conserved from invertebrates to humans, plays a role in apoptotic pathways. The role of this protein in angiogenesis and its link to KRIT1 and MGC4607 remain to be investigated.

♦ CCM4

Initial estimates suggested that 40% of individuals with familial CCM might be linked to the *CCM3* locus,[23,63] but recent data indicate that this number is too high. In a report by Bergametti et al.[61] identifying the *CCM3* gene, mutations in the *PDCD10* gene were identified in only 8 to 20 families with the CCM phenotype. Because the 20 families in this study were included on the basis of a negative screening for *CCM1* and *CCM2* mutations, a higher proportion of *PDCD10* mutations would have been expected. This observation is supported by additional research from Doug Marchuk's group at Duke (D. Marchuk, personal communication, 2005) who found a *CCM3* mutation in only 10% of families without a *CCM1* and *CCM2* gene mutation. Although several hypotheses can be raised to explain this discrepancy, the authors concluded that the possibility of a fourth CCM gene cannot be excluded.

♦ Conclusion

Familial cavernous malformations result from mutations affecting at least three distinct loci. Based on available data, at least two of these loci (*CCM1* and *CCM2*) appear to be involved in the regulation of β_1 integrin signal transduction, which plays a crucial role in the regulation of cell adhesion and migration during angiogenesis. The third locus (CCM3) involves an apoptotic pathway. The role of the latter in angiogenesis and its link to KRIT1 and MGC4607 in the formation of cavernous malformations remains to be investigated.

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5

Cavernous Malformations as Dynamic Lesions: De Novo Formation, Radiologic Changes, and Radiation-Induced Forms

Eugenio Pozzati

Cavernous malformation (CM) (and its synonyms cavernous angioma and cavernoma) occurs in an estimated 0.45 to 0.9% of the population and in two forms, sporadic and familial. Mutations in *KRIT1*, a gene located at the CCM1 locus on chromosome 7q21 that helps determine endothelial cell shape and function, are responsible for the majority of inherited cases.[1,2] Until recently, CM was considered congenital in relation to a developmental but yet unsettled event disrupting local capillary-venous pattern formation between the third and eighth week of gestation[1–4]: The finding of intrauterine CMs confirms this origin.[5] However, an increasing number of "de novo" lesions have recently been reported suggesting different mechanisms of induction.[6–12] The relationships and reciprocal prevalence between congenital and acquired CMs are still obscure.

Whatever the origin, the end result is a lesion consisting of closely packed sinusoids lined by endothelium and filled with slow-flowing blood, thrombotic material, and hemorrhagic cysts separated by reactive connective strands. This fibrosis of the walls of the cavernomatous vessels suggests that other cells in the subendothelial layer must be present to produce this reaction and participate in the pathophysiology of CMs.[13–15] Substantial interendothelial cell gaps evidenced by electron microscopy may explain the tendency for CMs to undergo repetitive microhemorrhages, which constitute the basic, but not unique, mechanism leading to the main clinical manifestations (headache and seizures) and ignite a cascade of pathologic events responsible for the progression of the disease.[15,16] If compared with the other cerebrovascular malformations (arteriovenous malformation [AVMs], telangiectasis, and venous angioma), CMs demonstrate unique dynamic peculiarities (growth and de novo occurrence) and changeable hemorrhagic propensity, which reflect their uncertain behavior suspended between a vascular malformation and a hamartoma.

With telangiectasias and thrombosed AVMs, CMs traditionally belong to the old subgroup of "angiographically occult" vascular malformations characterized by an almost imperceptible and elusive flow; computed tomography (CT) scanning partially made up for this diagnostic failure, but only magnetic resonance imaging (MRI) proved to be very sensitive for detecting CMs and has greatly increased accuracy of their diagnosis. The concept of an "acquired" cavernoma arose only when the de novo appearance of this lesion was observed in patients with previously normal MRI. It is likely that MRI does not cover the full spectrum of the disease. It is possible that at an early and fugitive stage of their development, CMs do represent a discrete functional abnormality that may be "MRI occult" and may appear only later as a "de novo" lesion after initial bleeding.[17]

When CT scanning began to detect an increasing number of CMs at the end of the 1970s, the impression was that of a solitary, epileptogenic, and indolent lesion. The first retrospective studies indicated a bleeding rate of 0.5 to 0.7 per year.[3,4] However, the increased experience gained with the introduction of MRI, the better knowledge of the familial form of the disease, the unpredictable hemorrhagic course, the better understanding of neoangiogenesis, and the de novo appearance of some lesions have greatly changed our thinking. Are we facing a lesion that for environmental, genetic, or host factors is changing its behavior? Is the familial form not only better diagnosed but also expanding? Are de novo lesions more the rule than the exception?

The role of altered angiogenesis in the behavior of CMs has been recently explored: A complex disturbance involving vascular growth factors and several structural and matrix proteins (fibronectin in particular) contributes to the formation and growth of these lesions.[18] Genetic factors, irradiation, and infection have all been implicated in the genesis of CMs.[9] Thus, their origin is not only multifactorial but also modulated by host elements (age, sex, location) that greatly influence the hemorrhagic tendency of the malformation. Cavernomas represent primary malformative lesions made up of abnormal vessels formed in response to injury occurring both during embryogenesis and, as also demonstrated, during one's lifetime.[18,19] Besides a genetic origin, cavernomas may represent a "convergent" vascular disease consisting of a labyrinthic aggregate of endothelial-lined connective tissue channels resulting from chronic hemorrhages and recanalization events[20,21] or from

thrombosis of small veins and/or venous hypertension triggering the formation of a capillary proliferation.[22]

Compared with the spectrum of cerebrovascular malformations, the CM is a primitive entity consisting of immature proliferating vessels, and it reasonably represents inappropriate vasculogenesis without subsequent angiogenesis.[23] This original and discrete endothelial structure may be targeted by an array of intra- and extravascular factors leading to the mature malformation[7] as is commonly believed and imaged.[24] The slow growth and hemorrhagic potential of CMs is mainly related to the interplay between passive processes (blood-flow and osmotic changes) and active factors both on the hematic component (fibrinolytic activity), the vascular wall (endothelial proliferation and angiogenesis), and the connective matrix. The growth patterns of CMs were mainly attributed to repeated intralesional hemorrhage and thrombosis, to recanalization of thrombotic material, to the expansion of hemorrhagic cyst cavities, to the deposition of hemosiderinic pigments, to calcification, and to reactive gliosis.[6,7] At the same time as hemorrhage stimulates fibroblasts and connective tissue proliferation leading to "mature" CMs, fibrous "pseudopodes" and connective laces may also connect CMs to satellite telangiectasias[25,26] providing further recruitment of new vascular spaces. Even though it generally represents a slow reparative process, growth by active connective tissue proliferation with reendothelialization and neovascularization may occur very rapidly.[27] In this form, some CMs complete the development to true vascular hamartomas, with strong growth potential and low hemorrhagic risk. Frim et al.[28] demonstrated that the fibrinolytic activity of tissue plasminogen activator in the endothelial cells of CMs may account for rebleeding and progressive growth. More recently, some immunohistochemical studies have addressed the influence of neoangiogenesis and endothelial proliferation in the development of CMs in response to hemodynamic stress, ischemia, or hemorrhage and mediated by several vascular growth factors in the lesion, the surrounding parenchyma, and serum.[29–34] A proliferative activity was confirmed by the staining of endothelial cells with proliferating cell nuclear antigen (PCNA), an antibody used as a proliferation marker, in the walls of CMs.[29]

In cavernomas, different areas are generally observed: PCNA-positive areas, composed of thin-walled capillaries, can be opposed to PCNA-negative and less cellular thick-walled areas. Lacy walls arranged in small and dense blood cavities are believed to precede thick walls in the evolution of cavernomas.[29] The concept of different compartments in the same lesion is also confirmed by the different expression of angiogenic factors in some caverns but not in others.[18] Sure et al.[29] have recently demonstrated the expression of the vascular endothelial growth factor (VEGF) and its receptor fck1 in CMs, suggesting angiogenic activity and potential de novo generation in these lesions. Neoangiogenesis and hemorrhage of cavernomas may be interconnected in a continuum of growth and hemorrhage. A trend toward an increased Ki67 proliferative index has been found in the endothelium of CMs with recent hemorrhage as compared with nonhemorrhagic lesions.[30] Endothelial proliferation and neoangiogenesis occur not only within the malformation but may also be triggered at the periphery of the lesion. A strong expression of basic fibroblast growth factor, a potent mitogen inducing angiogenesis, was found in surrounding astrocytes and might lead to the proliferation of endothelial cells and formation of the vascular spaces typical of cavernomas.[32] In extreme cases, intracranial tumors may induce erratic angiogenesis and the development of de novo vascular anomalies.[33] The powerful impact of vascular growth factors in the pathophysiology of CMs was demonstrated in one of our cases with a de novo CM inside a glioblastoma in a patient affected by the multicentric disease.

The complex pathologic hematic turnover and fibrous proliferation of CMs are most clearly seen in MRI, which is able to detect CMs mostly by the clotting or hemorrhage that has taken place in the malformation. Zabramski et al.[35] divided CMs into four types, which probably also represent different and changeable stages of evolution and clinical significance in an ordered progression of hematic changes.[35] De novo lesions offer the opportunity to better study the kinetics of these lesions and a possible clinico-radiologic correlation, both in the familial and nonfamilial (in particular postirradiation) subgroups, which differ in their evolution. MRI of a de novo CM is varied and reflects the pathogenesis of the lesion. For example, type I lesions are typical of postirradiation CMs, whereas type III lesions are more common in the familial form of the disease. In general, if type I and II correspond with dynamic expressions of the disease, type III signal characteristics might represent chronic lesions that are no longer hemorrhaging.[35] Recently, increased VEGF expression has been found in a type III lesion, suggesting that the CM may also be dynamic at this stage.[36] It is unclear if the changes from type I to III correspond with passive turnover of the hemorrhagic and thrombotic material or to remodeling with the regression of supernumerary vessels and the intervention of apoptotic factors in the biological behavior of this lesion.[37]

Type IV lesions represent the basic entity of the known pathologic spectrum of CMs and possess the potential of leading to the other types of lesions. Thus, they may represent capillary telangiectasias, true minute CMs, or a basic "hemorrhagic capillary malformation."[38,39] They appear in MR images as punctate hypointensities due to the susceptibility of microscopic deposits of hemosiderin and the original hemorrhage. MRI studies must include gradient-recalled echo (GRE) sequences documenting the absence of nascent lesions en route to a full-blown CM. Contrast enhancement may further help differentiate telangiectasia from CM.[39] Dynamic signal changes in serial follow-up MR images have demonstrated that type IV lesions are rather stable and only rarely complicated by overt bleeding.[38] This supports the theory that de novo lesions generally result from an abrupt hemorrhagic event in a differing pathogenetic context.

A precursor or nascent CM that may evolve into a mature lesion is often alluded to. This undefined structure has never been imaged, probably because it represents a functional phase of the malformation, and an intact CM may initially demonstrate extremely subtle signal changes not detected by MRI.[17] This hypothesis has been confirmed in patients with seizures and normal MRI who later develop a CM[40] supporting the existence of a "cryptic" cavernomatous state, a sort of hypothetic and fugitive "type V" lesion. We may have observed one of these cases, characterized by appearance and involution of a de novo thalamo-mesencephalic CM in a woman with multiple bleeding lesions

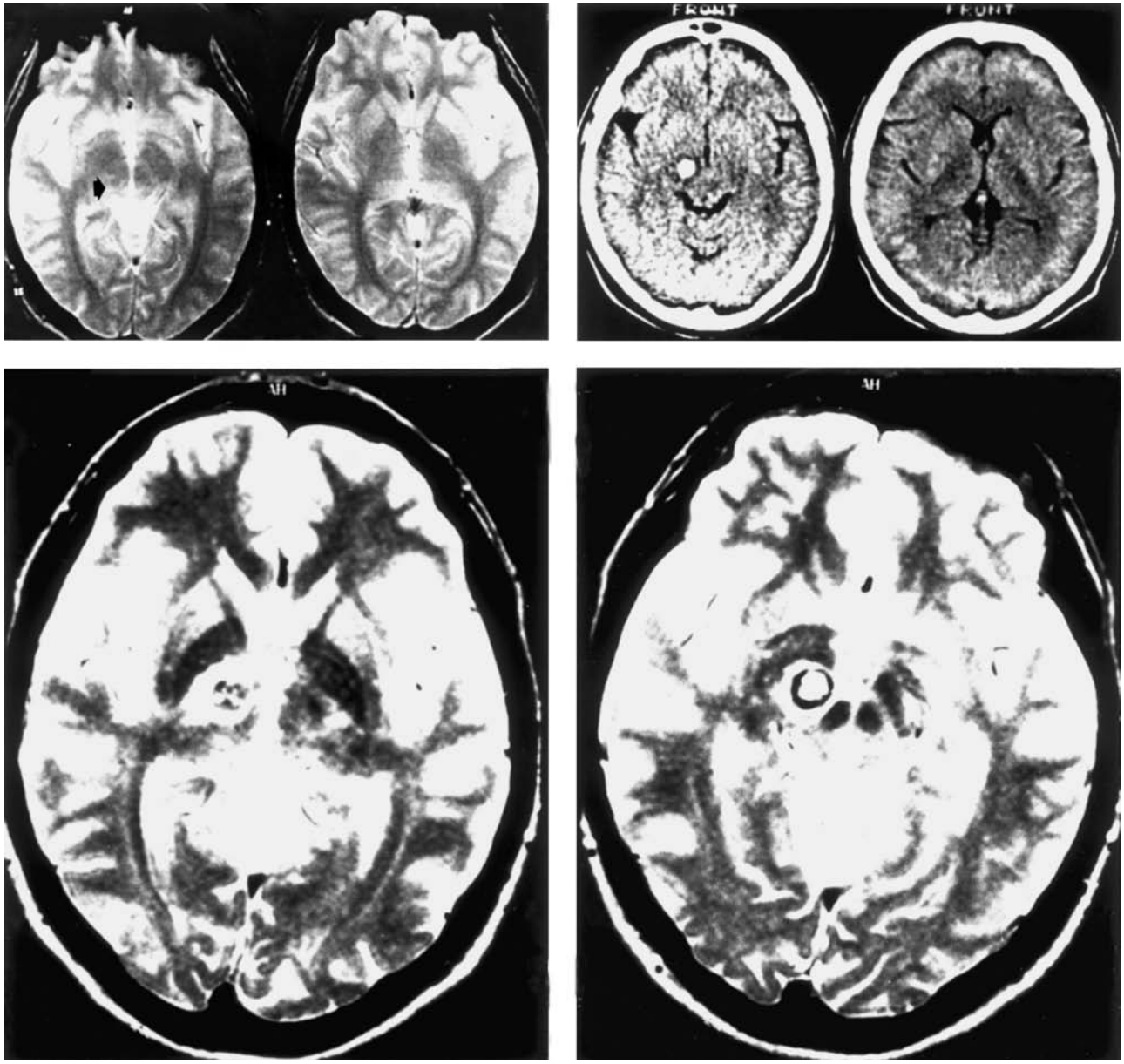

Figure 5–1 (A) Axial MR image of a 36-year-old woman with recurrent seizures secondary to a hemorrhagic CM of the right motor strip (not shown). The right thalamic region was considered initially normal, but further retrospective consideration disclosed a faint marginated hypointensity in the thalamo-mesencephalic region (*arrow*) at the site of the subsequent hemorrhage**. (B)** CT scan 15 days later, performed after sudden diplopia and left arm dysmetria, showing a subthalamic hemorrhage. **(C, D)** Axial MRI 1 month later showing the growth and hemorrhage of a thalamo-mesencephalic CM. The patient was managed conservatively: MRI at 1 year showed chronic hemorrhage with hemosiderin staining at the affected sites (not shown).

(Fig. 5–1). In a retrospective evaluation of MRIs, a faint, almost imperceptible, roundish hypointensity preceded (by a few days) the hemorrhagic onset and the late growth of the malformation, followed by its complete regression over 6 months. It is difficult to say if this course represented a vascular engorgement preceding the hemorrhagic onset or some endothelial build-up of the malformation. In keeping with this evolution, CMs may subsequently arise at the site of resolved intracerebral hematomas,[41] emphasizing their deceptive autodestruction and possible late formation.

All these factors are the necessary foundation for the in-depth discussion of de novo CMs. We have divided de novo CMs into two groups on the basis of their differing pathogenesis: familial and nonfamilial (postirradiation, hemodynamic, "convergent," and cryptogenetic).

♦ De Novo Familial Cerebral Cavernous Malformations

The familial form is treated elsewhere in this book, and it will be considered here only for its relevance to de novo formation of CMs. Its prevalence is increasing and may account for 30 to 50% of all CMs.[35] Zabramski et al.[35] were the first to document the de novo appearance of new lesions in

the familial form at a rate of 0.36 new lesions per patient per year in families of mostly Hispanic-American origin. Many of these new lesions were classified as type III and were asymptomatic. Type I lesions were found in 25% of the patients and were clinically silent. The incidence of symptomatic hemorrhage was 1.1% per lesion per year and 6.5% per patient per year.[35] Labauge et al. in their French series found a similar de novo formation rate of 0.4 new lesions per patient per year,[42] confirming a similar clinical trend in a different ethnic group.

Conversely, MRI of de novo nonfamilial (postirradiation in particular) CMs is often represented by a type I appearance indicating a prevalent hemorrhagic onset of the malformation with neurologic disturbances occurring in about half of the cases.[7,8,12] At this stage, the "mural" angiomatous nodule is minimal, and the main bulk of the lesion is constituted by blood. An escalation of hemorrhagic risk is found when sporadic, familial, and acquired CMs are compared. In one series of prospective MRI of CMs, type I characteristics occurred in only 6% of the lesions on initial examination.[43] In a series of familial CMs, type I CMs occurred in 16% of the cases,[35] and de novo lesions in the familial form had the type I pattern in 26% of the cases.[44] In our patients with de novo nonfamilial CMs, type I lesions occurred in around 70% of the cases, suggesting that a type I CM is highly indicative of the hemorrhagic onset of a de novo lesion. However, in some cases de novo CMs appear as a true growth of a compact tissue made up of a tangle of fibroendothelial spaces without apparent hemorrhage, the so-called cavernomatous matrix,[25] characterized by a peculiar "honeycomb" appearance without a dark ring on MR images and definitely supporting the intervention of angiogenic factors.

An open question in the familial form is the impact of "anticipation," which refers to the decrease of age at symptom onset in an inherited disease, increased severity in subsequent generations, or both.[45] The International Familial Cavernous Angioma Study (IFCAS) group found anticipation in age at symptom onset but not in the severity of the disease and suggested that, although one gene determines the occurrence of CMs, a second gene could affect the growth and size of angiomas, and, therefore, the onset of clinical manifestations. It is unclear if anticipation corresponds with a de novo occurrence or to an early clinical onset of a preexistent lesion. The observation of an early and aggressive onset in childhood may contrast with minor symptoms in relatives who are carriers of the mutation and should warn of the possible intrusion of an environmental factor and of a "modifying" gene.[1,45,46] Some authors have also noted an unusual increase in the number of de novo lesions after the age of 50, suggesting a modification of the epidemiology[47] and clinical activity in older patients. We have found a de novo type III lesion and a hemorrhagic CM in an 86-year-old patient with multiple CMs, confirming the continuing progression of the disease throughout one's lifetime.

Multiplicity, which is a landmark of the familial disease, occurs not only in the inherited form. Multiple and de novo lesions have also been described in patients with apparently sporadic CMs.[46,48] Although low penetrance in some families cannot be excluded, de novo mutations in the *KRIT1* gene have been demonstrated in patients with multiple and nonhereditary CMs.[48] The patient described by Lucas et al.[46] had an inheritable condition, representing a "founder" for a new lineage of individuals with familial CMs. This subgroup of multiple nonfamilial CMs is again poorly defined in terms of natural history and epidemiology. The rate of de novo lesions may be higher than that in familial cases. In eight patients with multiple and de novo nonfamilial CMs we have recently studied, new lesions were detected at a mean interval of 1.6 years and were sometime characterized by simultaneous activity (bleeding and growth) at multiple sites in a "crescendo" of hemorrhages, which we have called *cavernomatous crisis*.[49,50] This finding may suggest that multiple nonfamilial CMs tend to occur synchronously, whereas the familial form is characterized by a more gradual progression. A case of multiple sporadic CMs showing aggressive behavior has recently been reported. In this case, endothelial proliferation induced by a spike of serum VEGF has been suggested as a possible mediating factor[36] and disease progression was positively altered by the administration of glucocorticoids. Surgery is problematic in patients with multiple symptomatic CMs, and the suppressive effects of glucocorticoids on serum VEGF levels may provide a useful strategy in the management of CMs.

♦ De Novo Nonfamilial Cerebral Cavernous Malformations

The second group of de novo CMs represents an etiologic spectrum and encompasses lesions that appear in patients without familiarity and are mainly attributable to host and external agents (irradiation, infection, iatrogenic seeding, and hemodynamic factors).[7–11,51,52] De novo formation of CMs without a family history, previous cranial radiation, or other apparent reason has also been reported (cryptogenetic CMs).[7,9,40] Overall, we have treated 25 patients with de novo nonfamilial CMs. Most of them are postirradiation, and a minority encompass hemodynamic and cryptogenetic malformations, including lesions that appeared during and after pregnancy and were hypothetically attributed to hormonal factors.[7]

Radiation-Induced Cerebral Cavernous Malformations

It has recently been demonstrated that therapeutic irradiation of the central nervous system (craniospinal, whole brain, local field, and focused), with its effects on the cerebral vasculature (endothelial injury and proliferation, fibrinoid necrosis, and capillary telangiectasia induction) plays a role in the delayed genesis of a vascular entity mimicking a CM, unaccompanied by other manifestations of radiation damage.[6,8,10–12,53–58] Telangiectasia has previously been described as a result of radiation to the brain at the site of the transition between radiation necrosis and the normal parenchyma. In contrast, this acquired vascular entity occurs in an otherwise normal brain, more often near the gray-white junction.[11] Probably, this lesion is not a typical CM but instead a pathologic variant deranged by irradiation.[7] Other terminologies have been used (telangiectasia, occult cerebrovascular malformation, hemorrhagic vasculopathy)[8,11,56] to describe the same entity, which likely represents a spectrum of postirradiation vascular changes and proliferations with the same radiologic and pathologic characteristics.

The most significant confirmation is represented by one case of de novo lesion in a patient with multiple nonfamilial CMs who was irradiated using a Gamma Knife for an expanding CM of the basal ganglia and later operated on, indicating the powerful effect of the irradiation over a hidden cavernomatous focus. The new lesion had some peculiar characteristics: pluri-hemorrhagic presentation, cystic expansion with fluid level, and a lacy pathologic configuration.[8]

Since the first descriptions at the end of the 1980s,[6,10] several cases have been reported, and now postirradiation CMs constitute the best-known group of de novo nonfamilial lesions. Such occurrences are very rare, and the precise prevalence is poorly understood. Some centers having a large referral have not reported de novo lesions,[59] whereas an accrual of cases occurs elsewhere, without apparent reason.[8,12] In one retrospective study, children with a medulloblastoma who received whole-brain radiation therapy had a 4.8% incidence rate of CM development occurring on the average 5.5 years after irradiation.[53] Probably, the true prevalence of postirradiation CMs is similar to this figure in childhood, but it lowers to ~1% when adults are included[11] due to the greater deleterious effect of the radiation on the developing nervous system and its vasculature.[12]

A release of VEGF promoted by irradiation has been found to be expressed mostly in children and may result in the induction of angiogenesis.[58] Postirradiation CMs have occurred in patients treated for a great variety of neoplasms, particularly in childhood. Craniospinal and whole-brain irradiation for acute lymphocytic leukemia (ALL) plays a preponderant role in induction of CMs in infancy **(Fig. 5–2)**, and the extensive irradiation certainly amplifies the basic damage responsible for the disease. In the patients who underwent whole-brain radiotherapy, CMs seem to occur more frequently in the temporal lobe.[57] The majority of postirradiation CMs seem to appear within 5 years of the treatment and particularly in children irradiated before 10 years of age.[58] Multiple CMs are more likely to occur in patients who were irradiated at a younger age[53] and may have a different latency in the same individual, with new lesions occurring at different times even several years apart: careful MRI follow-up is necessary in these cases, particularly in children receiving whole-brain irradiation. It is believed that no significant increase in the frequency of CMs is associated with chemotherapy[55]; only one report refers to the possible occurrence of a CM associated with chemotherapy.[60]

The pathogenesis of postirradiation CMs is still debated and may range between direct induction and formation from a preexistent lesion[8,11,12] considering that CM and telangiectasia may represent a spectrum within a single pathologic entity. Gaensler et al.[11] suggested that radiation of the brain may induce a telangiectasia and varying amounts of hemorrhage. These thin-walled vessels appeared to be ectatic venules and capillaries, which may represent collateralization of venous drainage from areas of postirradiation congestion or occlusion.[24] Radiation may preferentially affect the endothelium of veins, producing a veno-occlusive disease with subsequent development of venous hypertension and promotion of ischemia, microhemorrhages, and angiogenic factor production.[61] These changes may compact and originate a vascular entity with the overall effect of mimicking a cavernoma. The report of a postirradiation CM formed at the site of a venous angioma confirms this mechanism.[62] Otherwise, Larson et al.[12] have suggested that radiation may trigger a proliferative endothelial pathway, causing a preexistent capillary telangiectasia to evolve into a CM.

Alternatively, irradiation may trigger a genetic or other type of latent predisposition. CMs can arise as a result of radiation-induced mutation in the *KRIT1* pathway, a "second hit" in an area of genetically predisposed vascular tissue.[44,55] We were surprised that none of the cases of postirradiation CMs manifested any family history of the lesion also at sites with high familial occurrence of the disease,[9] as if a different type of host predisposition and genetic aberration might be operative in these patients. Some relationship with latent hereditary hemorrhagic telangiectasia (HHT) has been suggested[59] considering that brain irradiation may induce an erratic proliferative vasculopathy and interfere with the basic genetic mechanism of this condition. It is intriguing that both HHT and cerebral CM are characterized by disruption of normal vascular morphogenesis.[63] Interestingly, in children, radiation therapy for acute lymphocytic leukemia constitutes a large percentage of postirradiation CMs, as if neoplasms and vascular malformations might represent two different manifestations of a same disease characterized by a high sensitivity to irradiation and a predisposition to malignancies, as occurs in ataxia-telangiectasia or Louis-Bar syndrome.

Postirradiation CMs initially reflect a prevalent endothelial structure lacking the typical aging changes and often assume an *en dentelles* configuration characterized by closely packed sinusoids with scarce fibrous tissue[8,26] associated with telangiectatic foci and a thrombosed venous drainage.[8] Some inhibition of fibrous proliferation may characterize postirradiation CMs and differentiate the evolution of this subgroup from its spontaneous counterpart. Clinical features of postirradiation CMs are related to the onset of a moderate cerebral hemorrhage and include epilepsy, headache, and vomiting: Focal signs occur more often in patients with brain-stem lesions. Massive intracerebral bleeding is rare. A discrete percentage of patients (four in our series, or 30% of cases) remain asymptomatic during the course of the disease, but it is possible that this percentage may even be higher.[57] An increased risk of hemorrhage is generally reported in radiation-induced CMs compared with spontaneous lesions, and "opening" intracerebral bleeding appears to be associated with postirradiation CMs in 25 to 50% of cases[8,11,12] with a risk of hemorrhage varying from 3.6 to 6.7% per year, as calculated in one series.[12,55] Our experience in 13 patients is less severe, with an overall risk of bleeding of 1% per year, which increases to 1.4% per year in children. We have also found hemorrhagic accrual during the first 2 years in three cases with recurrent bleeding. These findings may probably also be extended to the overall subgroup of de novo CMs and reinforce the recent observation of clustering hemorrhages in the first years after presentation.[64] This bleeding pattern adapts well to a relative clinical instability of the lesion after its formation and to the progressive quiescence related to the later acquisition of a stable histologic structure.

It is interesting to document other histopathologic differences between congenital and postirradiation CMs. Challa et al.[65] believe that the presence of small amounts of neural parenchyma may help differentiate postirradiation from true cavernous angiomas. The intralesional parenchyma probably reveals a relatively recent formation of the lesion,

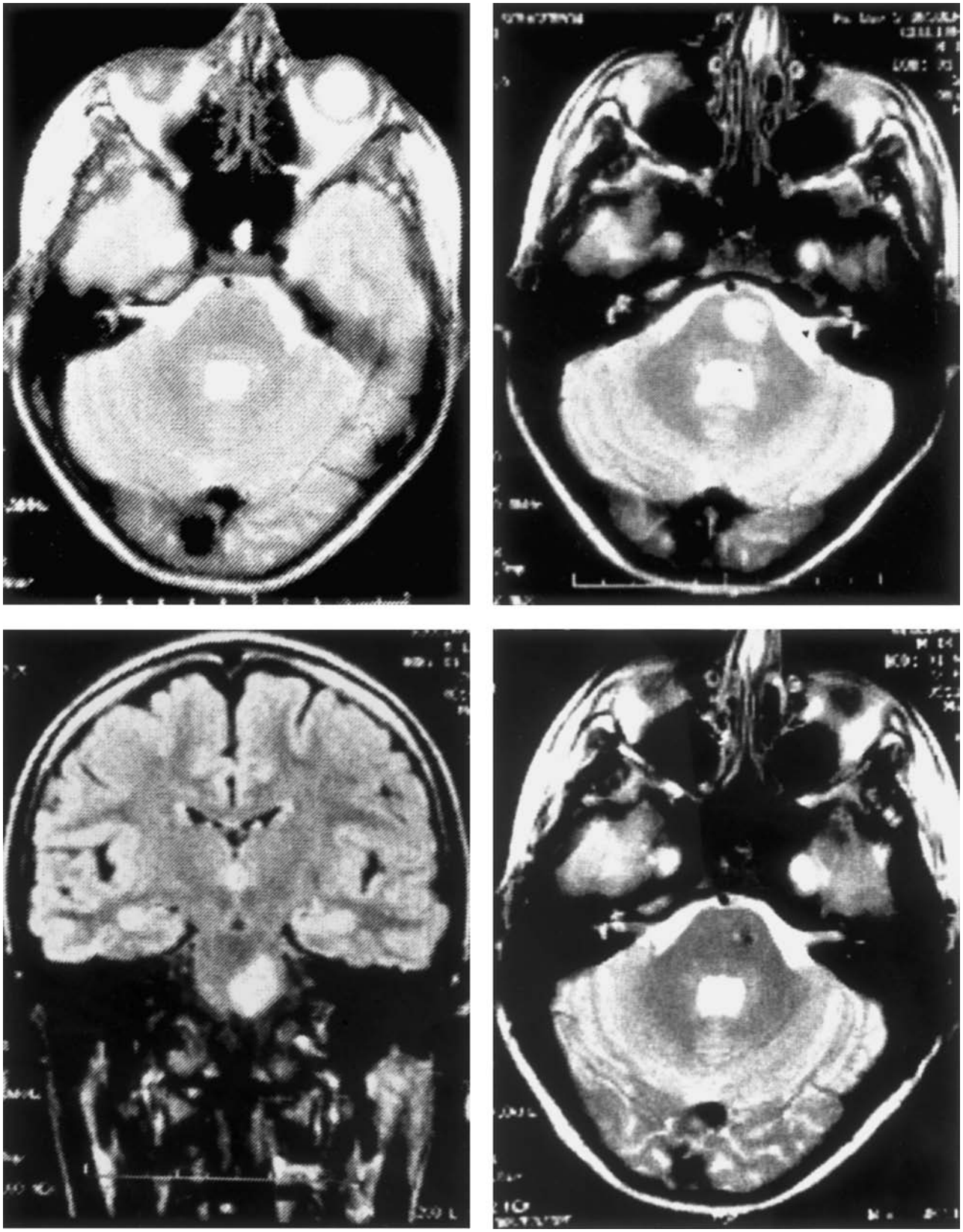

Figure 5–2 Case 11 from **Table 5-1 (A)** Axial T2-weighted MR images of the brain of a boy treated at 12 years for acute lymphocytic leukemia obtained 1 year after whole brain radio therapy (WBRT): The brain stem is normal. **(B, C)** In the images obtained 5 years later (axial and coronal views), an area of subacute hemorrhage is seen in the pons: The patient only complained of headache, but the neurologic examination was normal. **(D)** Six months later, the lesion only consisted of chronic hemorrhage.

well before substitution of intervening neural tissue by progressive reactive fibrosis and gliosis. This conformation may increase the interfacing brain-cavernoma and the possible interaction with vascular growth factors expressed in the adjacent brain[32] with the recruitment of new endothelial vessels. This microenvironment may represent a structural distinction in the central nervous tissue that may predispose to different lesion activity as suggested by Porter et al.[66] Irradiation may promote cyst formation with a fluid level in relation to permeability-inducing factors, osmotic properties, and alterations of the blood-brain barrier in the nascent malformation.[8,16,56] Sedimentation of red blood cells may represent the equivalent of a rebleeding in a resolving hematoma, similar to the hemorrhagic events in chronic subdural hematomas and possible expression of an altered fibrinolytic system resulting from irradiation.[53]

We have summarized our experience between 1980 and 2003 with 13 cases of postirradiation CMs (five craniospinal or whole-brain, seven local field, and one focused irradiation) in **Table 5–1**. Irradiation was performed for brain tumors in eight cases (three cerebral or cerebellar astrocytomas, one medulloblastoma, two invasive pituitary adenomas, one giant cell tumor, and one dysgerminoma), lymphoma or acute leukemia in four cases, and cavernous angioma in one case. The radiation dose varied from 800 to 5400 cGy. All lesions were within the radiation ports. No dose-response relationship was observed. The time interval between irradiation and the detection of the CM varied from 3 to 18 years (mean, 8.1 years). The ratio of female to male was 9:4. Four children received craniospinal irradiation for acute leukemia or lymphoma. Eleven patients were less than 16 years old when first irradiated: The mean age at diagnosis of the CM was 22.4 years (range, 10 to 51 years) and at irradiation was 13.8 years (range, 2.5 to 43 years).

One patient had multiple lesions developing at different times after the initial irradiation and one also had induction of a different lesion (meningioma). Six patients presented with acute symptoms due to hemorrhage (headache, vomiting, and focal signs), four with seizures (one of these had overt hemorrhage), and four were asymptomatic (one of these had overt hemorrhage) when the lesion was detected. The initial MRI appearance was that of a type I lesion in nine cases, type III in two cases, and type II in two cases (one patient had only CT scanning). Cystic changes with fluid levels occurred in five cases. The type II lesion, which represents the most typical aspect of a CM with its reticulated appearance and black ring, occurred in an absolute minority of postirradiation cases, as if some derangement of the usual sequence of progression to a more organized fibroendothelial structure could be aborted. Type I lesions changed to type III in four patients treated conservatively, and one type III lesion changed to type I in one patient.[8]

Six patients were operated on within 2 years of symptom onset (two had recurrent bleeding before the operation), and seven are undergoing radiologic and clinical monitoring. Pathologic analysis of the specimens showed areas with features of CMs associated with telangiectatic changes and thrombosed venous channels.[8] Recurrent hemorrhage did not occur in six cases during the observation period at a mean interval of 3.2 years (range, 8 years to 6 months).

After the treatment of 13 patients with postirradiation CMs, we have gained more experience concerning the clinical behavior of these lesions. Although they certainly represent a subset of lesions with aggressive natural history in terms of hemorrhagic presentation, we are less worried thanks to better knowledge and prolonged follow-up. Some patients remain asymptomatic or have self-limiting courses, and histologic confirmation is generally unnecessary.[54] Surgical resection is recommended only in clinically aggressive malformations with hemorrhagic and growth propensity. An additional observation in line with the "fragility" of de novo CMs relates to their surgical characteristics: In contrast with the compact conglomeration of congenital forms, new lesions tend to be elusive, and the surgical specimens often consist of faint endothelial spaces and hemorrhagic material.

Hormones and De Novo Cerebral Cavernous Malformations

Hormones may influence the clinical course of CMs, but their biologic effect is again unknown. CMs may show a more aggressive behavior in adult women, particularly during pregnancy, in relation to the influence of gestational hormones (estrogens in particular) or of hemodynamic changes on the malformation.[4,7,67,68] Growth, bleeding, and de novo appearance have been documented in pregnancy.[7] In one series, CMs occurred during pregnancy in 3.5% of cases,[69] but comprehensive epidemiologic studies have not been conducted. We encountered two women with bleeding CMs during pregnancy and three women who presented with a de novo CM during or after pregnancy, supporting that the endothelial proliferation may also occur in the absence of hemorrhage. The adverse effect of estro-progestinic medications on a thalamic CM has also been described.[69] The key finding of hormonal receptors, which could influence the evolution of the lesion, remains uncertain. In a study performed in our institution, orbital cavernous angiomas (which differed from intracranial cavernomas for their thick and highly cellular vascular walls), when tested for steroid receptors, revealed marked positivity for progesterone but not for estrogens.[70]

Cavernous malformations of the third ventricle, which frequently demonstrate rapid growth and repeated hemorrhages, could be under hormonal influences because of their location.[71] Supporting a hormonal influence, we found five women with associated pituitary adenomas and cavernomas. This association may represent a chance occurrence, but a relationship with hormonal factors cannot be excluded. In particular, the de novo appearance of a cavernoma in two patients with an invasive pituitary adenoma (one after irradiation) may support some hormonal influence of the biology of these vascular malformations.[7]

Venous Anomalies and De Novo Cerebral Cavernous Malformations

If the coexistence of cerebral venous anomalies and CMs is well-known, their mutual relationships are still unclear. Venous hypertension secondary to congenital or acquired stenosis of the main collector seems to be responsible for bleeding and de novo occurrence of CMs,[72] as was the case in one of our patients with progression of multiple CMs associated with a huge venous anomaly of the deep venous

Table 5–1 Thirteen Cases of Postirradiation Cavernous Malformations (1980 to 2003)

Patient	Age at Irradiation (y)	Sex	Latency (y)	Dose (cGy) and Radiation Field	Reason for Irradiation	Onset	MRI Findings (Type)	Location of the Malformation	Treatment	Pathologic Findings
1	10	F	6	3000 LF	Cerebellar astrocytoma	Headache, vomiting	CT scan; multiple hemorrhages, cystic evolution	Parieto-occipital	Surgery	Cavernoma
2	43	F	7	5050 LF	Pituitary adenoma	Asymptomatic	Type I → Type II CT scan; multiple hemorrhages,	Frontal	Surgery	Cavernoma/vein
3	15	F	7	5000 LF	Dysgerminoma	Headache, vomiting	Type I	Frontal	Surgery	Cavernoma/vein
4	15	F	9	2500 GK	Previous cavernoma	Seizure	Type I, Fluid level. Multiple lesions 2 bleeding	Frontal	Surgery	Cavernoma/ telangiectasia
5	12	M	3	5400 LF	Cerebral astrocytoma	Headache, vomiting	Type III → Type I	Cerebellum	Conservative	
6	16	F	4	4500 LF	Cerebral astrocytoma	Seizure	Type II	Parietal	Surgery	Cavernoma
7	2	M	15	2400 WB	Lymphoma	Ataxia,	Type I	IV ventricle	Surgery	Cavernoma
			4			seizure	Type I	Parietal		
8	27	F	9	1100 LF	Giant cell tumor	Asymptomatic	Type I → Type III	Temporal	Conservative	
9	5	F	5	2400 WB	ALL	Seizure	Type I → Type III	Frontal	Conservative	
10	4	F	18	3600 CSI	Medulloblastoma	Seizure	Type II	Temporal	Conservative	
11	12	M	5	800 CSI	ALL	Headache	Type I → Type III	Brain stem	Conservative	
12	21	F	15	4000 LF	Adenoma	Asymptomatic	Type I	Temporal	Conservative	
13	8	M	4	2400 CSI	ALL	Asymptomatic	Type I	Cerebellum	Conservative	

Abbreviations: ALL, acute lymphocytic leukemia; CSI, craniospinal irradation; GK, Gamma Knife; LF, local field; WB, whole brain.

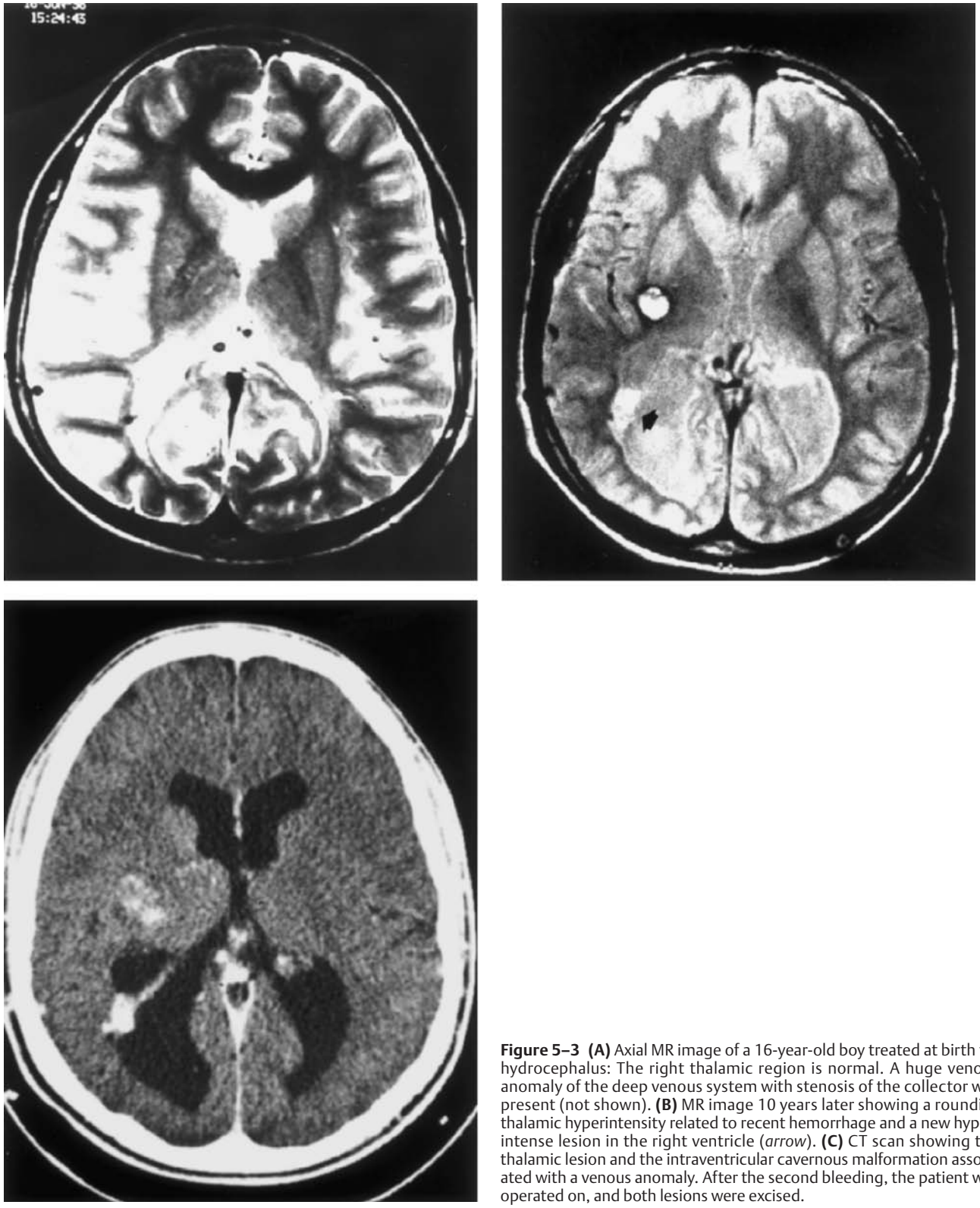

Figure 5–3 (A) Axial MR image of a 16-year-old boy treated at birth for hydrocephalus: The right thalamic region is normal. A huge venous anomaly of the deep venous system with stenosis of the collector was present (not shown). **(B)** MR image 10 years later showing a roundish thalamic hyperintensity related to recent hemorrhage and a new hyperintense lesion in the right ventricle (*arrow*). **(C)** CT scan showing the thalamic lesion and the intraventricular cavernous malformation associated with a venous anomaly. After the second bleeding, the patient was operated on, and both lesions were excised.

system **(Fig. 5–3)**. Alterations in regional blood flow with variations of vascular shear stress forces and growth factor induction may also be associated.[73] Cavernous malformations freely communicate with the venous sinus system, and variations in the venous pressure may be transmitted to their brittle structure,[74] as we have found in one patient with a hemorrhagic CM and primary pulmonary hypertension. In addition, there may be differences in the deep venous drainage system that promote changes in CMs at a higher rate.[66] A venous angioma that drains through the brain stem to a petrosal sinus is probably at a greater risk of bleeding,[75] particularly if perilesional edema becomes

evident at MRI.[76] It is noteworthy that recurrence of CMs occurs mainly in the brain stem where they present the most aggressive clinical course. Recurrence of CMs may occur after complete excision in patients with associated venous anomalies.[7] Although venous anomalies should be absolutely respected at surgery, we wonder if selective occlusion of fine venous radicles at the interface with a recurrent cavernoma should be performed to obtain a definite cure.[7] Although it does not represent properly a de novo lesion, regrowth at the same operative site constitutes another aspect of the dynamic properties of the disease.

Infection and Cavernous Malformations

Sporadic CMs may be environmentally caused, and an infective origin has been tentatively suggested.[10,40,77–79] The possibility of origin of CMs from viral infection, although experimentally demonstrated in an animal model, is almost completely unsettled in humans. The polyoma virus has been used to induce the formation of intracranial CMs in immunodeficient rats.[9] The random finding of cytomegalovirus (CMV) DNA by hybridization in the matrix of some CMs may support this pathogenetic connection. Possible stimulation of the fibroblast growth factor and neoangiogenesis due to CMV infection has been suggested, but this theory requires confirmation and further study.[79] Hypothetically, viral infection in patients with germ-line mutations at loci associated with CCMs may promote the formation of these lesions. Trapping of infective agents (bacteria or other) may occur in slow-flow CMs and constitute a possible origin of inflammatory reaction and growth of the malformation.[78] Postinfective cerebral thrombophlebitis in patients with intracranial infection may lead to formation of a capillary proliferation mimicking a de novo CM.[22]

♦ Conclusion

Currently, de novo origin of CMs is accepted only if at least two high-field MRI studies are comparable. The next step is to understand whether the lesion we are observing in the absence of previous neuroradiologic examinations may be congenital or de novo, with the important clinical implications relative to its differing natural history. The report of new lesions is not only a clinical curiosity, but also it offers an attractive model for studying their precise origin and progression. Genetics and de novo lesions should be matched for a better understanding of the pathophysiology of CMs, particularly in the subset of carriers of the mutation in the KRIT1 protein who do not demonstrate malformations at MRI.[46] Correlation of the spectrum of mutations in CMs with patient phenotype may permit identification of risk factors at the genomic level and their impact on de novo lesions.[80] How control of angiogenesis may be influenced by mutations in the KRIT1 protein pathway constitutes the missing link of the pathophysiology of this lesion.

The absence of evidence is not evidence of absence: de novo CMs may initially represent a phase of the disease at low neuroradiologic penetrance due to hemodynamic factors or to discrete endothelial proliferation in the phase of tubulogenesis and erratic capillary development.[2]

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6

Systemic Cavernous Malformations

Eugenio Pozzati

Cavernous malformations (CMs) or cavernous angiomas (CAs) or cavernomas are encountered by the neurosurgeon throughout the central nervous system, in the orbit, vertebral bodies, and epidural spinal space. Cerebral CMs (CCMs) occur in two forms: sporadic and familial. Although the sporadic, single form was believed to be preponderant, the familial form is now being diagnosed with increasing frequency and constitutes up to 50% of cases. It is characterized by an autosomal dominant mode with variable expression and incomplete penetrance, by multiple lesions, and by the de novo appearance of new malformations at a rate of 0.2 to 0.7 per year.[1]

The concept of CM is evolving. CM is usually considered a vascular malformation, with its basic endothelial structure arranged in closely packed sinusoids without intervening parenchyma, but some peculiarities (growth, neoangiogenesis, and de novo appearance)[2] may cause this lesion to resemble a hamartoma. Furthermore, the possible occurrence of CMs at multiple levels (brain, eye, skin) can support their inclusion among the phakomatoses, or hereditary disorders with cutaneous, ocular, and neurologic manifestations.[3–6] It has been correctly suggested that familial CMs might represent a *forme fruste* of a neurocutaneous disorder in which the cutaneous and ocular disturbances have incomplete expression or are not fully recognized.[7]

♦ Systemic Cavernous Malformations

The combined occurrence of familial CMs inside and outside the CNS (eye and skin in particular) has always been considered exceptional, but the increasing number of reports leads us to revise our opinion. Two different situations exist: (1) widespread occurrence of inherited CMs in multiple organs and tissues (brain, eye, skin, and liver), which we may refer to as systemic CMs and consider as a phakomatosis; and (2) participation of CMs in a sporadic vascular disease, which may show prevalent segmental involvement of several tissues (skin, vertebra, and spinal cord) throughout an entire dermatome.

Wider multiorgan involvement has also been reported (kidney, heart, and spleen), but it constitutes an absolute rarity.[8] Similarly, diffuse neonatal hemangiomatosis represents a rare, and often fatal, disease characterized by multiple cutaneous and visceral hemangiomas in the liver, lungs, intestine, and central nervous system. Death generally results in the newborn from hemorrhages or cardiac failure.[9] The coexistence of CMs with a complex segmental maldevelopment has been reported in a family with systemic CAs (brain, skin, retina, and liver) in which two relatives had terminal transverse defects at the mid-forearm.[10]

The prevalence of systemic CMs is unknown, but it grossly parallels the availability of magnetic resonance imaging (MRI) and the increasing knowledge of the familial form. Some observations are necessary regarding the genetic origin and for better understanding of systemic CMs. Three distinct loci are associated with familial CMs: CCM1, CCM2, and CCM3 are located on three chromosomal loci 7q, 7p, and 3q, respectively, indicating genetic heterogeneity. Mutations in the *KRIT1* (KREV1 interaction trapped 1) gene, a binding protein with tumor suppressing activity, are responsible for CCM1[11] and have been demonstrated in patients with associated CMs of the retina[12] and with hyperkeratotic cutaneous capillary-venous malformations (HCCVMs),[13,14] which expand the phenotypic spectrum of the disease.[15] *KRIT1* plays an important role in cutaneous, retinal, and cerebral vascular development. The occurrence of CMs in various organs is not coincidental but corresponds with the effects of this mutation at these levels.[12]

Some types of cerebrovascular malformations (telangiectasias and arteriovenous malformations in particular) are part of well-known neurocutaneous vascular disorders (Sturge-Weber disease, Rendu-Osler disease, Louis-Bar syndrome, Wyburn-Mason syndrome, and Klippel-Trenaunay syndrome) characterized by their association with peculiar cutaneous stigmata.[5] Systemic CMs are not yet considered in the usual classification of these diseases[5] and represent an ill-defined but distinctive neuro-oculo-cutaneous syndrome, with changeable phenotype and possible overlapping with other neurocutaneous vascular disorders and phakomatosis (von Hippel-Lindau disease in particular). Whereas the cutaneous and ocular features of systemic CMs are essentially benign, the cerebral localization is sometimes the origin of significant neurologic disability.

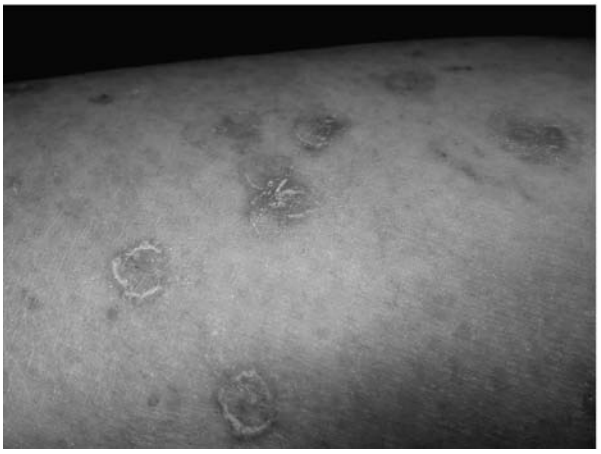
Cerebral and Cutaneous Cavernous Malformations

Since the original report of the first case of familial intra- and extraneural CAs,[16] other observations of associated skin, retina, and brain cavernomas have been published

by Weskamp and Cotlier,[17] Gass,[6] Schwartz et al.,[18] and Dobyns et al.,[3] who recognized the autonomy of the disease and suggested that this complex might represent a true phakomatosis. The triad may be incomplete, with cutaneous or ocular participation in the disease being inconsistent. The varied location pattern probably represents one entity with ubiquitous lesions.[19] The affected families may differ in the distribution of their CAs, but it seems incorrect to split these families into subcategories.[4] The involvement of the different organs may occur several years apart: The precise follow-up of the peripheral localization (eye and skin) may lead to an early diagnosis of the central lesions in family members.[20] In the systemic disease, cerebral CMs have the usual conformation, but the histopathology of the cutaneous vascular lesions may be an "equivalent" and differ from the classic cavernomatous structure. Dermatologists should be aware of the protean manifestations of the skin lesions and delve deeper into the screening of their patients for a timely diagnosis of the cerebral disease.

Various cutaneous vascular lesions are associated with familial CCMs, and their number is growing, although some terms are probably synonymous: cherry angiomas, blue rubber bleb nevi, angiokeratomas, true CAs, and recently described HCCVM. The simple association between familial cerebral and cutaneous CAs has been rarely reported.[21] The cutaneous CA appears as a purple, minimally elevated papule not blanching on compression. Similarly, cherry angiomas have been described in families with CCMs,[22] but the relevance of this association is unclear because of the common occurrence of skin lesions.

Recently, an association between autosomal dominant CCMs and a distinctive HCCVM has been reported in some families with mutation of *KRIT1*,[13,14] suggesting that these lesions are based on a common genetic mechanism. These crimson-like cutaneous lesions were mainly located in the lower limbs and were predominately of capillary type with a venular component in association with an overlying hyperkeratotic epidermis.[14] This distinctive cutaneous vascular malformation was observed in 4 of 57 French families with CCMs indicating a non-negligible occurrence and representing a first indication of the extent of this association. In families in which these lesions coexist, all members who manifest HCCVMs also have CMs[14] and the penetrance of the cutaneous lesions co-occurring with CCMs is around 40%. Furthermore, this cutaneous phenotype seems to be correlated with a particular molecular alteration found in the *KRIT1* gene.[14,15] The association between CCMs and HCCVMs is relatively uncommon but probably underdiagnosed. We encountered a patient with familial HCCVMs who, only after 20 years and a long history of epileptic seizures, had a diagnosis of frontal cavernoma **(Fig. 6–1)**. She also had a hepatic cavernoma, and her daughter had renal and hepatic cavernomas, indicating an unreported extension of the phenotype of this association. In addition, these cutaneous lesions were extremely sensitive to sun exposure, suggesting a inherited origin of the disease consistent with biallelic loss of function favored by ultraviolet radiation.[22]



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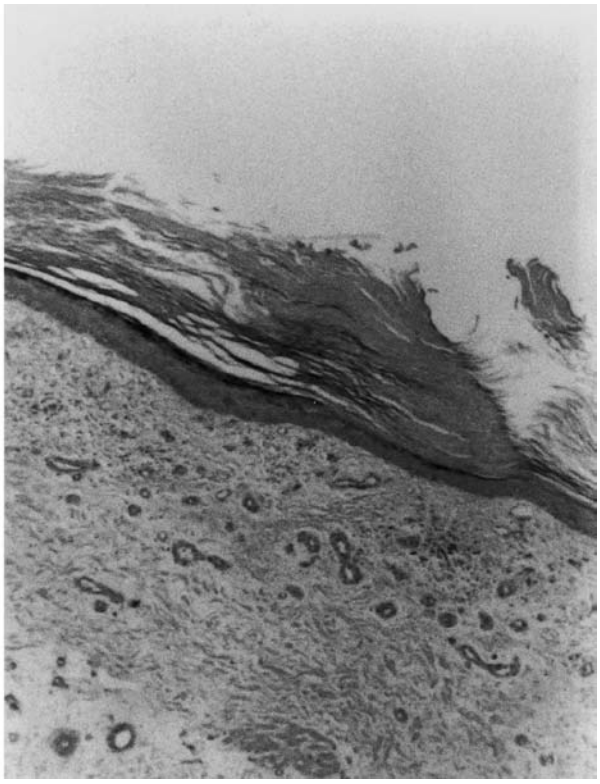


B

Figure 6–1 (A) This 58-year-old woman with epileptic seizures had a cavernous angioma of the left frontal lobe (not shown). The photograph is of the patient's calf showing multiple crimson-colored macules with a pinkish discoloration of the skin. Her grandfather had the same skin lesions. **(B)** Photomicrograph of the cutaneous surgical specimen showing hyperkeratosis associated with dilated vessels in the upper dermis consistent with hyperkeratotic cutaneous capillary-venous malformation (HCCVM) (hematoxylin and eosin, magnification × 25). (Courtesy of Dr. R. Davalli, Dermatologist, Bellaria Hospital, Bologna, Italy.) A cavernous angioma was found in the liver. The patient's daughter had cavernous angiomas in the liver and kidney.

Cutaneous CMs may also be associated with other types of intracranial vascular malformations. Leblanc et al.,[23] reporting on a hereditary neurocutaneous angiomatosis characterized by the coexistence of vascular nevi (generally CA) with cerebral arteriovenous malformation (AVM) and venous malformations, noted a preponderance of male patients and suggested a possible hormonal influence on the expression of the gene. Nonvascular cutaneous lesions may be sometimes associated with inherited CCMs. Café-au-lait skin lesions typical of neurofibromatosis were associated with widespread cerebral and spinal CMs in a patient with a genetic alteration in *KRIT1/CCM1*, adding to the range of skin lesions found in familial CMs.[24] Similarly, we observed a 40-year-old woman with multiple and de novo cerebral CMs, possible familiality (a daughter had epileptic seizures), a myriad of café-au-lait lesions, and a cutaneous angioma of the inferior eyelid irradiated in infancy. Overlapping manifestations of CMs and von Recklinghausen disease may also occur, but their mutual relationships are still obscure.

Cerebral and Retinal Cavernous Malformations

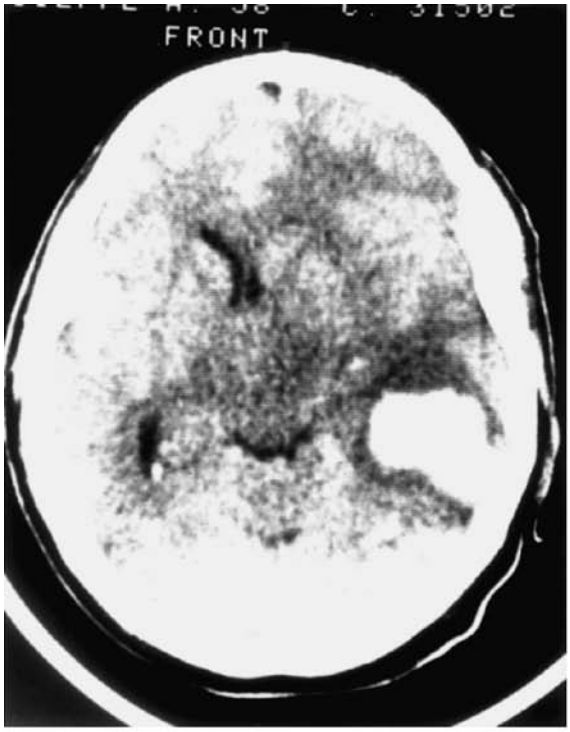
Cavernous angioma of the retina is the third element that, with brain and skin, often completes the triad: It is an unusual vascular hamartoma that consists of an isolated sessile cluster of retinal thin-walled saccular aneurysms filled with dark venous blood.[25–28] Similar to its cerebral counterpart, plasma-erythrocytic separation within the vascular spaces is common.[6] The prognosis is generally good, although occasional bleeding into the vitreous and subretinal space has been described.[27] The optic nerve head may also be involved, and bilateral retinal occurrence has been reported.[27] Recently, Sarraf et al.[19] described a family with skin, eye, and brain CMs related to a mutation at the level of the 7q locus. Similarly, Couteulx et al. reported a case of a *KRIT1* mutation in a patient with retinal and cerebral CAs, confirming the genetic background of the disease.[12] The possible presence of choroidal and iris hemangiomas expands the ocular spectrum of this phakomatosis.[26,27] Twin retinal vessels, which may be found in von Hippel-Lindau disease as an early diagnostic sign, may also be present in familial CAs of the brain and retina.[28] Associated CMs and hemangioblastomas were reported by Russel and Rubinstein,[4] who suspected a common etiologic link. A family with "peripheral" von Hippel-Lindau disease and CCMs has been reported, again suggesting possible overlap between these disorders.[29]

An important difference between the systemic and classic forms of CMs is shown by the clinical relevance of CCMs. In the review of Dobyns et al,[3] 68% of the patients with cerebral and retinal CMs had neurologic disturbances and 48% of these had intracranial hemorrhage, indicating a higher risk in the systemic disease. Several stroke-related deaths have also been reported.[25] These findings underscore the need for a precise diagnosis of the extraneural manifestations when evaluating patients with familial CMs. Available data seem to indicate a poorer clinical history of the cerebral lesions in the systemic form compared with pure CCMs. We treated a patient with multiple CCMs and associated angiomas of the wrist and eye. This patient required a remote eye excision due to an "ocular hemorrhage" and had two brain hemorrhages caused by the angiomas **(Fig. 6–2)**. This is an additional example of oculoneuro-cutaneous CAs with aggressive biological behavior.

Drigo et al. described a syndrome consisting of familial cerebral and retinal CAs associated with peculiar hepatic involvement.[29] Such massive hepatic participation is quite unusual but again poorly defined in the usual screening of familial CAs. Although the association of cerebral and retinal CMs with hepatic involvement has until recently been considered as a chance occurrence of two unrelated diseases,[15] screening of the liver is recommended in the management of multiorgan CMs. This family demonstrated genetic anticipation by manifesting seizure onset at an early age, a phenomenon already reported in CCMs,[20] and indicating a decrease of age at symptom onset in an inherited disease, increased severity in subsequent generations, or both. The contribution of genetic anticipation may be very important in the clinical behavior of systemic CMs, and it should be determined whether or not it induces a progressive increase of the multiorgan involvement in consecutive generations. A recent update of this large family (P. Drigo and I. Mammi, unpublished data) disclosed the additional presence of cutaneous, epidural, calvarial, and vertebral angiomas (in particular of the atlas and axis), confirming the rare finding of a vertebral involvement in the familial disease, and the unrelenting multiorgan progression.[30] Notably, some members of a family with CCMs that we are treating have peculiar calvarial thickening, which probably corresponds with an unreported angiomatous involvement of the bone. CAs are one of the most common tumors affecting the spine, and their association with familial and cerebral lesions constitutes an important implication for diagnosis and treatment of the affected patients.

Cobb Disease and Blue Rubber Bleb Nevus Syndrome

In addition to autonomous systemic CMs, recent observations suggest that two known vascular neurocutaneous syndromes may be associated with the presence of CMs in the CNS and orbit: Cobb disease and the blue rubber bleb nevus syndrome. The blue rubber bleb nevus syndrome (BRBNS) is characterized by multiple, distinctive angiomas of the skin, mucous membranes, and gastrointestinal tract. The oral cavity, which constitutes an important clue to the diagnosis of a vascular disorder, also may be involved in the disease.[4,5,31–34] The cutaneous lesion is characterized by bluish, thin-walled, soft, and compressible nevi. Pathologically, BRBNS reveals large blood-filled spaces separated by fibrous septa of varying thickness similar to a CA. Although some cases are sporadic, many patients have been described with an autosomal dominant pattern of inheritance.[31] The risk of bleeding from gastrointestinal vascular malformations is the most serious clinical feature of BRBNS. More recently, it has been recognized that BRBNS may include cerebral and orbital vascular malformations. There is enough evidence in the literature to establish a relationship between BRBNS and developmental venous anomalies, sinus pericranii, and venous thrombosis.[31] Vascular skin findings suggesting BRBNS have been recently described in one patient who presented with cerebral hemosiderosis occurring after previous hemorrhage by multiple cerebral CAs.[32] Waybright et al.[33] described a young man with BRBNS and cortical CAs, capillary telangiectasias, and a thrombosed AVM of the vein of Galen, representing



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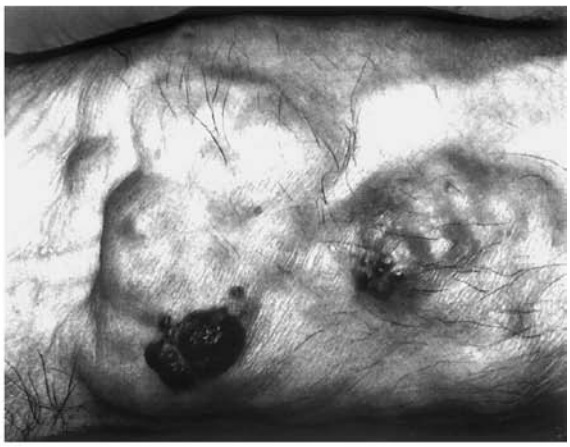

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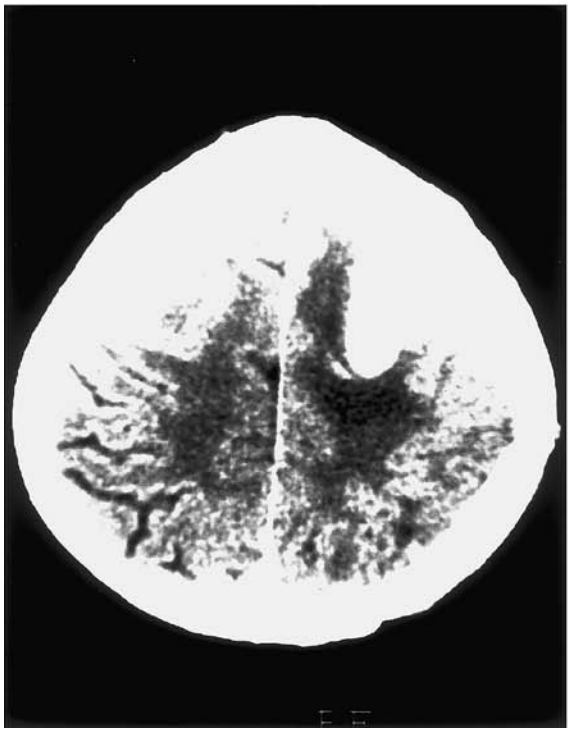
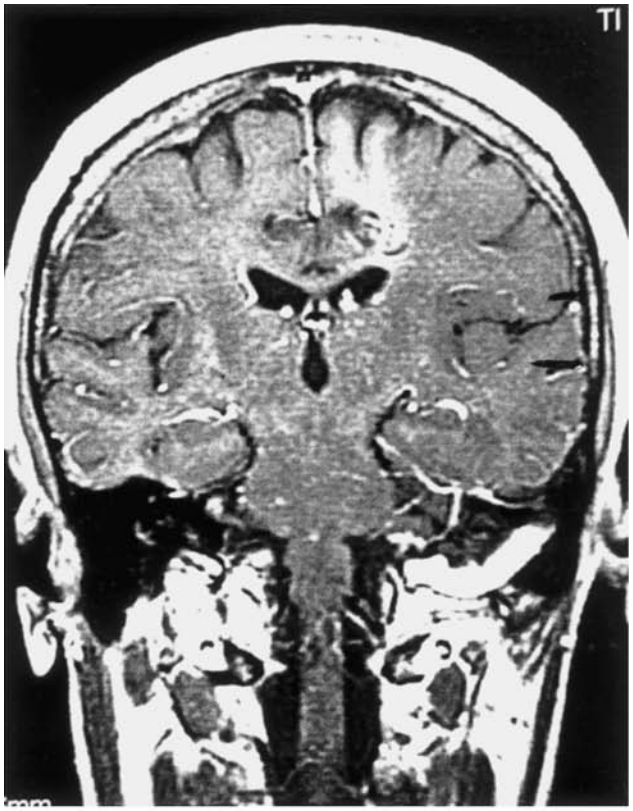


C

Figure 6–2 (A) CT scan of a 52-year-old man revealing a left parietal hematoma: The left frontal region was normal (not shown). Cerebral angiogram was normal. At operation, a cavernous malformation embedded in the hematoma was excised. **(B)** After 20 days, the patient complained of sudden headache: CT scan showed a small frontal hemorrhage. The patient was treated conservatively. **(C)** Photograph of the patient's wrist showing a huge cavernous malformation that was present at birth. The patient underwent an ocular excision for a "hemorrhage" that occurred a few days after his birth.

possible overlap between the BRBNS and Rendu-Osler syndrome. In particular, mono- and bilateral orbital CAs have been described associated with BRBNS[34] and with Maffucci syndrome, a rare nonhereditary disease characterized by hemangiomas and enchondromas.[35]

One case that we recently encountered emphasizes the association of oral angiomas and cerebral cavernoma with a venous malformation overlapping to possible BRBNS. This 52-year-old woman was admitted to our hospital for excision of a neurofibroma of the thigh. After the operation, an epileptic seizure occurred and MRI showed a CM of the parietal lobe associated with a venous anomaly **(Fig. 6–3A, B)**. The patient also reported diffuse vascular lesions of the tongue and oral cavity **(Fig. 6–3C, D)**, and two bleeding "polyps" of the colon had been excised 2 years before. The patient also stated that her daughter had been irradiated for an angioma of the upper lip. A biopsy was performed of an accessible oral lesion, and histopathology confirmed a CA of the oral gum **(Fig. 6–3E)**. She is on antiepileptic medication. The cerebral lesions remain stable on MRI follow-up. Radiologic screening of the family is under way. Our case demonstrates that the oral cavity and tongue, like the



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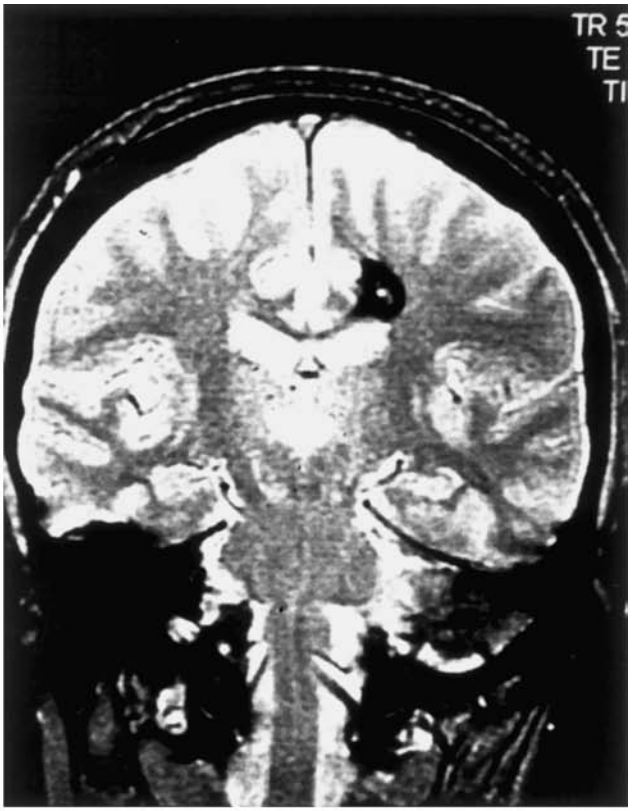

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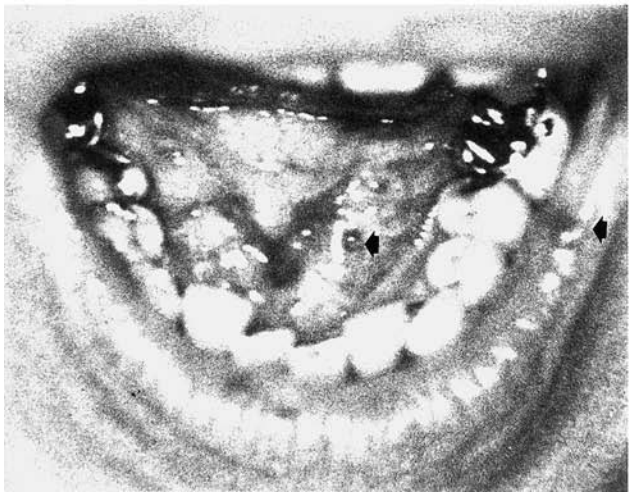

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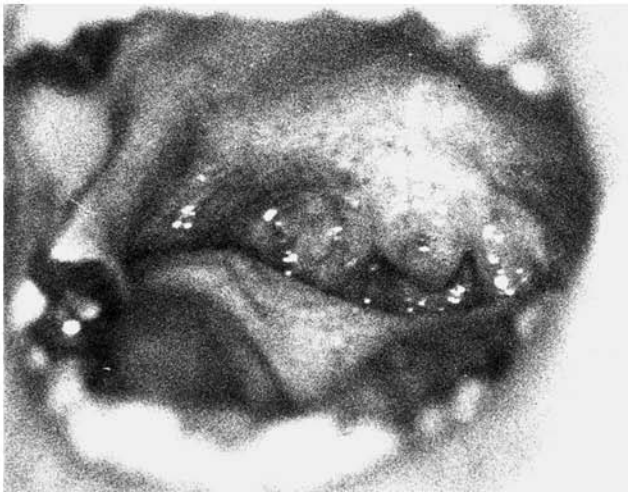

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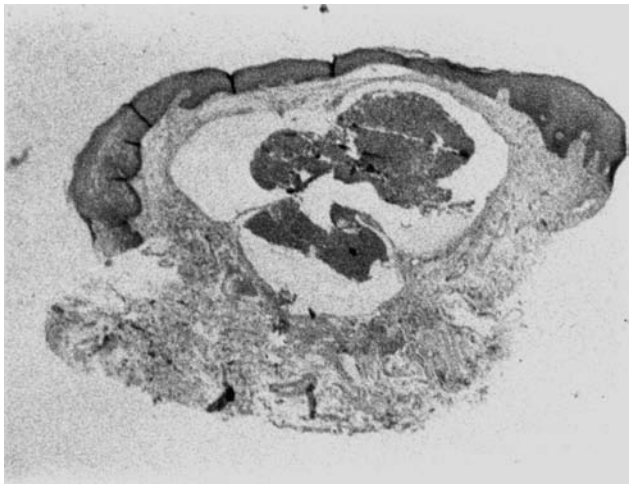

E

Figure 6–3 (A, B) Coronal T1- and T2-weighted MR images of a 52-year-old woman revealing a frontal venous anomaly and an associated cavernous malformation. **(C, D)** Photograph of the patient's mouth demonstrating several angiomas of the lip, gum, tongue, and palate (*arrows*). **(E)** Photomicrograph of the oral surgical specimen demonstrating dilated vascular spaces lined by endothelium and fibrous tissue (hematoxylin and eosin, magnification × 20).

skin, should be carefully checked in patients with neurocutaneous angiomatosis.

Segmental Cavernous Malformations

An important concept in the setting of intra- and extraneural CMs is their participation in a segmental vascular disease involving the spine in particular. The association of a spinal cord vascular malformation, namely an AVM, with a cutaneous angioma, generally a nevus flammeus, in the overlying dermatome is known as Cobb syndrome.[4,5,36] It roughly corresponds with the Sturge-Weber syndrome in the spinal cord. However, the histopathology of the vascular lesion both in the skin and spinal cord may be highly variable. Wakabayashi et al.[36] reported a case of multiple CMs of the brain and spinal cord associated with angiokeratomas in the same metamere, mimicking Cobb syndrome. Similarly, a combination of vertebral hemangiomas, overlying HCCVM, and familial CCMs recently described by Clatterbuck et al.[30] emphasizes the importance of a segmental disease expression associated with widespread cavernomatous involvement of the CNS. This may be the result of a second hit during development, implying biallelic loss of function as relevant molecular pathogenetic mechanism.[30] The vertebral column should be included in the screening of tissues that can be affected by CMs, and certainly the morbid effects and the clinical boundaries of the familial form are further extended.[30] The coexistence of CAs in the brain and vertebral column is again rarely verified, but, because of their frequency, constitutes an intriguing field of investigation and clinical interest.

♦ Conclusion

The treatment of patients with familial CCMs includes screening of other tissues that can be affected (eyes, skin, liver, and spine) and the participation of appropriate specialists in the routine evaluation of this disorder. Most importantly, it is advisable to consider possible cerebral involvement in patients with a variety of cutaneous angiomas, the HCCVMs in particular.

Systemic CMs are more frequent than previously realized, but cases continue to go unrecognized. Their diagnosis needs careful attention to extraneural manifestations of the disease and a good knowledge of inherited vascular disorders. This will permit more effective clinical management and genetic counseling.

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7

Capillary Telangiectasias, Cavernous Malformations, and Developmental Venous Anomalies: Different Expressions of the Same Disease Process?

Quoc-Anh Thai, Gustavo Pradilla, and Daniele Rigamonti

Cerebral vascular malformations are hamartomatous lesions[1,2] originally classified by McCormick and colleagues into four separate categories: arteriovenous malformations (AVMs), cavernous malformations, capillary telangiectasias, and venous malformations.[3] These disorganized vascular structures have distinct gross, histologic, radiographic, and clinical characteristics that generally differentiate them from one another. However, a spectrum of intermediate forms of the above categories has been described, suggesting that these lesions may actually be a continuum of progression of a single pathologic process. As such, it would be expected that combinations of these variants, in different stages of development, would be detected over time, and several of these lesions would be associated together within close proximity to each other. Reports have associated venous malformations with cavernous malformations,[4–11] cavernous malformations with capillary telangiectasias,[8,12,13] capillary telangiectasias with venous malformations,[14,15] and venous malformation with both a cavernous malformation and capillary telangiectasia.[2,8] With the continuing development of better imaging techniques, these lesions are being followed much more closely than before, and recent reports have also noted de novo formation of cavernous malformations in association with a venous malformation.[5,6,11,16,17] These reports make a compelling story for a common pathway of disease, however, there is still no direct evidence supporting such a theory at this time.

This chapter focuses on the known pathologic processes of the venous malformations, cavernous malformations, and capillary telangiectasias. We will then discuss the reported associations of the various forms of vascular malformations and examine possible pathologic links between them.

♦ Cerebral Vascular Malformations

Capillary telangiectasias, cavernous malformations, and venous malformations are all vascular malformations that occur on the capillary-venous side of the cerebral circulation. Morphologically, they are a group of disorganized vessels that resemble primitive anastomotic plexuses present during embryogenesis.[18] In autopsy series, the incidence of cerebral vascular malformations is 4.6%.[19] Venous malformations are the most common (3%), followed by capillary telangiectasia (0.8%) and cavernous malformation (0.3%).[19]

Capillary Telangiectasia

Capillary telangiectasias are collections of ectatic, thin-walled, endothelial-lined vascular channels separated by normal neuropril.[20] These capillary-like channels lack smooth muscles and elastic fibers, and they range in size from saccular dilatations of capillary vessels to groups of channels that resemble cavernous spaces.[12] They can be found throughout the brain or spinal cord, but they are more common in the posterior fossa, in the pons, as well as in the cerebral cortex and basal ganglia.[15] They are thought to have a benign natural history[20] and usually become symptomatic when there is hemorrhage. Instances of hemorrhage have been associated with the coexistence of a cavernous malformation.[21]

The etiology of capillary telangiectasia is thought to be congenital. Failure in the involution of brain capillaries, which normally occurs during the second month of gestation,[21] results in formations of capillary telangiectasias associated with dilated draining veins and normal feeding arterioles.[22] The hereditary form of capillary telangiectasia is autosomal dominant and is part of the Osler-Weber-Rendu syndrome, which is characterized by the development of capillary telangiectasias in the skin, gastrointestinal tract, nasal mucosa, and central nervous system.[23] Capillary telangiectasias have also been reported to form de novo after radiation.[24]

Magnetic resonance imaging (MRI) is the best imaging modality to visualize capillary telangiectasias. They are hypo- to isointense on T1-weighted images and iso- to hyperintense on T2-weighted images. There is uniform

enhancement with gadolinium contrast injection.[20] On gradient-echo images, there is signal loss due to blood oxygen level–dependent contrast.[25] Computed tomography (CT) and angiography are not as useful in detecting capillary telangiectasias. CT scans are often normal; there may be faint areas of increased density after contrast administration. Capillary telangiectasias are usually angiographically occult.

Cavernous Malformations

Cavernous malformations (also referred to as cavernous angiomas, cavernous hemangiomas, capillary hemangiomas, and cavernomas) are well-circumscribed lesions of endothelial-lined vascular sinusoids without intervening parenchyma.[26] These dilated vascular channels, or "caverns," occur throughout the brain and spinal cord, most commonly in the subcortical white matter, external capsule, and pons.[27] They resemble capillaries but have an abnormal basal lamina. There are no ensheathing pericytes, smooth muscle cells, or astrocytic processes, and there are gaps between endothelial cells lining the channels of the cavernous malformation.[28] This yields an incompetent blood-brain barrier that may contribute to their etiology.

The etiology of cavernous malformation has traditionally been presumed to be congenital and present at birth, but more recent reports of their ultrastructure, de novo formation, and pathophysiology suggest there may be other mechanisms. Cavernous malformations occur in a sporadic form, in which lesions are solitary, and in a familial form, which is accompanied by multiple lesions as well as a family history of seizures.[26] Ultrastructural analysis shows that there is an incompetent tight junction and lack of blood-brain barrier components, which may lead to leakage of red blood cells into the surrounding brain and cause seizures.[28] This leakage of red blood cells may account for the dynamic nature of cavernous malformations. A prospective MRI analysis showed that there is a tendency for progression from type IV to type I to type II to type III.[17] There are also growing reports of de novo formation of cavernous malformation. Zabramski and colleagues followed 21 members of 6 unrelated families with familial cavernous malformations for an average of 2.2 years and documented 17 de novo formations.[26] Cavernous malformations have also been reported to occur after stereotactic and radiation therapy[29] and have been associated with viral infection[23] and venous malformations,[5,6,11,16,17] suggesting that other pathophysiologic mechanisms are involved.

Cavernous malformations are visualized on MRI as having a reticulated core of mixed signal intensity surrounded by a hypointense rim of hemosiderin.[30] This gives it an appearance similar a "mulberry" or "popcorn-like" lesion, which represents hemorrhage in different stages of evolution. These different stages have been classified as type I (subacute hemorrhage), type II (mixed subacute and chronic; the classic popcorn-like lesions), type III (chronic), and type IV (small punctate hypointensity on gradient echo).[26] CT imaging usually shows an isodense to moderately hyperdense lesion on nonenhanced images; there could be little to prominent enhancement after contrast injection. Cerebral angiography has virtually no role for the sole purpose of studying cavernous malformations, as they are generally angiographically occult. However, as discussed later, they are sometimes associated with other vascular malformations that do appear on angiography.

Venous Malformations

Venous malformations (also referred to as developmental venous anomaly, venous angioma, or venous caput medusae) consist of a group of veins resembling a chandelier or *caput medusae* draining normal brain tissue.[31] The vessels are abnormally enlarged and are separated by normal parenchyma. These vessels then drain into a central venous trunk, which then drains into a venous sinus; there is no abnormal arteriovenous shunting. Found throughout the central nervous system in rough proportion to tissue volume, these lesions are relatively benign. Rarely, venous malformations may be associated with hemorrhage, and in those instances, there should be high suspicion of an associated cavernous malformation as the etiology.[4]

The etiology of venous malformations is thought to be congenital, resulting from failure of normal embryogenesis.[2] By 45 days of gestation, the vasculature consists primarily of primitive embryologic medullary veins with a single draining vein into a venous sinus. By 90 days of gestation, these structures have normally evolved into the superficial and deep venous systems.[32] Arrested development of this *venous caput medusae* during this window of development would result in a venous malformation that drains the surrounding normal brain structures. These hypotheses are corroborated by (1) findings of venous malformations in infants and children, (2) lack of mature venous systems surrounding these lesions, (3) angiographic opacification of venous malformations at the same time sequence as normal veins, (4) drainage of vascular malformations into normal extraparenchymal collectors, and (5) observation of venous infarction of the adjacent brain after removal of vascular malformations.[21,32,33] Alternatively, there could be a focal abnormality in the venous drainage system during development, leading to formation of collateral, dilated medullary drainage veins.[23]

The diagnostic study for venous malformations is an angiogram showing the pathognomonic caput medusae in the venous phase.[31] The arterial phase is usually normal, and there is sometimes a late capillary blush. On MRI, there are a series of tubular hypointensities on T1. These are better seen on T2, showing a venous plexus draining into a larger central vein, which exhibits high-velocity signal loss.[34] There is generalized enhancement with gadolinium. Nonenhanced CT scans typically do not reveal venous malformations well; they are usually normal or show a slightly hyperdense, ill-defined lesion. As with MRI, there is enhancement after contrast injection.[35]

♦ Mixed Patterns of Cerebral Vascular Malformations

Cerebral vascular malformations with mixed characteristics or a combination of characteristics are well documented and may represent a spectrum of the same disease process. The incidence of these structures is unknown, as is their etiology. These malformations are mostly thought to be congenital, resulting from failure of the primitive vasculature to mature, and they are generally thought to be benign and

static. However, reports have shown that some of these lesions are dynamic. A prospective MRI study showed that cavernous malformations evolve from being a type IV to type I to type II to type III.[17] There are numerous reports of de novo formation of cavernous malformation in the presence of a venous malformation.[5,6,11,16,17] Zabramski and colleagues[26] found an overall frequency of 0.4 new lesions per patient per year in their series of familial cavernous malformations. Also, there are associations of each of the lesions with one another. The increasing number of reports of associations of two or more lesions in close proximity to each other makes it less likely that this is due to coincidental appearances of different diseases. It is estimated that 20 to 30% of cavernous malformations are associated with venous malformations.[1,4,23] Also well documented is the association of cavernous malformations with capillary telangiectasias.[2,8] Associations of capillary telangiectasias and venous malformation are less common. Hypotheses regarding the linkages between these lesions have been postulated since the 1930s, beginning with the Russell theory stating that capillary telangiectasias are precursors for cavernous malformations. Since then, numerous other hypotheses have surfaced and will be discussed in the following sections.

Venous Malformations and Cavernous Malformations

The association of a cavernous malformation with a venous malformation is the most common of the vascular lesions, reported to be as high as 33% of cavernous malformations.[36] Venous malformations are the most commonly encountered vascular malformations of the brain, accounting for up to 60% of cerebral vascular malformations. These benign lesions are usually found incidentally.[31] They tend to become symptomatic when there is a hemorrhage, but this is usually always associated with a cavernous malformation.[28,31,32,37,38] This has led many to suspect the causal linkage between the two lesions.

Abnormal hemodynamics of venous malformations may induce the formation of a cavernous malformation. Numerous studies have cited abnormal venous drainage and pressure associated with the region drained by a venous malformation. A study of venous malformations that are associated with hemorrhages and cavernous malformations showed a high incidence of venous stenosis of the collector vein.[11] Nuclear medicine studies have shown increased activity in the venous phase of the region drained by the venous malformation, suggesting that venous outflow is delayed.[39,40] The result is a progressive venous overload and hypertension that is transmitted throughout the lesion.[41] Subsequently, endothelial cell damage and small breakdown of the blood-brain barrier may lead to deposition of hemosiderin as well as local production of angiogenic factors.[42] These events are hypothesized to form de novo cavernous malformations,[5,7,41,42] and this process has been referred to as "hemorrhagic angiogenic proliferation"[21] by Awad and colleagues. Reports of cavernous malformations appearing adjacent to venous malformations support the rationale that venous hypertension is linked with the pathogenesis of cavernous malformations.[6,41,43] Furthermore, venous malformations in association with a hemorrhage or de novo cavernous malformations were found to have a high rate of stenosis or obstruction of the venous outflow.[6,11] Therefore, whereas venous malformations are congenital, cavernous malformations appear to be hemodynamically acquired.[6,43] Other hypotheses have been proposed by Wilson, stating that intermittent diapedetic extravasation of blood through the capillaries is the initiating process.[42] This then results in stimulation of fibroblasts and the appearance of fragile capillaries prone to recurrent hemorrhage, leading to the formation of a cavernous malformation.[37,38,42] Once formed, cavernous malformations continue to change due to other factors, further suggesting that there is a continuum of disease progression.

An incompetent blood-brain barrier plays a role in the pathophysiology of cavernous malformations. From the first MRI description of cavernous malformations by Rigamonti and colleagues in 1987,[30] cavernous malformations have been shown to enlarge, to regress, and to form de novo.[17] This dynamic nature is attributed to abnormal venous pressure,[6,41,43] hemorrhage, and hemorrhage resolution.[17] As discussed, venous hypertension is generally thought to be associated with abnormal venous drainage of adjacent venous malformations. Intermittent hemorrhages may also be related to the venous pressure buildup. In addition, structural abnormality of basement membrane likely plays a major role. A recent ultrastructural and immunocytochemical study[28] provided evidence that there is a lack of appropriate junctional complexes as well as ensheathing cells. This translates into an incompetent blood-brain barrier and weakened vessels and increased propensity for recurrent episodes of hemorrhages followed by resolution. This is reflected in MR images by lesion heterogeneity and changes in size[17] showing blood of varying ages.[17,30]

Cavernous Malformations and Capillary Telangiectasias

The association of cavernous malformations and capillary telangiectasias has been described since 1931. Russell originally suggested that cavernous malformations could be formed from the fusion of adjacent, dilated loops of the capillary telangiectasia.[44] The Russell theory was not generally accepted, but other hypotheses linking the two lesions have also been proposed. This is partially due to observations that cavernous malformations and capillary telangiectasias occur adjacent to each other with higher frequency than expected from coincidence alone.

Increased venous pressure from capillary telangiectasias may lead to the formation of cavernous malformation. Capillary telangiectasias, similar to venous malformations, are thought to be congenital and remain relatively static during life. However, the abnormal vasculature is thought to induce venous hypertension and fragile vessels. This is hypothesized to cause clinically insignificant microhemorrhage.[42] Subsequently, the blood products cause a reactive angiogenesis with new vessel formation and coalescence.[21,42] This "hemorrhagic angiogenic proliferation" is thought to be responsible for formation of a cavernous malformation. Once formed, cavernous malformations have an ordered progression through the Zabramski classification, from type IV to type I to type II to type III.[17,26] However, the progression is not linear, and transition from type IV to type I is only at a rate of 0.05 per patient year.[45] There is no direct evidence showing this transition of

capillary telangiectasia to a cavernous malformation, specifically a type IV, which appears to be the precursor to larger, symptomatic lesions.

Indirect evidence from clinical, radiographic, and surgical-autopsy data support the hypothesis that capillary telangiectasias and cavernous malformations may represent two different manifestations of a single pathophysiologic process.[12,30,46] Rigamonti and colleagues reported that the division of cavernous malformations and capillary telangiectasias is arbitrary,[12] and there are transitional forms between the two lesions.[12] In their series of 20 cavernous malformation patients, 35% of cavernous lesions had brain parenchyma in its center. The presence of brain parenchyma (the key differentiating characteristic between capillary telangiectasia and cavernous malformation) in a lesion that would otherwise be characterized as a cavernous malformation suggests that these transitional states are underrecognized. In autopsy, there were transitional forms of capillary telangiectasias identified, and these were correlated with MRI findings of small focal decreased intensities.[12] In another report, Diamond and colleagues reported autopsy findings of pontine lesions showing a gradual transition from capillary telangiectasia to cavernous malformation; histology did not provide clear-cut distinctions.[47] These findings make the distinction between a capillary telangiectasia and a cavernous malformation, specifically a type IV, difficult and seemingly arbitrary.[12,47] However, Rigamonti and colleagues more recently reported that these are distinct entities, and the type IV cavernous malformations can progress through a series of MRI signal changes characteristic of types I, II, and III.[45] This establishes that these type IV lesions are not capillary telangiectasias; however, capillary telangiectasias may still be a precursor lesion for type IV cavernous malformations. MRI studies show that both lesions can manifest in the same patient 80% of the time when there is a familial history of a symptomatic cavernous malformation.[12] There is a positive correlation between the number of type IV lesions and the age of the patient,[48] suggesting that type IV lesions accumulate in a patient over time. As suspected, there are more small lesions than large lesions identified in a particular patient, given the slow rate of change from type IV to type I, and this is especially true in asymptomatic patients.[12,30,46] Given the coexistence of capillary telangiectasias and cavernous malformations, some shared characteristics, and correlation of type IV with age, it is plausible that there is a pathologic linkage between the two.

Capillary Telangiectasias and Venous Malformations

The association of capillary telangiectasias and venous malformations is rare. There are only three case reports of such an association,[8,14,15] so the hypotheses linking these two lesions is less compelling than that of the established associations discussed previously. However, the association with a venous malformation, which is known to have restrictive outflow and increased venous pressure, has led to speculations that there may be a causal linkage.

♦ Hemorrhagic Angiogenic Proliferation Hypothesis of Formation of Cerebral Vascular Malformations

Vascular malformations are congenital lesions with abnormal venous structures and associated hemodynamics that may more commonly lead to the formation of cavernous malformations and, in rare instances, the formation of a capillary telangiectasia. The central basis for this assertion is the findings of a restrictive outflow, decreased venous drainage, and increased venous pressure in venous malformations.[11,39–41] This leads to vessel friability and propensity for microhemorrhage. This results in a reactive angiogenesis and the formation of new vessels and eventual coalescence into a capillary telangiectasia.[21,42] Based on this hypothesis, venous malformations can be seen as the primary lesion when there are combinations of vascular malformations in a region.[15] It would, therefore, be expected that if venous malformations were the primary lesion in vascular malformations, one would expect to see it in association with both a capillary telangiectasia and cavernous malformation. Indeed, a recent report cited the juxtaposition of a venous malformation, capillary telangiectasia, and cavernous malformation in the brain stem of a patient.[8] Although this is the first published case report of such an association, the probability of such a constellation of vascular malformations adjacent to one another by chance alone is remote **(Fig. 7–1)**. The low occurrence of this is congruous with the fact that the association between vascular malformations and capillary telangiectasias is already a rare phenomenon. Another support for the "hemorrhagic angiogenic proliferation" hypothesis[21] is the finding of de novo formation of capillary telangiectasias after radiation.[24] Radiation-treated vessels are more friable and prone to leakage of blood

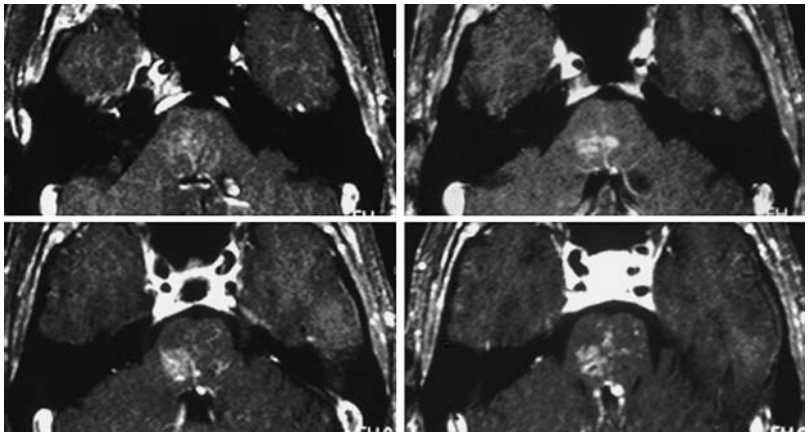

Figure 7–1 T1-weighted, post-gadolinium MRI showing a type II cavernous malformation left of the fourth ventricle with an associated venous malformation that extends toward the fourth ventricle. There is also a capillary telangiectasia anteriorly in the pons.

products, leading to the same cascade of events that ends with the formation of a capillary telangiectasia. This same course of events may also be involved in de novo formation of cavernous malformations after radiation therapy.[23]

♦ Conclusion

Cerebral vascular malformations are generally classified into four main groups: arteriovenous malformations, cavernous malformations, capillary telangiectasias, and venous malformations; and their incidence is 4 to 5% in autopsy series. Intermediate and mixed forms of the above categories have been described, suggesting a continuum of progression of a single pathologic process. Associations of each lesion to one another have been reported, with the most common being venous malformation with cavernous malformation. It is thought that the central process involved may be abnormal venous flow and venous hypertension, which leads to a hemorrhagic angiogenic proliferation of new lesions, such as a cavernous malformation. Indirect evidence supports such a hypothesis. Although direct evidence is lacking, the probability of such lesions appearing adjacent to each other by chance alone seems remote.

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8

Neuroradiology and Classification of Cavernous Malformations

Lawrence C. Wang, Michael T. Zagardo, Kenneth Fraser, and Giuseppe Lanzino

Cavernous malformations (CMs) have alternatively been referred to by several terms in the neuroradiologic literature, including cavernous hemangiomas, cavernous angiomas, and cavernomas. CMs account for a significant if not overwhelming percentage of (angiographically) occult cerebral vascular malformations.

♦ Computed Tomography, Angiography, and Radionuclide Imaging of Cavernous Malformations

Computed tomography (CT) and angiography have largely been supplanted by magnetic resonance imaging (MRI) for the diagnosis of CMs, being both insensitive and nonspecific. CMs were known for 50 years prior to the development of MRI, but they were not visualized on a consistent basis. When identified by CT, CMs may show a rounded and well-circumscribed high-density mass with variable focal calcification (**Fig. 8–1A, B**). There is generally minimal or no mass effect and typically no significant surrounding edema, with limited (**Fig. 8–1B**) or absent enhancement. Dynamic CT with bolus contrast administration may show slow progressive enhancement on delayed images. More cystic internal regions manifest as low-density foci. Smaller CMs are not consistently seen by CT. As the CT findings are nonspecific, differential diagnostic possibilities include other masses such as hematoma, vascular malformation, and calcified neoplasm.

CMs are generally angiographically occult (**Fig. 8–2A**). Conventional angiography including current digital subtraction techniques typically demonstrates an avascular mass without feeding arteries or draining veins. It is generally considered unnecessary if MRI is characteristic, with no suggestion of abnormal vascularity. In the pre–MRI era, Numaguchi et al.[1] described prolonged injection selective cerebral angiography (ICA injection at 3.75 mL/s for a total of 15 mL) for angiographic determination of small venous pools relating to CMs, not visible by less selective angiography with standard length injections. Angiography retains potential utility for differentiating parasellar extra-axial CMs from parasellar meningiomas, as discussed later in this chapter. Angiography will also define associated developmental venous anomalies.

Radionuclide imaging can similarly be helpful in the differentiation of parasellar extra-axial CMs from parasellar meningiomas, also discussed later in this chapter.

♦ Magnetic Resonance Imaging of Cavernous Malformations

Correlation of Findings with Pathology

The prototypical appearance of CMs by modern cross-sectional MRI correlates well with their typical pathology, representing benign hamartomas consisting of masses of sinusoidal vascular spaces that are endothelium-lined. These spaces are filled with blood and blood products in various stages of thrombosis and organization. These vascular spaces may be separated by collagenous, fibrous adventitial, or degenerative hyalin material, with no smooth muscle or elastic fibers. Their lack of intervening neural tissue and lack of prominent supplying or draining vessels serve not only to pathologically distinguish CMs from developmental venous anomalies, capillary telangiectasias, and micro-arteriovenous malformations, but also to account for their neuroimaging characteristics.

The pathologic correlates to modern neuroradiologic findings in CMs are presciently summarized by Simard et al.[2] in their timely 1986 survey of the literature (138 cases). This review was presented at the advent of common clinical usage of high-field MRI, before which CMs were considered rare lesions. They noted the well-established propensity of CMs to bleed, with internal hemorrhagic cystic cavities of varying chronology as a frequent and prominent finding. Microscopic evidence of prior hemorrhage in the form of hemosiderin-laden macrophages, cholesterol crystals, and hemosiderin deposition in surrounding tissues was common as well. Calcification was also common (though not dense and confluent), particularly involving vascular walls thickened with collagen and involving areas of thrombosis with subsequent organization. Various stages of recent and chronic thrombosis were noted within the vascular channels of CMs. Surrounding marginal gliosis was common. In his comment immediately after the

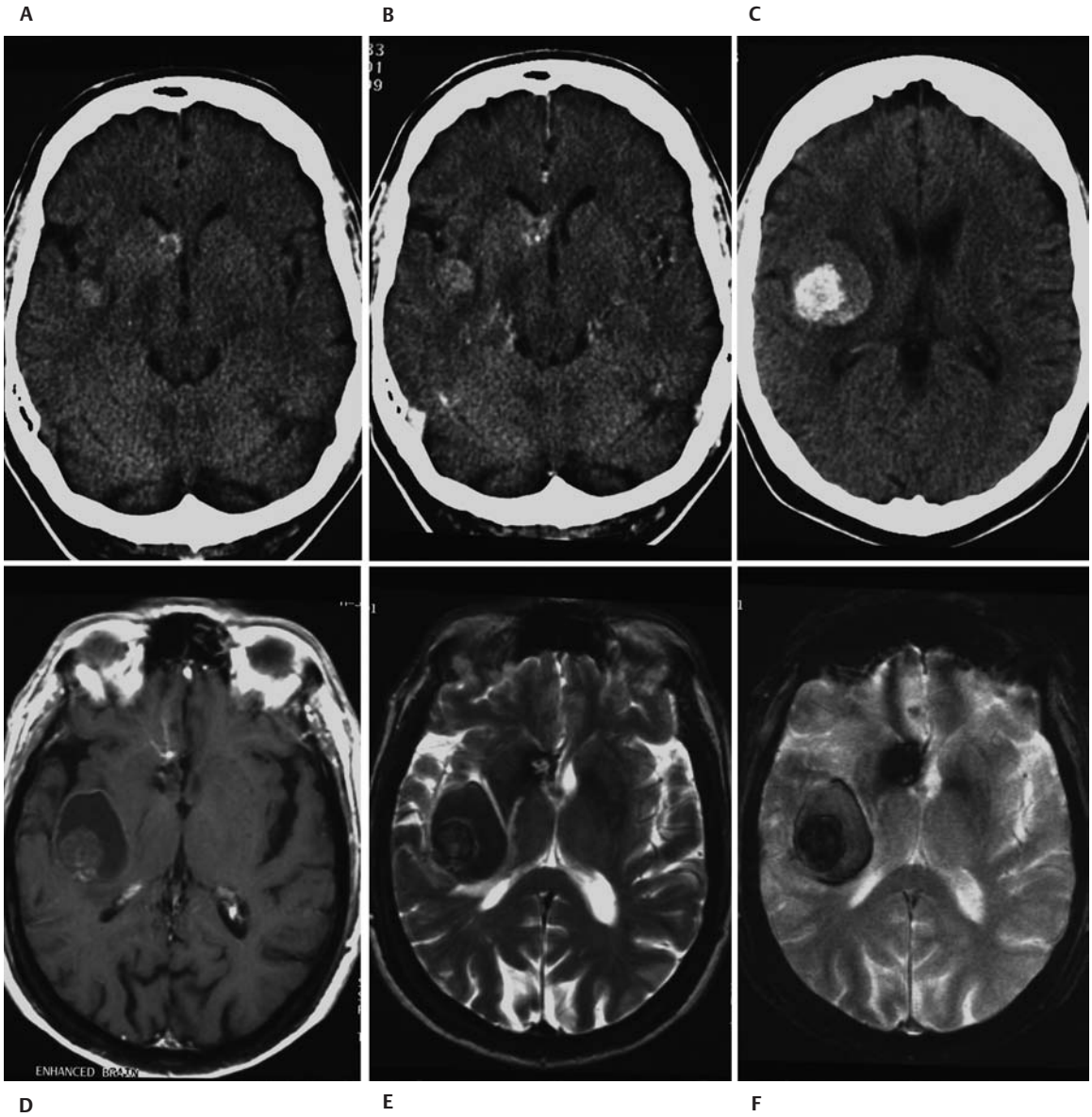

Figure 8–1 Multiple cavernous malformations in a 67-year-old woman presenting with left-sided weakness. **(A)** Axial noncontrast CT demonstrates a lesion in the inferior aspect of the right frontal operculum. There is also a lesion with punctate calcification involving the head of the caudate nucleus. **(B)** Axial postcontrast CT shows faint enhancement of both lesions. **(C)** In axial postcontrast CT, more superior slice shows the complex hemorrhage of the lesion centered at the right frontal operculum. There was no definite enhancement at this level. Parts **(D)** to **(F)** are MR images obtained 3 hours after the CT images. **(D)** Axial postcontrast T1-weighted image shows a faint curvilinear enhancement at the posterior aspect of the more nodular focus within the right frontal opercular/subinsular lesion. A thin hyperintense rim at the periphery of this lesion was present on the noncontrast axial T1-weighted images (not shown), thus representing early methemoglobin formation at periphery of clot. Linear enhancement extends from the anteroinferior aspect of the lesion at the caudate nucleus, corresponding to probable associated developmental venous anomaly. **(E)** Axial T2-weighted fast spin-echo (FSE) image of type II CM at caudate nucleus, with multinodular hyperintense core with complete hemosiderin rim, is apparent. In correlation with (**D**), the larger frontal opercular/subinsular lesion is likely for the most part composed of acute and early subacute hemorrhage, a variant type I CM. Edema surrounds the hemorrhage. **(F)** Axial gradient-echo image in which internal architecture of caudate nucleus lesion is not apparent, in contradistinction to internal morphology delineated in **(E)**. Incomplete susceptibility rim is shown about the larger frontal opercular/subinsular CM.

Simard review, J.B. Kirkpatrick offered his suspicion that local perilesional edema might contribute to mass effect by CMs.

More recently, Wong et al.[3] presented a transmission electron microscopic examination of CMs. The authors provided further insight into their propensity for recurrent hemorrhage and their imaging characteristics. They described caverns of varying size filled with resorbing intracavernous blood, with compromised interendothelial tight junctions suggesting deficiencies in the integrity of the blood-brain barrier, as well as attenuated cavern walls lacking subendothelial support.

With the widespread availability of MRI and its ability to detect differences in tissue contrast not visualized by angiography and CT, direct neuroradiologic-pathologic correlation is possible.

The often heterogeneous internal signal intensities of CMs on MRI thus represent acute to subacute blood products

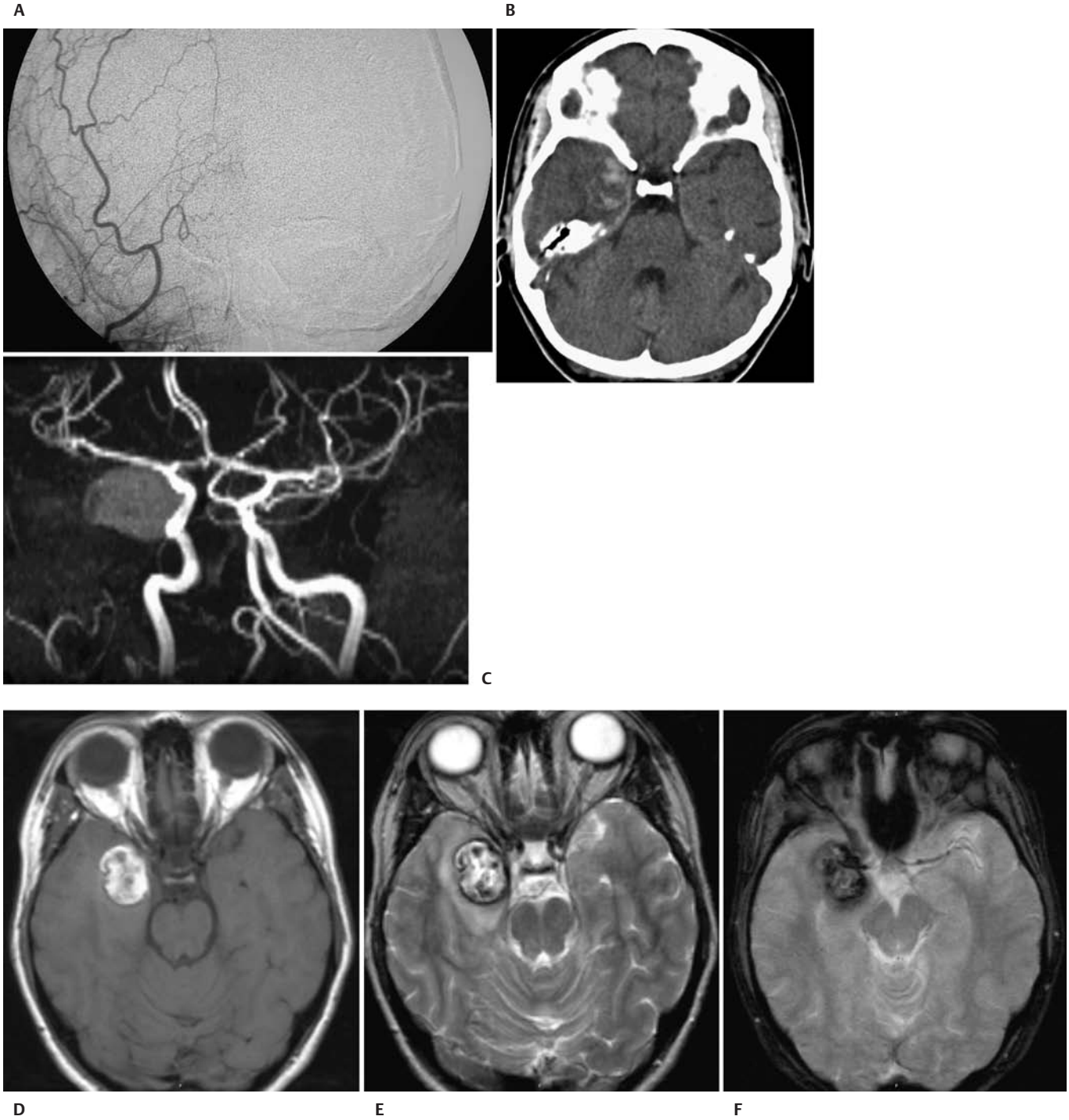

Figure 8–2 Cavernous malformation masquerading as aneurysm in a 41-year-old woman initially presenting with sudden onset of headache and right retro-orbital pain for 3 days, referred from outside the medical center with diagnosis of partially thrombosed aneurysm, after having had CT and MRI there. **(A)** Right external carotid angiogram has nonspecific finding of slight meningeal blush from a deep meningeal branch of the middle meningeal artery in the region of the previously identified lesion. Differential possibilities include a dural-based parasellar mass and dural recruitment from the vasa vasorum in relation to a thrombosed aneurysm. No identifiable aneurysm on internal carotid angiography (not shown). **(B)** Subsequent noncontrast CT shows heterogeneous densities within this ovoid parasellar lesion. No calcification is demonstrated. **(C)** Magnetic resonance angiography (3D TOF [time of flight] MIP [maximum intensity projection]) in which prolonged T2 relaxation of lesion is apparent. **(D** to **F)** MRI (T1-weighted, T2-weighted, and gradient echo) from an examination 1 month after presentation. Note lack of lamellated architecture more commonly seen with thrombosed aneurysms. Surrounding edema **(E)** and incomplete hemosiderin ring **(F)** associated with recent hemorrhage.

surrounded by hemosiderin, in conjunction with variable calcification and variable thickening of the walls of the sinusoids.

By conventional spin-echo imaging, both acute and chronic hemorrhage will manifest as hypointensity on T2-weighted images. This represents water proton dephasing due to the heterogeneous magnetic susceptibility of such hemorrhages. As this effect is proportional to the square of the magnetic field strength, T2-weighted images on low-field MRI units are not sensitive to such deoxyhemoglobin/hemosiderin effects.

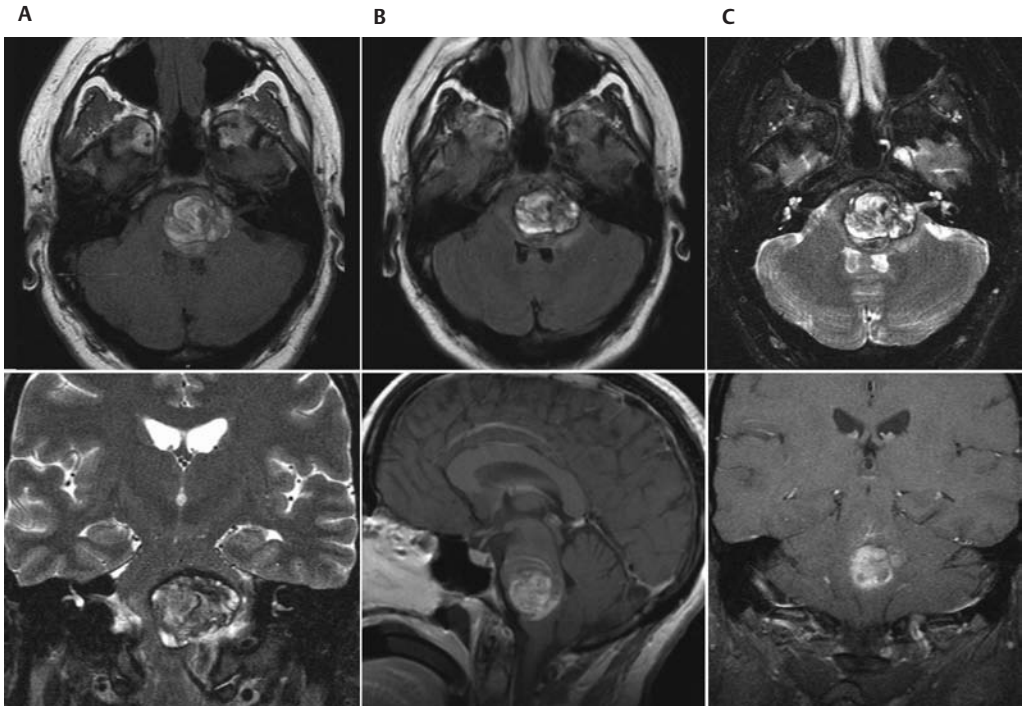

Figure 8–3 Pontomedullary cavernous malformation with associated transpontine developmental venous anomaly in a 31-year-old woman with severe nausea and vomiting. **(A)** Axial T1-weighted image shows intra-axial lesion with heterogeneous hyperintensity. **(B)** Axial fluid attenuated inversion recovery (FLAIR) image. Perilesional edema is well demonstrated. **(C)** Axial T2-weighted image. Extent of peripheral hemosiderin of CM approximates pial surface at, and anterior to, the porus acusticus. **(D)** Coronal T2-weighted image shows acute hemorrhage with perilesional edema and incomplete hemosiderin rim along inferior aspect of CM. **(E)** Sagittal postcontrast T1-weighted image shows transpontine developmental venous anomaly (DVA) along superior aspect of CM. **(F)** Coronal postcontrast T1-weighted image shows medullary veins of DVA converging radially.

Furthermore, the widespread adoption of fast spin-echo T2-weighted sequences on high-field systems has resulted in a decreased sensitivity to hemorrhage. The aforementioned proton dephasing is in large part prevented by the physics of fast spin-echo imaging, wherein the interecho times are shortened by a train of 180-degree refocusing pulses.

Gradient-recalled echo sequences omit a 180-degree refocusing pulse and thereby provide for increased sensitivity to magnetic susceptibility effects. The blood products in CMs will have accentuated signal loss, particularly when longer echo times (TE) and lower flip angle protocols are employed. However, internal signal characteristics of CMs can be obscured by this signal loss **(Fig. 8–1F)**.

Alternatively, Kim et al.[4] demonstrated artifactual increased signal intensity on gradient-echo imaging within lesions in a patient with multiple CMs. His group verified experimentally that hemosiderin deposits within CMs can act as point magnetic dipoles, with intravoxel dephasing resulting in a high-intensity ring artifact within the expected region of signal void on axial sections. Parallel to the main magnetic field (i.e., on coronal and sagittal sections on the typical MRI unit), trilobed and cloverleaf (four-lobed) hypointense artifacts on gradient-echo imaging were also observed. These susceptibility-induced intravoxel signal interference patterns could easily be respectively misinterpreted as a ring-like deposition of material within a CM or multiple contiguous lesions.

Another caveat associated with gradient-echo imaging is the lack of specificity of the aforementioned susceptibility effects and artifacts, which are not exclusive to hemosiderin. These findings can be seen with chronic hemorrhage breakdown products in the setting of parenchymal hematoma, as well as hemorrhagic or melanotic metastases, brain iron deposits, calcification, other paramagnetic ions, and susceptibility artifact near brain-air interfaces. The gradient-echo images should thus be correlated with the remainder of the MR examination and with the clinical context.

Postcontrast imaging of CMs is helpful for exclusion of coexistent developmental venous anomalies (DVAs), seen in approximately one quarter of patients with CMs in a recent large series[5] **(Figs. 8–1D, 8–3E, and 8–3F)**. This is prudent in patients for whom surgical resection of a symptomatic CM is contemplated, given the risks associated with inadvertent coexistent DVA resection.

Magnetic Resonance Imaging Of Intramedullary Spinal Cord Cavernous Malformations

Lesions of the spinal cord share common histologic features with those in the intracranial compartment. Intramedullary lesions exhibit a discrete central core, often of mixed signal intensity as with intracranial lesions, with variable surrounding low signal intensity hemosiderin on T2-weighted images. There can be CM perilesional cord edema manifested as increased signal intensity on T2-weighted images and short tau inversion recovery (STIR) images **(Fig. 8–4)**. Imaging of the entire neuraxis will often reveal the presence of multiple lesions.[6] CM localization by MRI does not only guide the specific surgical approach; indications of surgical accessibility based on

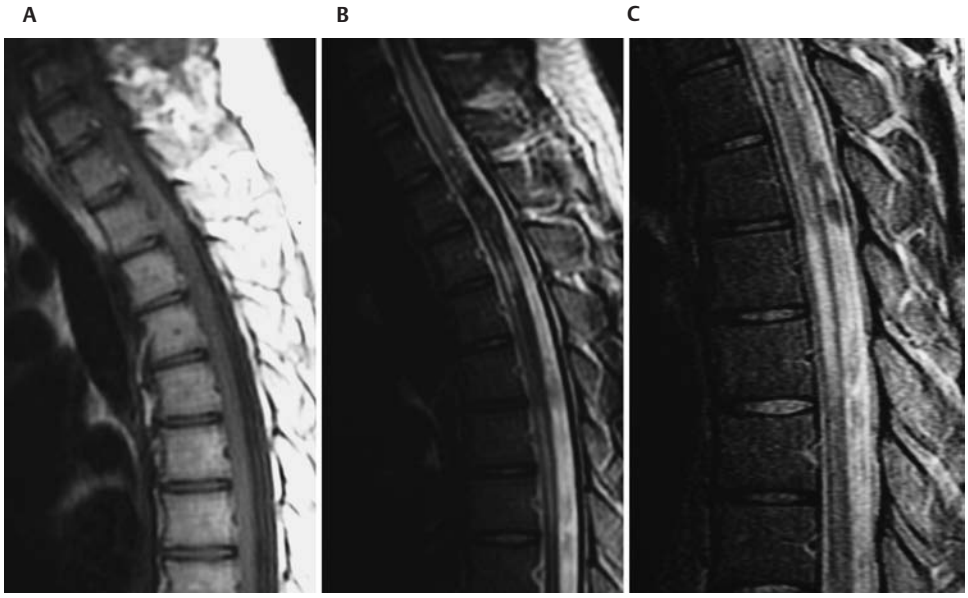

Figure 8–4 Intramedullary cavernous malformation in a 21-year-old man with progressive myelopathy and paraplegia after hemorrhage into previously demonstrated lesion. **(A)** Sagittal T1-weighted image. Intramedullary expansion at the lower T2 and T2-T3 vertebral levels. No appreciable enhancement on postcontrast images (not shown). **(B)** Sagittal T2-weighted image. Mixed signal intensity elongated ovoid focus within intramedullary lesion at lower T2 and T2-T3 with surrounding low signal intensity hemosiderin, particularly at its superior aspect. Cord edema superior and inferior to T2-T3 reflecting recent hemorrhage. **(C)** Sagittal short tau inversion recovery (STIR) image. Cord edema is particularly apparent at T5-T6.

MRI also help to determine whether to operate on, or to expectantly manage, patients who are asymptomatic or mildly symptomatic.

♦ Imaging of Extra-axial Cavernous Malformations

Whether at the cavernous sinus region, within the ventricles, at the sellar/suprasellar region, along cranial nerves, or even within the convexity dura,[7] extra-axial CMs often exhibit more prominent enhancement. They may contain calcification, but hemorrhage is rare.[8,9] Extra-axial CMs frequently lack the appearances characteristic of intra-axial intracranial CMs including a hemosiderin rim, characteristic central hemorrhage components, and calcification.

Momoshima et al.[10] and Savoiardo et al.[11] reviewed the literature regarding imaging of middle cranial fossa extra-axial CMs. In CT, the lesions are hyperdense, with homogeneous or inhomogeneous contrast enhancement. In angiography, they range from avascular to having a moderate late vascular blush. In MRI, the lesions typically demonstrate hypointensity to isointensity on T1-weighted images, and notable hyperintensity on T2-weighted images, with homogeneous enhancement.

♦ Postoperative Imaging After Cavernous Malformation Resection

Due to blood products within the central surgical bed, postoperative imaging can suggest remnant CM despite complete resection. Immediate postoperative imaging with subsequent follow-up imaging is helpful to establish that the lesion has been adequately resected.

♦ Differential Diagnostic Considerations When Reviewing Imaging of Cavernous Malformations

Based on MRI criteria, low flow and thrombosed arteriovenous malformations (AVMs) may resemble CMs. Thrombosed aneurysms might present heterogeneous internal signal intensities on MRI, but often have a more lamellated internal structure **(Fig. 8–2)**. Low-grade gliomas with calcification and hemorrhagic neoplasms (primary or metastatic) might also appear somewhat similar to CMs, with differentiation often possible based on lack of a complete hemosiderin rim and presence of surrounding T2 prolongation. In particular, follow-up imaging may be necessary for differentiation from hemorrhagic metastases in some cases.

In contrast, interval symptomatic progression of CMs, particularly in the brain stem, may result in their misdiagnosis as a hemorrhagic/infiltrative neoplasm. More acute/subacute hemorrhage within a CM may also dominate its appearance and, in conjunction with perilesional edema and the mass effect seen with recent hemorrhage, may cause the CM to appear noncharacteristic and to be confused with a hematoma in MR images **(Figs. 8–1 and 8–3)**. Close follow-up imaging to establish the expected temporal evolution of a nontumoral hemorrhage can be employed to corroborate the diagnosis of CM in such cases. The lack of underlying enhancing tissue can help to establish the diagnosis of CM as well.

The appearances of extra-axial CMs are often not characteristic. Intraventricular CMs may lack distinct surrounding

hemosiderin and exhibit interval growth, contributing to the erroneous diagnosis of neoplasm in this location as well.[12] A CM of the parasellar region could easily be mistaken for a parasellar meningioma of syncytial or angioblastic subtype by MRI, with angiography showing minimal or no abnormal blush and rare feeding arteries. Parasellar meningiomas may in contradistinction show irregular hypervascularity and arteriovenous shunting.[10] CT can be of value in this differentiation if findings typical of meningioma such as hyperostosis and blistering are noted. The observation of bone erosion and destructive change, on the other hand, may be seen with either entity. Radionuclide imaging can also be of assistance in this determination, with thallium 201 single photon emission CT showing low uptake in parasellar CMs and high uptake in syncytial/angioblastic meningiomas.[13]

A recent case report[14] highlights the rare possibility of hematogenous infection of CMs. The preoperative imaging showed perilesional edema and mass effect out of proportion to the size and morphology of the small frontal lobe CM. This was identified as a potential clue to the superimposed cerebritis and abscess that was subsequently identified.

Finally, a suprasellar CM with calcification might resemble an aneurysm or craniopharyngioma.[8]

♦ Classification of Cavernous Malformations

The most widely adopted classification scheme for cerebral vascular malformations, attributable to McCormick[15] and Russell and Rubinstein,[16] categorizes them into four overall categories: capillary telangiectasias, cavernous malformations, arteriovenous malformations, and venous malformations (i.e., venous angiomas/developmental venous anomalies). This represents a modification of the Cushing and Bailey 1928 three category classification of intracranial vascular malformations. The 1928 classification regarded angioma cavernosum (CM) as a true neoplasm.

Chaloupka and Huddle[17] suggest a well-conceived integrated classification scheme for central nervous system vascular malformations, taking into account recent advancements in our knowledge of the natural history, pathophysiology, and cellular/molecular biology of intracranial vascular malformations, in no small part contributed to by modern neuroimaging. Relevant to classification of CMs, he stresses the distinction between CMs and true hemangiomas of the central nervous system, which represent proliferating vascular tumors typically seen in the pediatric age group.

In 1994, Zabramski et al.[18] reported on their prospective evaluation of the natural history of familial CMs and analyzed a total of 128 CMs. They divided CMs into four subcategories, based on pathologic correlation and CT/MRI appearance, building on prior discussions by the Barrow Neurological Institute group[19] regarding this sort of correlation.

In our interpretation of the Zabramski intracranial CM classification scheme (type I to IV), type I lesions are commonly characterized by homogeneous hyperintensity on T1-weighted images, at least at their cores. This is related to domination by subacute hemorrhage, with T1 shortening effects due to strengthened dipole-dipole magnetic interactions. This strengthened dipolar interaction is in turn caused by shorter interdipole distances (between water protons and the unpaired electrons of iron) seen in the transition of deoxyhemoglobin to methemoglobin.[20] Conversion to more chronic breakdown products of hemorrhage may result in a hypointense rim best delineated on T2-weighted and gradient-echo sequences, the result of hemosiderin-laden macrophages and iron deposition in the white matter surrounding the lesion.

The fairly prototypical lesion having a multinodular, heterogeneous, and reticulated ("popcorn") core is labeled a type II CM. With both T1- and T2-weighted sequences, this core is heterogeneous because of the combination of hemorrhage in various phases (oxyhemoglobin, deoxyhemoglobin, intracellular methemoglobin, and extracellular methemoglobin) separated by the intervening fibrocollagenous septae along with calcifications, as previously mentioned. The core is completely surrounded by a hypointense rim best delineated on T2-weighted and gradient-echo sequences, as can be seen with the type I lesions **(Fig. 8–1E)**.

Type III lesions are characterized by more chronic hemorrhage and exhibit isointensity or hypointensity on T1-weighted images and hypointensity on T2-weighted images.

Finally, Zabramski et al. defined type IV CMs as punctate lesions best visualized on gradient-echo images as hypointense foci, accentuated by the susceptibility effect of small amounts of hemosiderin. These lesions are often not defined on other MRI sequences **(Figs. 8–5 and 8–6)**.

Shi et al.,[21] based on retrospective study of 10 patients seen over a 12-year period, have proposed a classification for parasellar CMs, dividing these lesions into two subtypes. By our interpretation, subtype A consists of lesions that at surgery are soft, with more prominent pulsation, able to be compressed, and rebounding immediately upon release of compression. Puncture of these lesions was said to yield reddish blood, with subtype A pathologically corresponding with prominent vascular sinusoids, and little intervening connective tissue. At surgery, these are lesions that bleed profusely and are difficult to entirely resect.

Subtype B of parasellar CMs of the Shi classification represents lesions that at surgery are firmer in consistency, with lesser tumor pulsation. Pathologic examination of subtype B reveals more solid parenchyma and connective tissue. At surgery, these were more readily completely extirpated.

Mixed intracranial vascular malformations most commonly involve the association of CMs and developmental venous anomalies, as mentioned above in the discussion of postcontrast imaging. This association was first pointed out by Rigamonti and Spetzler[22] and Takamiya et al.[23] There is additionally the association of CM and capillary telangiectasia, first reported by Rigamonti et al.,[24] who postulated that the two entities might be within the continuum of a single pathologic entity. In a comment on a case report by Clatterbuck et al.[25] that is highly suggestive by MRI of the combination of capillary telangiectasia, CM, and developmental venous anomaly in the brain stem of one patient, Awad suggests that CMs may represent hemorrhage

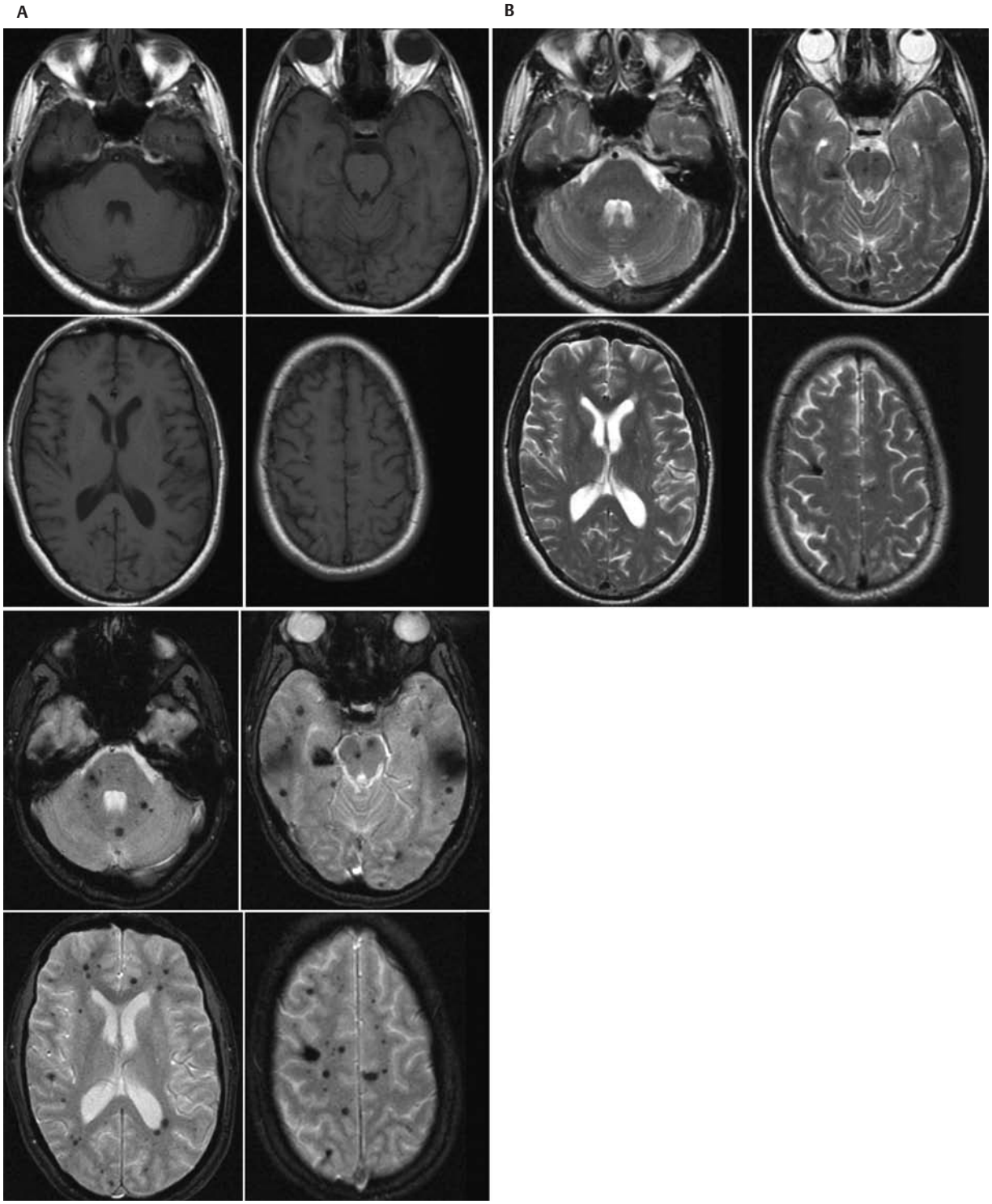

Figure 8–5 Familial cavernous malformations in a 53-year-old man with headaches and with multiple intracranial cavernous malformations that have remained clinically and radiologically stable over a period of 5 years. **(A)** Axial T1-weighted images. Inconspicuous lesions. **(B)** Corresponding axial T2-weighted images. Larger lesions are evidenced by hypointense foci. **(C)** Corresponding axial gradient echo images. Multiple Zabramski type IV lesions are apparent.

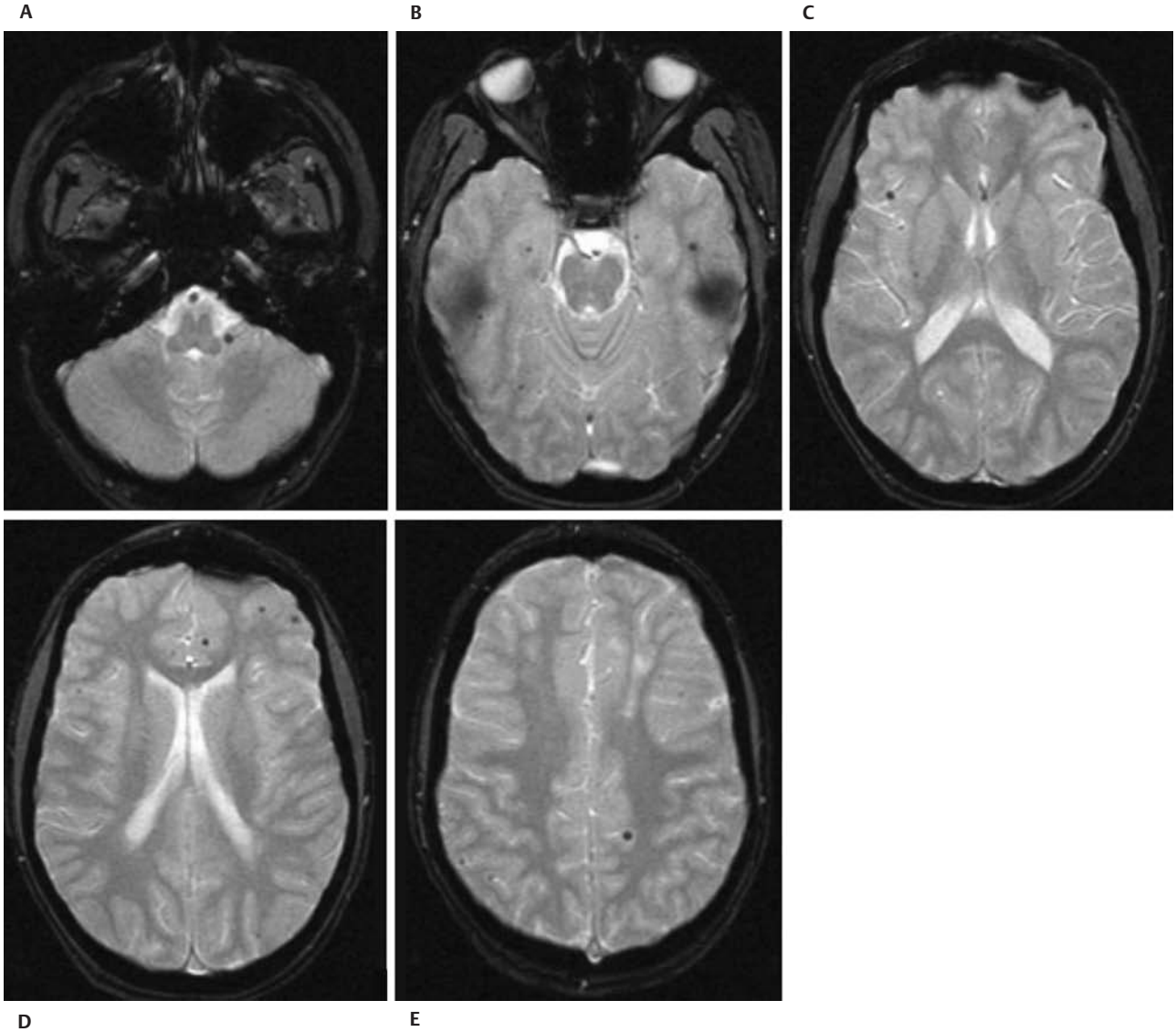

Figure 8–6 Differential diagnosis of cavernous malformations versus other hemorrhagic foci in a 15-year-old female with history of Fontan procedure for hypoplastic left heart syndrome. **(A** to **E)** Axial gradient-echo images, from inferior to superior, showing multiple 1- to 2-mm foci of hemosiderin deposition, likely secondary to embolic events or coagulopathy, mimicking type IV CMs.

and proliferative activity within preexisting capillary telangiectasias.

In a discussion of cryptic (occult) vascular malformations, Dillon[26] suggested that some degree of imprecision and confusion may be inherent in pathologic classifications of cryptic malformations solely based on analysis of tissue fragments without radiologic correlation. With MRI, these lesions are no longer "occult" or "cryptic" to presurgical imaging. These lesions by MRI criteria are often characteristic of CMs, if not of DVAs or capillary telangiectasias. This terminology, therefore, might reasonably be considered to have been rendered obsolete.

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Section II

Clinical Presentations, Indications for Surgery, Surgical Techniques, and Outcomes

9

Supratentorial Cavernous Malformations

Carlo Bortolotti, Beniamino Nannavecchia, Giuseppe Lanzino, Paolo Perrini, and Alvaro Andreoli

Cerebral cavernous malformations (CMs) have a prevalence of 0.5%,[1] and their distribution is proportional to the volume of the various portions of the central nervous system. Approximately 80% are distributed above and 20% below the tentorium. The majority of the supratentorial lesions occur in the cortical or subcortical regions.[2] Thus, supratentorial CMs are frequently encountered in clinical practice. In this chapter, we will focus our attention on supratentorial lobar and insular CMs because deep-seated supratentorial CMs and CMs in atypical locations (i.e., cranial nerves) are treated in detail elsewhere.

Cavernous malformations located in the supratentorial compartment are often located under the cortical mantle and adjacent to eloquent areas; therefore, they still represent a challenge for the neurosurgeon in terms of operative morbidity. The introduction and further development of image-guided neurosurgical systems has greatly facilitated some of the challenges encountered in the surgical removal of these lesions.[3–9] As a result, several recent surgical series have reported excellent results after excision.[10–14]

♦ Clinical Presentation and Indications for Treatment

Clinical manifestations of supratentorial CMs include seizures, hemorrhage, or progressive neurologic deficits with or without frank hemorrhage. With the widespread use of magnetic resonance imaging (MRI) a significant number of supratentorial CMs are discovered incidentally.[15] Symptoms often present in the third or fourth decade of life, although supratentorial CMs can occur in childhood and older adults. Supratentorial CMs are relatively benign lesions with a small annual incidence of bleeding.[16–25] The strategy in the management of cerebral CMs is to balance the natural history of these lesions (annual bleeding rate estimated to be between 0.25 and 0.7% per person per year in absence of prior history of hemorrhage) with the patient's condition and the risk of surgery.[26]

The most frequent clinical presentation is seizure.[14,27] Seizures secondary to supratentorial CM can often be controlled with medical treatment only, and the risk of hemorrhage is low in patients who present with seizure. For these reasons, some authors question the need to consider surgery in such cases unless the seizures cannot be medically controlled. However, numerous studies have reported improved seizure control after lesionectomy, and an inverse relationship exists between presentation-to-surgery interval and seizure control after surgical excision. Successful control of seizure is greatest in patients who undergo resection soon after onset of symptoms. The indications to consider surgery in patients with seizures are discussed in more detail elsewhere in this book. Overall, in the case of a patient with a single seizure at presentation or seizures of recent onset, surgery should be considered whenever safe because a short latency between the onset of seizures and surgical resection seems to correlate with better outcome.

Unlike cerebral arteriovenous malformations, CMs rarely cause large intracerebral hemorrhage, and the incidence of symptomatic recurrent hemorrhage is relatively low.[19] Nevertheless, surgery should be considered in patients with symptomatic hemorrhage as supratentorial CMs can be resected with a very low morbidity in the majority of cases.[10–14] More challenging from a diagnostic point of view are those patients presenting with headache in absence of acute hemorrhage. Although CMs can cause headache, it is our policy to consider for surgical resection only those patients with refractory headache that clearly localizes to the area of the CM.

Recently a "dynamic nature" of CMs in terms of "growing lesions" has been recognized.[28–37] Surgical excision should be recommended in the case of lesions that have shown progressive enlargement on serial neuroradiologic studies even in the absence of symptoms. Observation is usually indicated in patients with incidental, asymptomatic lesions that remain "quiescent" and do not show any growth on serial MRI studies. The role of radiosurgery is limited for supratentorial non–basal ganglia CMs as currently these lesions can be simply resected and localized with very low morbidity and mortality.[38,39]

♦ Surgical Treatment

Cavernous Malformations in Eloquent Areas

Cavernous malformations are frequently located adjacent to primary functional areas and can affect brain functions by mass effect, irritative effect, and consequence of hemorrhage. With recent refinements of minimally invasive surgery supported by neuronavigation systems, it is possible to surgically resect the majority of supratentorial CMs with low surgical morbidity[3,6–8] **(Fig. 9–1)**. Moreover, intraoperative recognition of eloquent cortex areas by integration of functional data (fMRI) with stereotactic or intraoperative MRI further facilitates safe and radical resection of CMs even in the primary motor, sensory, or speech areas.[4,5,9,40]

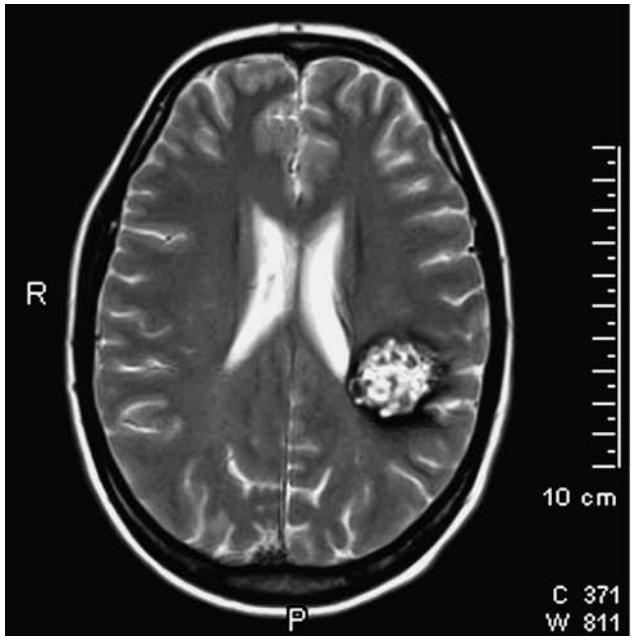
Schlosser and coworkers[41] performed fMRI studies in 24 patients harboring vascular malformations (22 AVMs [arteriovenous malformations] and 2 CMs) adjacent to primary somatosensory, motor, or visual cortex. They analyzed functional MRI (fMRI) imaging before and after therapeutic intervention and correlated the results of post-therapeutic fMRI studies with the patients' clinical status. Functional activation did not lie within the nidus of the lesion in any of the 24 baseline studies. Jannin et al.[5] reported their results using neuronavigation during surgery of supratentorial CMs through a transsulcal approach. They used 3D MRI reconstructions to select and transfer the sulci close to the CM to the neuronavigation system and superimposed the graphics into the right ocular of the microscope. This application of the neuronavigation system resulted in shorter skin incisions as well as less brain trauma by using the course of a sulcus as trajectory. More recently, Gralla and coworkers[4] retrospectively analyzed the postoperative results of 26 patients with deep-seated CMs or CMs adjacent to critical areas operated with the aid of neuronavigation and intraoperative fMRI. They concluded that the intraoperative visualization of eloquent cortical areas by integration of functional information with neuronavigation allowed fast recognition of critical brain areas improving the safety of surgical resection.

Cavernous Malformations of the Insula

Despite significant advances in the surgical resection of symptomatic CMs in critical areas, insular CMs still pose significant challenges. Only a few reports are available to detail surgical resection of CMs in this area, and a mere 24 cases of surgical resection of insular CM were found in the literature (only six located in the left insula). Because of the particular surgical pitfalls of operating lesions located in the "fifth lobe," a brief review on the anatomy and vascularity of this area is appropriate.

Microsurgical Anatomy and Vascularization of the Insula

The insular cortex or isle of Reil is a very complex structure that histologically represents several areas differing in their cortical organization: allocortex, located in the antero-inferior part, mesocortex surrounding the first one, and isocortex in the most superior and posterior portion.[42–44] Of the cerebral lobes, the insula is the only one that cannot be seen on the surface of the brain because it is entirely covered by the frontal, parietal, and temporal opercula. This anatomic configuration, the complex vascularization provided by middle cerebral artery (MCA) branches, and the proximity of the basal ganglia/internal capsule complex makes operating in this region a technical challenge. This complexity also explains why many of the insula neurophysiologic functions have only recently been discovered.[43]



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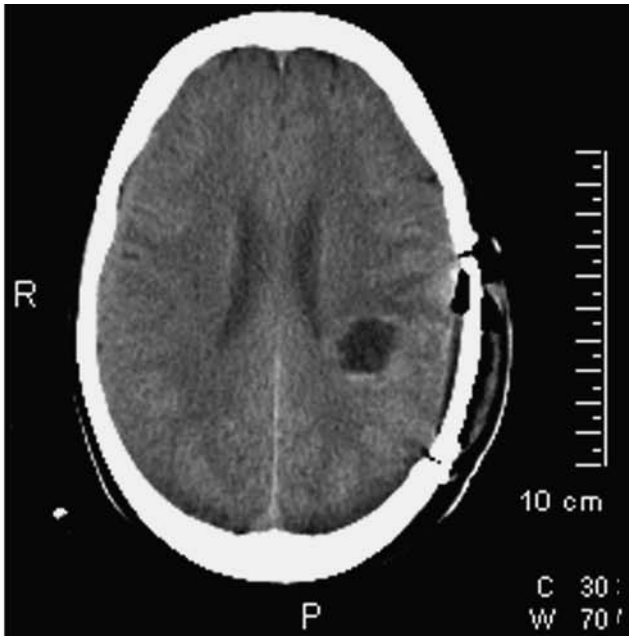

B

Figure 9–1 (A) Axial T2-weighted image demonstrates a typical supratentorial CM with the characteristic heterogeneously hyperintense reticuled central matrix surrounded by a continuous circumferential rim of T2 hypointense hemosiderin. **(B)** Postoperative CT scan after total removal of the lesion.

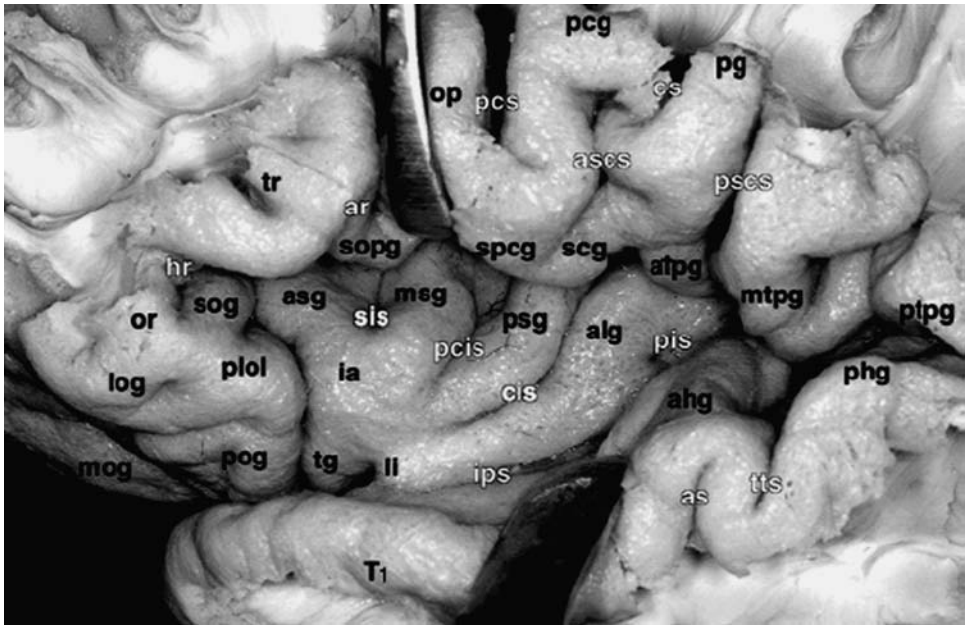

Figure 9–2 Surface anatomy of the insula. alg, anterior long insular gyrus; as, acoustic sulcus; ascs, anterior subcentral sulcus; asg, anterior short insular gyrus; atpg, anterior transverse parietal gyrus; cis, central insular sulcus; cs, central sulcus of Rolando; hr, horizontal ramus of Sylvian fissure; ia, insular apex; ips, inferior peri-insular sulcus; li, limen insula; log, lateral orbital gyrus; mog, medial orbital gyrus; msg, middle short insular gyrus; mtpg, middle transverse parietal gyrus; op, pars opercularis of F3; or, pars orbitalis of F3; pcg, precentral gyrus; pcis, precentral insular sulcus; pcs, precentral sulcus; pg, postcentral gyrus; phg, posterior Heschl gyrus; pis, postcentral insular sulcus; pog, posterior orbital gyrus; plol, posterolateral orbital lobule; pscs, posterior subcentral sulcus; psg, posterior short insular gyrus; ptpg, posterior transverse parietal gyrus; sis, short insular sulcus; sog, suborbital gyrus; sopg, subopercular gyrus; spcg, subprecentral gyrus; tg, transverse insular gyrus; tr, Pars triangularis of F3; tts, transverse temporal sulcus; T1, superior temporal gyrus. (From Ture U, Yasargil DC, Al-Mefty O, Yasargil MG. Topographic anatomy of the insular region. J Neurosurg 1999;90:720–733. Reprinted with permission.)

Morphologically, the insular lobe has a pyramidal shape. It is separated from the rest of the cortex by anterior, superior, and inferior peri-insular sulci (**Fig. 9–2**). Laterally it is bounded by the frontal, parietal, and temporal opercula and medially (from lateral to medial) by the extreme capsule, claustrum, external capsule, lenticular nucleus, and internal capsula.[44–46] The triangular surface of the insula is divided into an anterior and posterior part by the central sulcus of the insula, which extends obliquely from the superior peri-insular sulcus to the limen insulae. In about two thirds of cases, this sulcus represents the prolongation of the central sulcus. The anterior part of the insula is normally composed of three main gyri: the anterior, middle, and posterior insular gyri; whereas the posterior portion consists of an anterior and a posterior long insular gyri.

In planning the surgical approach to an insular lesion, a key point is the knowledge of the arteries supplying this region. The insula is supplied mainly by the M2 segment of the MCA (**Fig. 9–3**). After dividing into the superior and inferior trunks at the level of the limen insulae, the M2 segments of the MCA fan out over the insular cortex and give rise to several arterial branches (**Fig. 9–3**). In their microanatomical study of the insular arterial supply, Ture et al.[45] described an average of 96 insular arteries. Eighty-five to 90% of these arteries are classified as short insular arteries supplying the insular cortex and the extreme capsule (**Fig. 9–4**). Ten percent are medium-sized arteries and supply the claustrum and external capsule. The remaining 3 to 5% are long arteries reaching the corona radiata. Another contribution to the vascularization of the insula may come from the lateral lenticulostriate arteries (LLAs). The LLAs usually arise from the inferomedial aspect of the M1 segment, penetrate the anterior perforated substance, and supply the head and body of the caudate nucleus, the lenticular nucleus, the internal capsula, and the corona radiata.[45] In some cases,[47,48] the LLAs may originate from M1 as well as from the M2 segment and supply more lateral structures such as the claustrum and the external capsula. Ture and colleagues[45] reported an M1 origin of the LLAs in 78% of their specimens. In the same study, the LLAs originated from the frontal or temporal branch in 18% of cases and from the superior or inferior trunk of the M2 near to the main bifurcation of the MCA in 4% of cases. During surgery for insular lesions, it is very important to be aware of these anatomic variations. Occlusion of one of these vessels while trying to reach a deep-seated insular CM may result in postoperative hemiplegia.

The M3 segment of the MCA begins at the anterior, superior, and inferior peri-insular sulci where the arteries angle abruptly and supply the hidden medial surface of the frontoparietal and temporal opercula. They then continue their course on the surface of the Sylvian fissure to supply the cortical surface of the convexity becoming the M4 segments. In a microanatomical study of the insular vessels, Varnavas and Grand[49] found that in 90.6% of the specimens, the same artery supplying the central insular sulcus continued on to become the rolandic artery. During surgery in this region, it is imperative to avoid damaging this vessel.

Surgical Considerations and Technique

Because of its location under the perisylvian opercula and its complex vascular supply, the insula presents numerous surgical pitfalls. Refinements of neuronavigation systems and

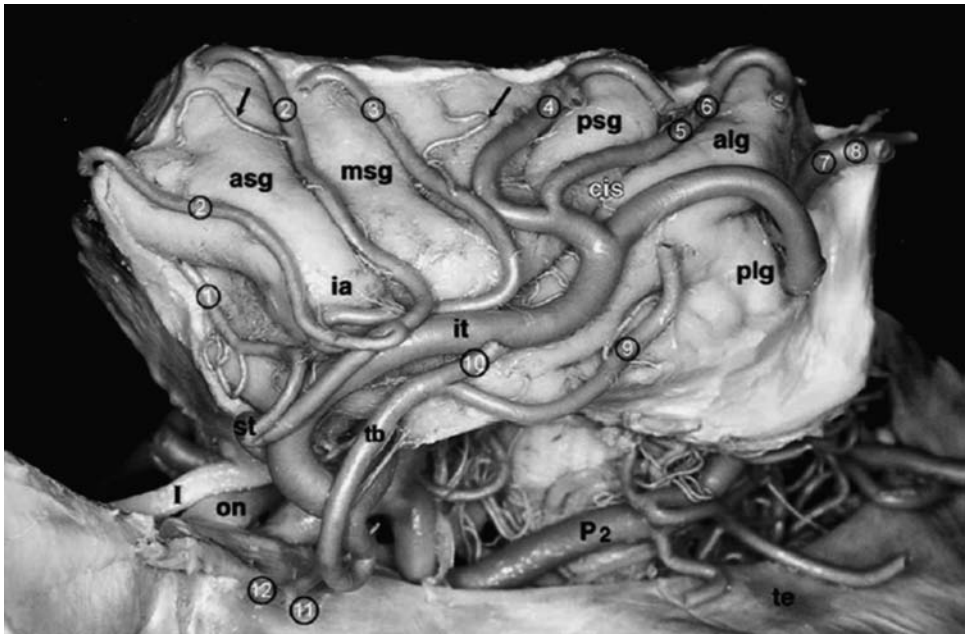

Figure 9–3 Vascularization of the insula. alg, anterior long insular gyrus; asg, anterior short insular gyrus; cis, central insular sulcus; I, olfactory nerve Ia, insular apex; It, inferior trunk of M1; msg, middle short insular gyrus; on, optic nerve P2, ambient segment of posterior cerebral artery; plg, posterior long insular gyrus; psg, posterior short insular gyrus; St, superior trunk of M2 segment; tb, temporal branch of MCA; te, temporal edge. (From Ture U, Yasargil MG, Al-Mefty O, Yasargil DC. Arteries of the insula. J Neurosurg 2000;92:676–687. Reprinted with permission.)

improved understanding of the anatomy and physiology of this region have increased the safety and accuracy of microsurgery of the insular region. In planning surgery to an insular lesion, the nature of the lesion itself is very important in allowing safe resection. Unlike primary glial tumors, CMs are very well demarcated lesions that displace rather than infiltrate normal brain parenchyma. Thus, they lend themselves to be removed through a limited exposure. Outcome in surgery of insular CMs depends basically on four steps: (1) meticulous and wide opening of the Sylvian fissure while preserving the integrity of the perisylvian opercula and the Sylvian vessels; (2) microsurgical dissection of the M2-M3 branches and of the lenticulostriate vessels; (3) choice of a convenient trajectory to reach and remove the lesion that does not appear on the cortical surface; (4) respect of the internal capsula especially in deep-seated insular CMs. In our opinion, neuronavigation is an important aid in points (3) and (4) because precise localization of the lesion and avoiding damage of the internal capsule in deep-seated insular CMs still represent a challenge even for the most experienced and skilled neurosurgeon.

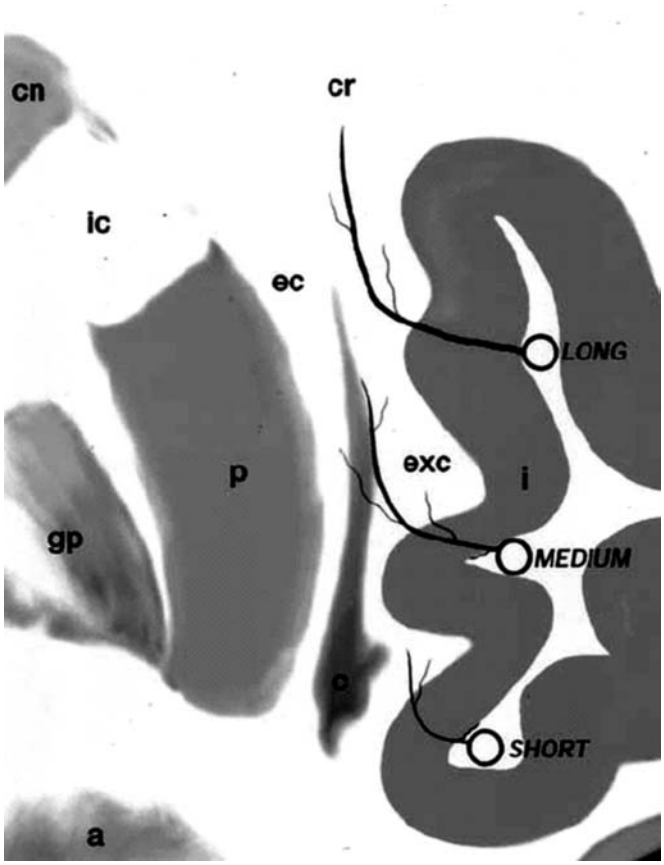

Figure 9–4 Classification of insular arteries. a, amygdala; c, claustrum; cn, caudate nucleus; cr, corona radiata; ec, external capsule; exc, extreme capsule; i, insula; Ic, internal capsule; gp, globus pallidus; p, putamen. (From Ture U, Yasargil MG, Al-Mefty O, Yasargil DC. Arteries of the insula. J Neurosurg 2000;92:676–687. Reprinted with permission.)

Bertalanffy and colleagues[12] reported on 10 deep-seated supratentorial CMs removed through a transylvian-transinsular approach. Six lesions were located in the insular region, three in the basal ganglia, and one in the posterior limb of the internal capsula. New severe postoperative neurologic deficits occurred in 7 of 10 patients and were attributed to the manipulation of the lenticulostriate arteries and to excessive resection of the perilesional hemosiderin-stained brain tissue. Heffez[39] analyzed the results after stereotactic, transylvian-transinsular resection of deep-seated lesions. With the aid of the stereotactic intraoperative localization, Heffez resected 10 lesions in the insular region, including 5 CMs, all located under the insular surface. In this series, the lesions were located at a depth ranging from 5 mm to 2 cm under the cortex. One CM extended and involved the lateral aspect of the posterior limb of the internal capsule. No new neurologic postoperative deficits were observed. Heffez stressed the concept that the insula and white matter tracts lateral to the internal capsule (extreme capsule, claustrum, external capsule) can be disrupted without inducing disabling neurologic deficit and that unilateral disruption of the lenticular nucleus while

preserving the motor cortex and the internal capsule does not results in any significant motor deficits.

More recently, Tirakotai and coworkers[7] summarized their results in eight patients with symptomatic insular or subinsular CMs all treated with the aid of neuronavigation. Unlike their previous results,[12] no new permanent neurologic deficits occurred postoperatively. These improved results were attributed to the introduction of neuronavigation. To minimize the effects of intraoperative brain shift, they suggest rotating the patient's head 90 degrees from the midline toward the side opposite to the lesion. In this manner, cortical displacement due to brain shift is limited only to the vertical plane, and shift of the insular surface did not exceed 5 mm in any patient.[50] Only in one case were multiple cortical incisions required to reach the lesion. Lesions located in the left insula present additional challenges because of the contiguity of speech areas. Duffau and Fontaine[3] resected a left anterior insular lobe CM in a 33-year-old patient using neuronavigation in addition to awake surgery for language monitoring. The lesion was radically removed, and the patient did not suffer new postoperative deficits.

We also use frameless stereotactic to aid in the localization of insular CMs reached through a transsylvian-transinsular approach as first described by Suzuki and Sato in 1972.[51] The patient is positioned in the supine position (with the head slightly rotated to the contralateral side). A question-mark skin incision (starting 1 cm in front of the tragus, extending anteriorly to the ipsilateral midpupillary line behind the hairline) is fashioned. After a standard frontotemporal craniotomy and dura opening, we open the distal Sylvian fissure. Sometimes the venous vascular pattern of the Sylvian fissure makes the opening very difficult and the surgeon has to preserve bridging veins that cross the surgical field working in a small surgical corridor. In these situations, to obtain an adequate exposure of the lesion without an excessive retraction of the perisylvian opercula, a small resection of noneloquent parenchyma may be necessary. For these reasons, some authors propose resection of the superior temporal gyrus, as first described by Heros et al. in 1982,[52] to approach insular lesions.

Once the insular cortex has been exposed, its surface is inspected closely for discoloration or for bulging parenchyma suggestive of an underlying lesion. Two techniques can be used to reach deep lesions under the cortex: the transulcal or the transgyral approach.[53,54] It is still not clear whether disruption of U fibers in two adjacent gyri (which occur in the transsulcal approach) is less dangerous than disruption of vertical fibers (which occurs in the transgyral approach). If a transsulcal approach is preferred, care should be taken to avoid injury of the sulcal vessels. If necessary to reach a deep lesion, structures lateral to the internal capsula can be safely dissected without severe permanent neurologic deficits. Once the CM has been identified, the well-demarcated aspect of these lesions usually allows easy dissection from the surrounding parenchyma. However, in some situations such as large CMs or in the presence of an overt hemorrhage, recognition and preservation of the microvascularization of the insula and of the internal capsula can be quite difficult.

Cavernous Malformations of the Brain Associated with Developmental Venous Anomalies

Developmental venous anomalies (DVAs) of the brain are considered the most common form of cerebral vascular malformations occurring in up to 4% of the population. The natural history of DVAs is benign with the vast majority (if not all) of these lesions remaining clinically silent,[20, 55] although several reports in the past have described an aggressive course with intracerebral hemorrhage.[56,57] With the widespread use of MRI, CMs and DVAs are frequently observed to coexist on imaging studies. As summarized elsewhere in this text, the current theory is that there is a causal relationship between the DVA and the CM. In the future, better understanding of this causal relationship will shed light on the pathogenesis of CMs. Kamezawa et al. studied the clinical implications of DVA associated with CMs and observed a higher tendency to hemorrhage and thus a more aggressive clinical course in those patients with CMs and associated DVAs on imaging studies.[58]

When a CM is associated with a large DVA, it has been traditionally recommended to spare the DVA to avoid the risk of venous infarction. However, a provocative recent report by Wurm and coworkers suggest coagulation of the DVA to prevent recurrence of the CM.[59] These authors reviewed the clinical and surgical aspects of 15 patients (out of a total of 58) with CM and venous anomalies. They resected the CM and coagulated the transcerebral draining vein in nine patients: six at the first operation and in the remaining three patients after hemorrhage from a recurrent CM. They did not observe any evidence of brain edema or hemorrhagic infarcts as a result of the DVA sacrifice. Although we do not recommend coagulation of the associated DVA, we think that further investigation into the issue of the mutual relationship between DVA and CM is warranted to improve our understanding of CMs and better guide our therapeutic approach. It cannot be excluded that by treating the CM, we are treating the symptom and not the disease itself, which might indeed be the DVA.

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10

Deep-Seated Cerebral Cavernous Malformations

Uygur Er, Robert F. Spetzler, Andrea Cardia, and Giuseppe Lanzino

Deep-seated cavernous malformations (CMs) constitute a subgroup of lesions located in the basal ganglia, thalamus, periventricular area, insular-subinsular region, ventricular system, and brain stem. These lesions pose significant challenges because of the critically important neurologic functions associated with these small and vulnerable cerebral regions. This chapter considers only CMs located in the thalamus and basal ganglia because CMs located in the ventricles, insular-subinsular region, and the brain stem are treated elsewhere in this book.

♦ Epidemiology

Analysis of the published literature in relation to CMs of the thalamus and basal ganglia is difficult as only a few reports have concentrated on these particular locations,[1] and many series have considered these deep-seated lesions in conjunction with brain-stem CMs. Similar to CMs located in other locations throughout the central nervous system (CNS), thalamic and basal ganglia CMs have been considered to occur infrequently, and little was known about their clinical significance. The widespread introduction of magnetic resonance imaging (MRI) has dramatically increased detection of these lesions.[2–5] The distribution of CMs is representative of the distribution of the neural tissue along the cranio-spinal axis.[2] However, CMs of the thalamus and basal ganglia are reported to range between 6.9% and 21.7% of all CMs in the literature.[1,3,6–8] This great variability probably reflects referral biases inherent to these series, which are primarily surgical series from prominent tertiary referral centers.

A recent report has calculated the incidence of the deep-seated CMs to be ~3.2/1,000,000 per year and 0.8/1,000,000 per year when symptomatic and incidental lesions are considered, respectively.[9] Some series suggest a significant difference in the sex predilection of thalamic and basal ganglia CMs[6] with a female preponderance observed especially among symptomatic patients.[1,3] Other authors, however, have observed equal distribution between the two sexes.[7] The age range at diagnosis varies between 5 and 54 years with most lesions diagnosed in the third and fourth decades of life[1,7] **(Table 10–1)**.

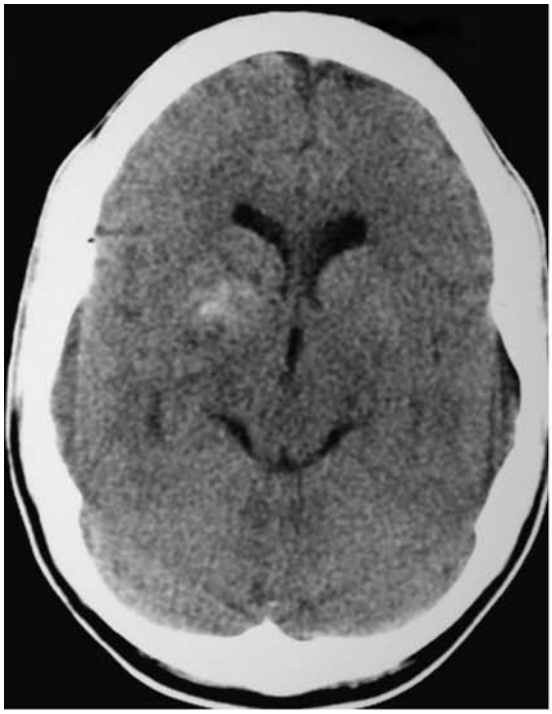
♦ Natural History and Clinical Presentation

The clinical presentation of deep-seated CMs is quite different than lesions located in other portions of the CNS. Patients with symptomatic lesions often suffer from the sudden onset of various constellations of symptoms and signs. The onset of symptoms generally occurs before the third decade of life. Symptoms and signs at presentation are closely related to the location of the lesion. Patients with thalamic CMs frequently present with acute motor and/or sensory symptoms and signs with or without headache. Lesions located in the medial thalamus or those lesions with extension toward the third ventricle can cause hydrocephalus[1,7,9] **(Fig. 10–1)**. Hydrocephalus as presenting symptom can occur in up to 15% of thalamic CMs.[9] Of course, seizures as presenting symptom are less frequently observed in deep-seated lesions when compared with more superficial ones.[1,8] Lesions located in the basal ganglia can also cause hemichorea, focal dystonia, and other basal ganglia–related symptoms.

Although the likelihood of hemorrhage appears approximately equal among CMs, regardless of their location,[2] CMs in critically eloquent areas such as the thalamus become symptomatic even with minimal volumetric changes of the lesion and give a false impression of higher hemorrhage rates when compared with CMs located in less eloquent areas.[10] The incidence of hemorrhage also varies according to the criteria used in defining it (clinical, radiologic, or both). The fact that different criteria have been used to define hemorrhagic risk in the literature makes it difficult to compare different series. This also explains the great variability in the rate of first hemorrhage. It is calculated that the overall risk of first hemorrhage from a thalamic or basal ganglia CM ranges between 0.7% and 5% per year. In patients with prior history of hemorrhage, the reported annual subsequent bleeding rate varies between 4.5% and 30%.[10,11] There is no significant difference in the annual bleeding rate between familial and sporadic cases. History of prior hemorrhage is the most important risk factor for subsequent hemorrhage. The location of the CM (thalamus or basal ganglia) does not correlate with subsequent hemorrhage risk.[11] Similar to CMs located in other areas, deep-seated supratentorial CMs can increase in size over time.[5]

Table 10–1 Summary of Literature of the Natural History of Deep-Seated Cavernous Malformations

Author (Year)	Location		Mean Age (Years)	Sex		Risk of Hemorrhage and Events (%/Year)	Follow-up (Years)
	Thalamus	Basal Ganglia		M	F		
Bertalanffy et al. (1991)[7]	2	3	24	3	2	—	2.5
Aiba et al. (1995)[3]	7		35	4	3	11	6.5
Kondziolka et al. (1995)[11]	20		—	—	—	2.9	2.8
Pozzati (2000)[1]	12	—	36	2	10	6.1	6.5
Mathiesen et al. (2003)[9]	12	11	—	13	10	—	4.6



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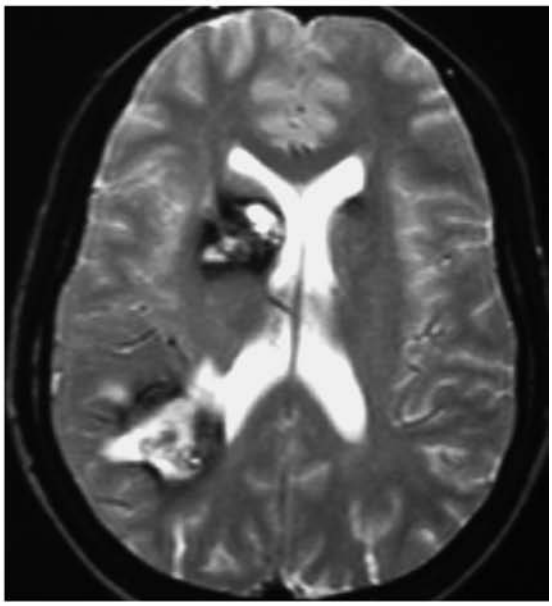

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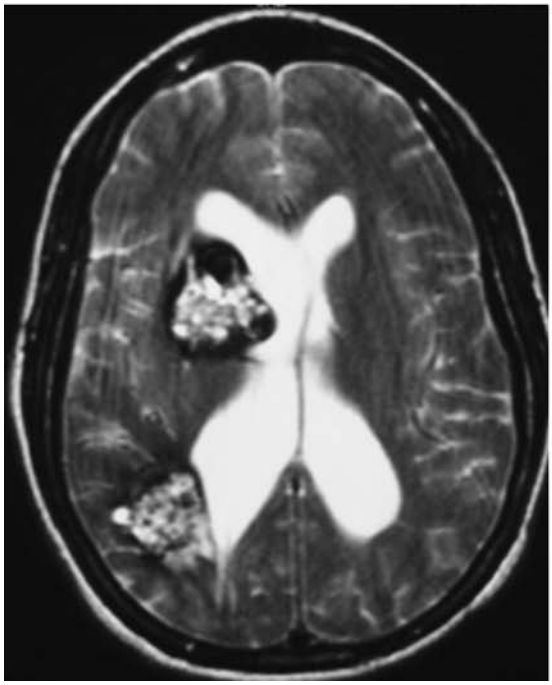


C

Figure 10–1 (A) Computerized tomography of the brain done in 1990 shows multiple calcified lesions. The patient, at that time 20 years old, was followed with serial MRI studies. **(B)** Axial, T2-weighted MRI done in 1993 reveals the presence of a right anterior thalamic lesion in addition to other abnormalities with the characteristic appearance of CMs. The patient continued to remain asymptomatic until 1998 when **(C)** she developed signs and symptoms of hydrocephalus. She has been treated with bilateral ventriculoperitoneal shunts and has remained symptom-free since. Further MRI studies have shown no evolution of the multiple CMs.

Multiple lesions are observed in up to 2.5% of patients with deep-seated CMs.[7,9]

♦ Surgical Treatment

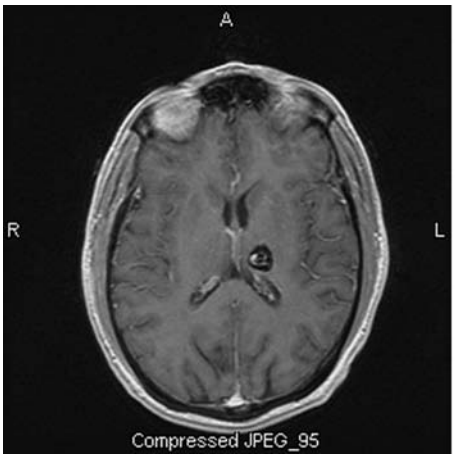
Indications and Surgical Technique

Surgical treatment of deep-seated CMs is indicated in symptomatic patients who have suffered prior hemorrhage. Radical surgical excision of the lesion eliminates the risk of subsequent bleeding and may result in improvement of symptoms in patients suffering from mass effect.[9,12] Similar to CMs located in other highly eloquent areas such as the brain stem and the spinal cord, the decision on whether or not to surgically excise these lesions depends on their location in relation to the pial or ependymal surface. Lesions that abut the ventricular or pial surface can be safely excised without the need of traversing eloquent structures. However, in the case of basal ganglia and thalamic CMs, recent surgical experience indicates that surgical excision can be successfully performed also in the case of symptomatic lesions located deep within the brain surface without causing additional morbidity.[9] In patients who present with symptomatic hydrocephalus without a history or neuroradiologic documentation of hemorrhage, treatment of hydrocephalus alone is a reasonable option **(Fig. 10–1)**. The role of alternative treatment modalities (i.e., Gamma Knife) in surgically inaccessible lesions is controversial[4,13–15] and is discussed extensively elsewhere in this book.

There is no consensus about the timing of surgery in patients who have suffered a hemorrhage. Some authors prefer to wait 4 weeks to permit neurologic recovery and stabilization of the lesion.[12] Others suggest operating in the subacute period because the fresh hemorrhage makes recognition of the cleavage plane and dissection of the lesion easier. In addition, it has been observed that hematoma organization and formation of an adherent gliotic plane around the lesion over time can make the dissection more difficult, and it is associated with an increased risk of postoperative transient and permanent neurologic deficits.[9] It is our preference to perform surgery whenever possible in the subacute phase (within 2 to 3 weeks) after a symptomatic episode. A shorter time interval between a symptomatic hemorrhage and surgery also decreases the risk of further deterioration from additional hemorrhages, which seems to be higher in the first 18 to 24 months after an initial episode.[16]

Surgical planning depends on the specific location of the lesion and its position in relation to the ependymal or pial surface. Assessment of the resectability of these lesions and their relationship to the pial or ependymal surface should be based on the T1 sequence of the MRI (**Fig. 10–2**). On the T2-weighted images, a "blooming" artifact from the hemosiderin-stained surrounding tissue may give a false impression of superficiality. Intraoperative frameless localization has been in our and other authors'[12] experience an invaluable tool in facilitating the intraoperative localization and resection of such lesions. Because of their central location, usually there are no problems related to inaccuracy of the frameless system secondary to intraoperative brain shift. This is true even in case of lesions approached through a transventricular approach during which significant amounts of cerebrospinal fluids are drained.

Deep-seated lesions of specific sites require different surgical approaches. Schematically, CMs of the thalamus and basal ganglia can be divided in medial and lateral lesions. Most thalamic CMs can be reached through an ipsilateral or contralateral interhemispheric transcallosal approach.[9,12,17–19] We prefer a contralateral approach in which the patient is placed supine with the head positioned with the sagittal suture parallel to the floor and elevated 45 degrees **(Figs. 10–3A, B)**. Too much neck torsion should be avoided to prevent venous return obstruction. The side bearing the lesion is placed up. By approaching the lesion from the contralateral side, a more direct view of the CM is obtained when compared with the ipsilateral interhemispheric approach **(Fig. 10–4)**. In addition, gravity drops the ipsilateral (to the approach) hemisphere so minimal or no retraction is required **(Fig. 10–4A)**. The contralateral approach also affords better visualization of the



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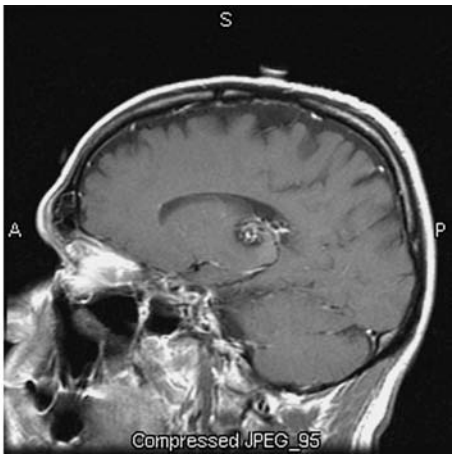


B

Figure 10–2 (A) Axial and **(B)** sagittal T1-weighted MRI of a 58-year-old man who presented with right hand incoordination and weakness. There exists a lesion with the typical appearance of a CM involving the midposterior aspect of the left thalamus. (From Lanzino G, Wanebo JE, Spetzler RF. Contralateral interhemispheric resection of thalamic cavernous malformations with frameless stereotaxy. Operative Techniques in Neurosurgery 2002;5:191–197. Reprinted with permission.)

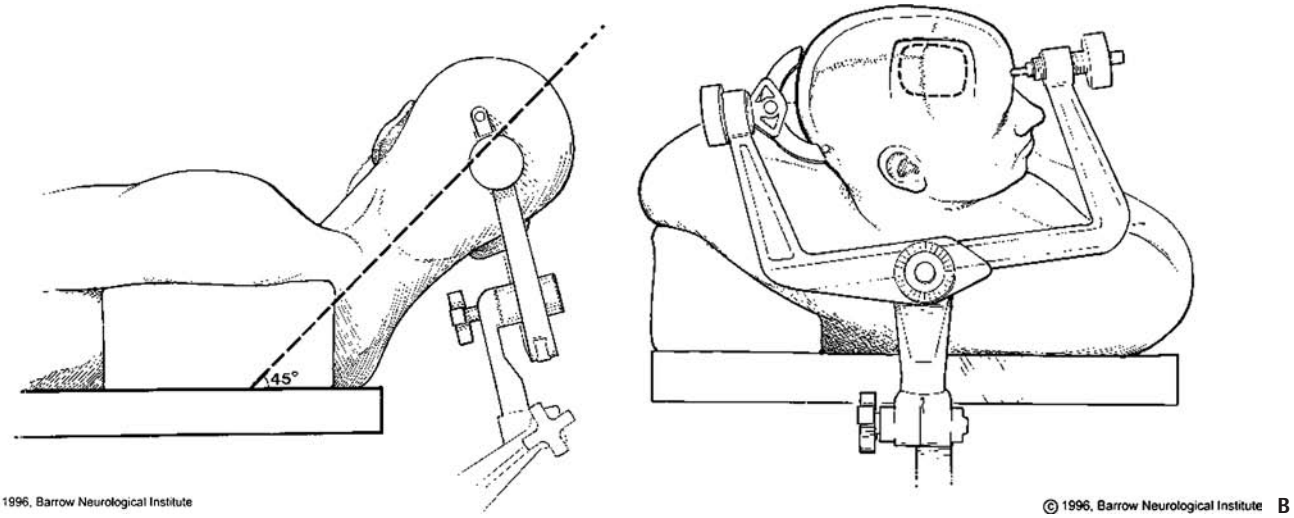


Figure 10–3 (A) In the contralateral interhemispheric approach, we place the patient head flexed laterally ~45 degrees to obtain an ideal angle of view. The side bearing the pathology is placed up. **(B)** We prefer a horseshoe-shaped skin incision carried across the midline to the contralateral side. (Used with permission from Barrow Neurological Institute.)

most lateral aspect of the lesion, which would be hard to visualize from an ipsilateral approach without significant retraction of the ipsilateral hemisphere (**Fig. 10–4A**). We prefer a frontoparietal U-shaped skin incision that extends across the midline (**Fig. 10–3B**). The craniotomy is performed with two-thirds of the bone flap anterior and one-third posterior to the coronal suture (**Fig. 10–3B**). The craniotomy is taken across the superior sagittal sinus, and the dura is opened in a curvilinear fashion with the dura flap based on the superior sagittal sinus. The dura is then tented to the contralateral side. This maneuver elevates the lateral margin of the sinus improving the surgeon's view into the interhemispheric fissure. The angle of the approach can be tailored to the position of the specific lesion (**Fig. 10–5**). Through this approach, lesions localized in the posterior thalamus can also be successfully resected. The corpus callosum is then identified and a small callosotomy done with microsurgical dissection following the indications of the frameless stereotactic system (**Figs. 10–6A, B**). In some cases, after entering the ventricle, the lesion may not be visible on the surface of the thalamus (**Fig. 10–7A**). In such cases, the incision on the thalamic surface is made in correspondence with the thinnest layer of eloquent parenchyma covering the CM as indicated by the frameless system (**Fig. 10–7B**).

Lateral lesions involving the basal ganglia can be reached through a transsylvian approach.[20,21] The key point of this approach is preservation of the lenticulostriate arteries.[17,22] Care also has to be exercised in the resection of those lesions involving the internal capsule, particularly the genu and the posterior limb, which contain fronto-bulbar, cortico-spinal, and thalamo-cortical pathways. Injury to these regions where the long-tract fibers run packed together causes severe motor and sensory deficits. To avoid damage to these structures, it is critical to minimize the use of self-retaining retractors. Microsurgical dissection

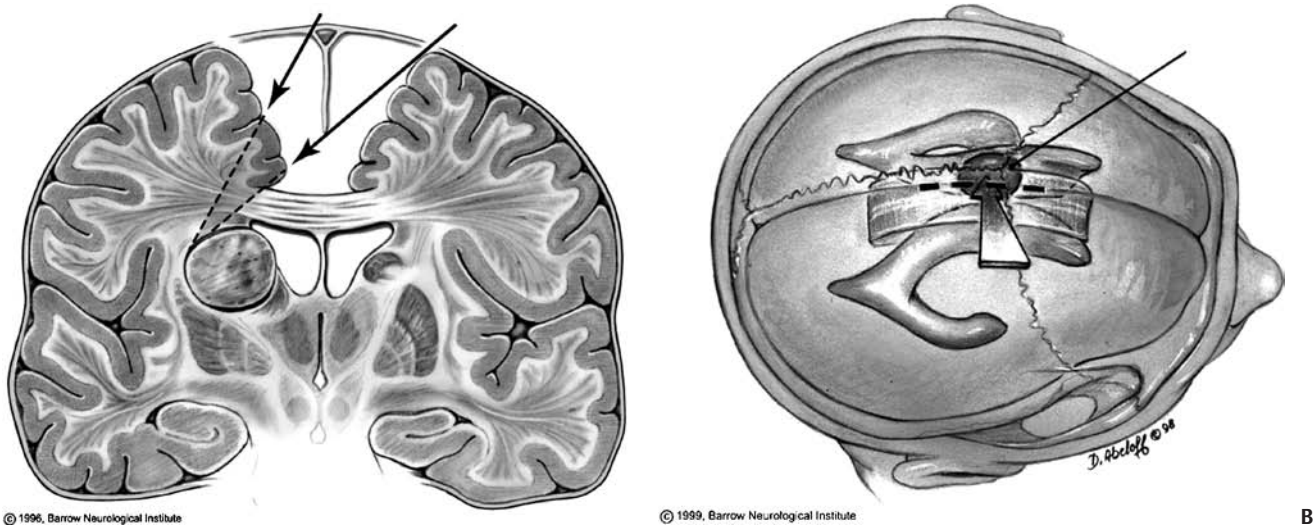


Figure 10–4 (A) By placing the lesion on the upper side to the approach, gravity pulls the ipsilateral (to the approach) hemisphere down so that retraction is minimized. The contralateral approach also offers a better angle to the most lateral portion of the lesion, which would be very difficult to expose from an ipsilateral (to the lesion) approach without significant retraction. **(B)** The contralateral interhemispheric approach provides the surgeon with a direct angle of view to the target lesion. (Used with permission from Barrow Neurological Institute.)

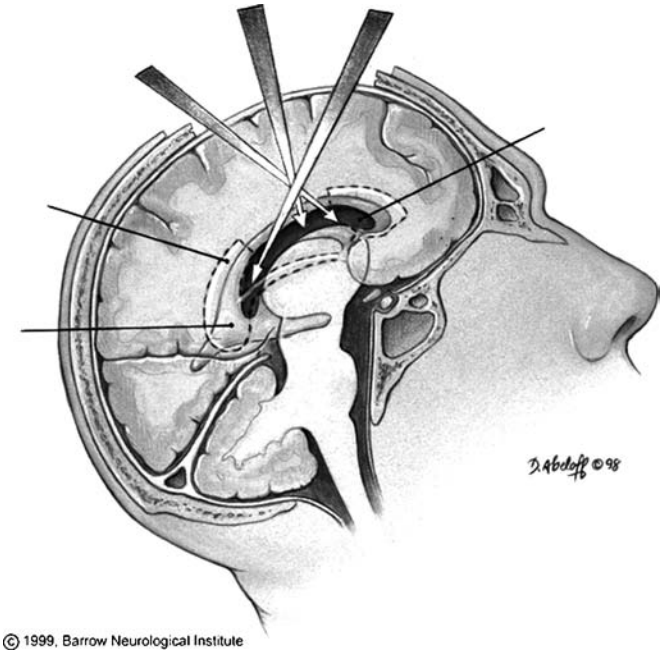
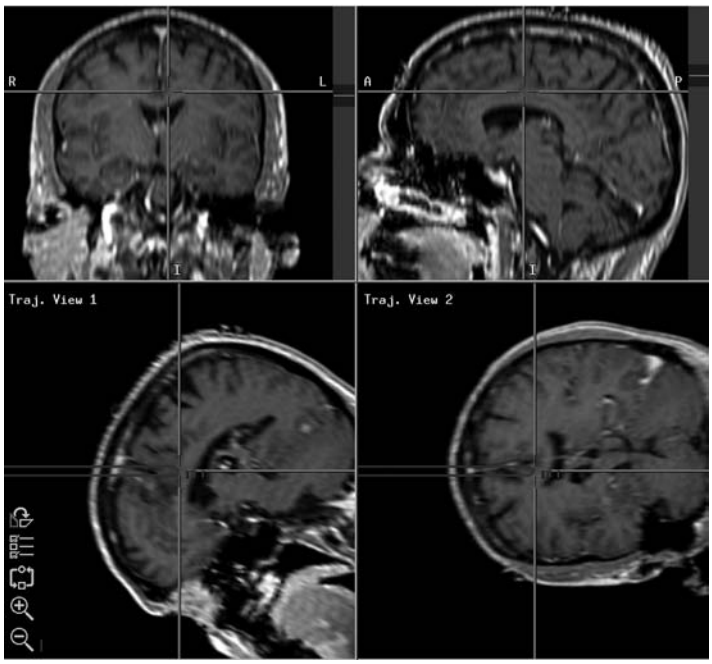


Figure 10–5 By changing the angle of the approach, lesions located throughout the entire thalamus can be reached. (Used with permission from Barrow Neurological Institute.)

and sparing of the lenticulostriate arteries supplying the internal capsule is obviously another critical step in minimizing complications.[22,23]

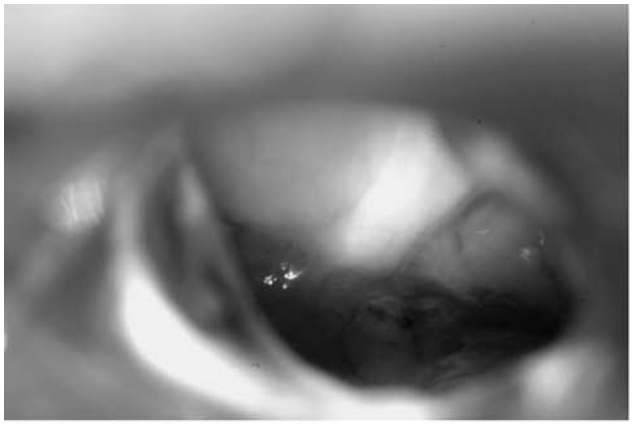
Careful microsurgical techniques under high-power magnification is essential for safe and successful surgical excision of deep-seated CMs. In deep-seated locations, excision of the lesion is often performed through an incision smaller than the CM itself. Therefore, to accomplish this goal, the lesion is resected in a piecemeal fashion. Fresh or subacute hematoma is removed first after entering the CM. Once the lesion has been internally decompressed, a plane of cleavage at the periphery of the lesion is sought and developed with a round, sharp dissector. This maneuver both isolates the CM and protects the viable parenchyma surrounding the lesion. A plane of cleavage is easily found if surgery is performed within a few weeks (2 to 4 weeks) after a hemorrhage. Such a plane may be difficult to develop as a pseudocapsule form in the adjacent brain if surgery is delayed by several weeks or months after hemorrhage.[9] In such cases, portions of the CM might be tightly adherent to areas of gliotic, hemosiderin-stained brain. Resection must be limited to the CM, and hemosiderin-stained brain should be left intact to avoid damage to viable structures. Most bleeding

A

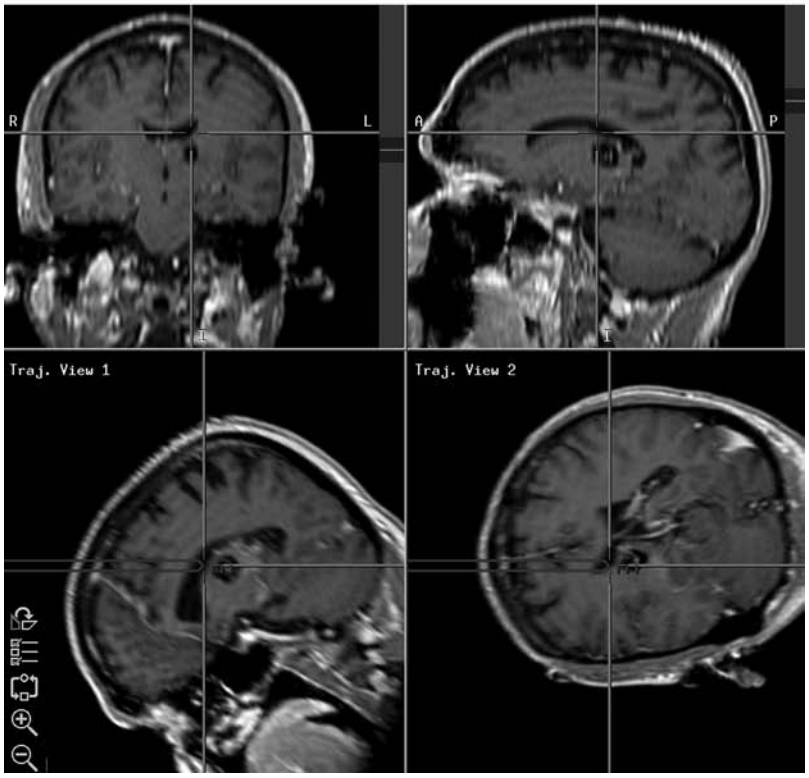


B

Figure 10–6 (A) Intraoperative microscope view of the corpus callosum. **(B)** Intraoperative frameless system confirms that the exposed portion of the corpus callosum is on the same side and aligned with the thalamic cavernous malformation. (From Lanzino G, Wanebo JE, Spetzler RF. Contralateral interhemispheric resection of thalamic cavernous malformations with frameless stereotaxy. Operative Techniques in Neurosurgery 2002;5:191–197. Reprinted with permission.)



A



B

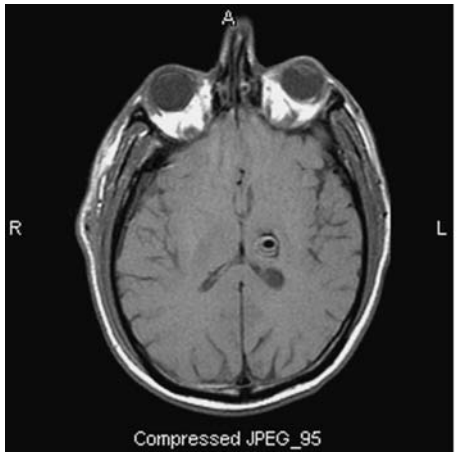
Figure 10–7 Same case as **Fig.10–6. (A)** After performing the callosotomy, the lateral ventricle is entered and the dorsal aspect of the thalamus can be seen. The CM did not reach the surface of the thalamus. **(B)** However, the intraoperative frameless system confirms that the CM lies just underneath the surface of the exposed portion of the thalamus. (From Lanzino G, Wanebo JE, Spetzler RF. Contralateral interhemispheric resection of thalamic cavernous malformations with frameless stereotaxy. Operative Techniques in Neurosurgery 2002;5: 191–197. Reprinted with permission.)

encountered during removal of lesions is low-pressure hemorrhage from the dilated sinusoidal spaces forming the CM. This bleeding can usually be easily controlled with gentle pressure and local application of a hemostatic agent. After resection of the lesion, low-pressure venous ooze from a draining vein that is almost always associated with a CM is encountered. This bleeding is also easily controlled with gentle pressure and local application of hemostatic agents. If use of bipolar cauterization becomes inevitable, very fine, low-power coagulation is advised to limit the spread of current to surrounding neural tissue. Meticulous inspection of the surgical bed under high-power magnification is necessary to identify residual "tongues" of CM. Radical resection is paramount to realize the benefits of surgical excision because residual CMs in the thalamus and basal ganglia have been associated with recurrent hemorrhage with catastrophic clinical consequences.[9,10,22]

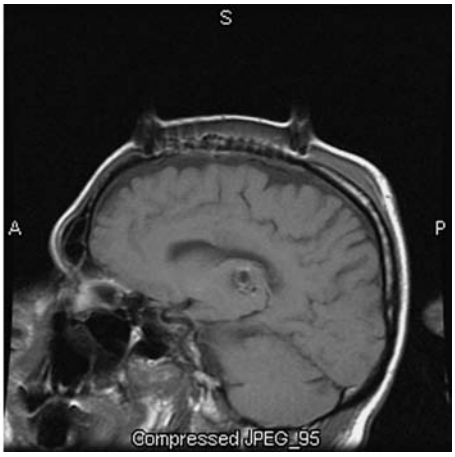
♦ Complications and Surgical Outcomes

Postoperative neurologic dysfunction due to direct manipulation of eloquent tissue during surgery of deep-seated lesion is not uncommon.[9,12,18,23] These complications are more likely to be transient. As stated previously, mild deterioration after surgery is very common and usually transient. During preoperative education, we instruct patients who have recovered from a prior symptomatic hemorrhage that even after successful surgery, they are likely to experience transient symptoms similar to those after their previous hemorrhage.

Permanent neurologic deterioration can occur from compromise of associated developmental venous anomalies (DVAs). DVAs are frequently associated with deep-seated CMs despite not being always visible on preoperative imaging studies. Sparing these veins is key to successful and safe surgery as these veins often contribute to the normal venous drainage from the thalamus, deep nuclei, and internal



A



B

Figure 10–8 (A) Postoperative axial and **(B)** sagittal T1-weighted MRI (same case as **Figs. 10–2, 10–6, and 10–7**). A baseline MRI study is obtained to establish a baseline because it is often difficult to assess the extent and completeness of surgical removal. Clinical and long-term neuroradiologic follow-up is critical in these patients to indeed confirm complete resection of the lesion. (From Lanzino G, Wanebo JE, Spetzler RF. Contralateral interhemispheric resection of thalamic cavernous malformations with frameless stereotaxy. Operative Techniques in Neurosurgery 2002;5:191–197. Reprinted with permission.)

capsule.[7,20] Devastating permanent deficits can also occur from injury of the lenticulostriate arteries, which can occur particularly in cases of transsylvian transinsular approaches to these lesions. Differentiation of perforating lenticulostriate arteries from small feeding arteries during dissection is important. The danger of residual malformation in this location with the risk of subsequent catastrophic hemorrhage cannot be emphasized enough.[9,12] Recurrent hemorrhage has been observed even after postoperative neuroradiologic demonstration of complete surgical resection.[12] Long-term neuroimaging is therefore critical in these patients. We usually perform postoperative MRI the day after surgery **(Fig. 10–8)**. Patients are then recommended to have serial MRI studies 1, 3, and 5 years after treatment.

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11

Brain Stem Cavernous Malformations

Jeffrey D. Klopfenstein, Iman Feiz-Erfan, and Robert F. Spetzler

Based on autopsy and magnetic resonance imaging (MRI) data,[1–7] cavernous malformations (CMs) of the central nervous system (CNS) affect 0.2 to 0.9% of the population. These lesions account for 5 to 16% of CNS vascular malformations.[8–10] Of all CNS CMs, 9 to 35% are found in the brain stem accounting for 13% of vascular malformations of the posterior fossa.[10–13] Importantly, CMs of the brain stem are more likely than their supratentorial counterparts to become symptomatic and, given their location, to have significant repercussions for affected patients.

With recent technological advances (e.g., stereotaxy, neurophysiologic monitoring) and mastery of posterior fossa anatomy, the earlier reluctance to operate on the brain stem has given way to an ever-increasing ability of experienced neurosurgeons to resect brain-stem CMs safely and effectively. However, given the complexity of posterior fossa surgery and its potential sequelae, surgeons must understand the surgical indications for patients with intrinsic brain-stem CMs. This chapter presents the natural history, clinical characteristics, surgical indications, operative techniques, and treatment outcomes for brain-stem CMs as a guide for managing patients with these complex lesions.

♦ Epidemiology and Natural History

Age and Sex Predilection

Over the past decade, several large series focusing on brain-stem CMs have provided important epidemiologic and natural history data (**Table 11–1**). These series suggest that the age of patients at presentation with symptomatic lesions ranges between 32 and 38 years.[11,14–20] Whether one sex is more likely than the other to harbor a brain-stem CMs is unclear. Some studies suggest that the incidence is highest among males,[8,18,20,21] whereas others indicate the opposite.[13–15,19,22,23]

Hemorrhage and Re-hemorrhage Rates

One of the most important issues related to the natural history of brain-stem CMs is their frequency of hemorrhage. The re-hemorrhage rate after an initial hemorrhage is also vital to physicians planning treatment: At presentation, 81 to 100% of patients with brain-stem CMs are symptomatic, most often related to hemorrhage.[11,14–20] The important question is whether lesions that have already hemorrhaged at least once have a higher risk of bleeding again compared with those with no history of hemorrhage.

Among reported studies, there is little uniformity in terms of how hemorrhage and re-hemorrhage rates have been evaluated. This variability makes it difficult to interpret outcomes. First, some studies are prospective, whereas others are retrospective based on the assumption that the lesions were present since birth. As has been well documented, brain-stem CMs can appear de novo. Therefore, assuming their presence since birth will underestimate the frequency of hemorrhage.[24,25] Second, some hemorrhage rates are presented as per person per year, whereas others are reported as per lesion per year. Third, the definition of hemorrhage ranges from a clinical apoplectic event to the definitive presence of acute lesional or extralesional blood on radiographic studies. Finally, almost all large series of brain-stem CMs are from specialized neurosurgical centers; thus, the issue of referral bias arises. Given these limitations, the range of published hemorrhage rates must be considered individually and as a whole to derive a reasonable estimate of hemorrhage and re-hemorrhage rates for brain-stem CMs.

Based on published series with more than 20 patients with brain-stem CMs, overall hemorrhage rates have ranged from 2.5 to 7% per patient (or lesion) per year without respect to the number of hemorrhages per patient.[11,15–20] (In two studies, hemorrhage rates were based on both brain-stem and deep supratentorial lesions ([i.e., thalamus and basal ganglia]; no breakdown was provided although most lesions were in the brain stem).[16,19] Mathieson et al. found that patients who presented with symptoms had a hemorrhage rate of 7% per person per year, whereas asymptomatic patients had a rate of 2% per patient per year.[16] Porter et al. found that when hemorrhage was defined as an apoplectic clinical event without respect to radiographic findings, the overall hemorrhage rate increased from 3.8 to 10.6% per patient per year.[18]

Whereas the overall reported rates of hemorrhage are reasonably consistent, the data for re-hemorrhage rates are

Table 11–1 Summary of Epidemiologic Data from Large Studies ($N \geq 37$) of Brain-Stem Cavernous Malformations

Author (Year)	Study Design	Sex (% Male)	Mean Age (Years)	Number of Patients	Symptomatic at Presentation (%)	Overall Hemorrhage Rate	Re-hemorrhage Rate	F/U (Months)	Comments
Fritschi et al. (1994)[11]	Retro	49.6	32	139	100	2.7%/lesion per year	21%/lesion/y	30	Bleed rates determined retrospectively
Kupersmith et al. (2001)[15]	Retro	40.5	38	37	95	2.5%/person per year	5%/person/y	59	(1) Unclear denominator for bleed rate calculations (2) Possible selection bias
Mathiesen et al. (2003)[16]	Retro/pro	52.9	N/A	68*	81	1. 2%/person per year (asymptomatic patients) 2. 7%/person per year (symptomatic patients)	Not done	55	(1) Bleed rates determined prospectively in nonoperative patients ($n = 39$) (2) Calculated bleed rates include some patients with thalamic or basal ganglia lesions
Porter P. et al.[17] (1997)	Retro/pro	N/A	38	52	88	3.8%/person per year	Not done	46	Bleed rate determined prospectively in nonoperative patients ($n = 52$)
Porter R. et al. (1999)[18]	Retro	38.0	37	100	97	5%/person per year	30%/person/y	35	Bleed rates determined retrospectively
Steinberg et al. (2000)[19]	Retro	44.0	32	56†	100	6.5%/person per year	Not done	56	(1) Bleed rates determined retrospectively (2) Calculated bleed rates include some patients with thalamic or basal ganglia lesions
Wang et al. (2003)[20]	Retro	58.4	34	137	"Most"	6%/person per year	60%/person/y	52	Bleed rates determined retrospectively

*Cohort included 45 brain-stem lesions and 23 thalamic or basal ganglia lesions.

† Cohort included 46 brain-stem lesions and 10 thalamic or basal ganglia lesions.

Abbreviations: retro, retrospective; pro, prospective; N/A, not available.

less consistent. In the large published series, the re-hemorrhage rates for brain-stem CMs with a single previous hemorrhagic episode have ranged from 5.1 to 60% per patient (or lesion) per year.[11,15,18,20] Kupersmith et al. reported a re-hemorrhage rate of 5.1%, but the study had major limitations. First, the denominator in the rate calculations was unclear. Second, the series consisted of patients referred to a neuroophthalmology service, suggesting potential bias from a less morbid subgroup compared with other studies.[15,26] If this study is excluded from consideration, the published hemorrhage rates vary from 21 to 60% per patient per year.[11,18,20] Despite the limitations, these numbers suggest that lesions that have already hemorrhaged are likely to have an increased risk of subsequent hemorrhage compared with those that have never bled. This likelihood must be considered when selecting patients for surgical management.

When the risks of hemorrhage (2.5 to 7%) and re-hemorrhage (21 to 60%) of brain-stem CMs are compared with the hemorrhage (0.25 to 3.1%) and re-hemorrhage (4.5 to 22.9%) rates per patient per year, respectively, for all CNS CMs, brain-stem CMs may be more likely to hemorrhage than their supratentorial counterparts.[2,6,12,17,18,27,28] Two hypotheses have been suggested to explain this apparent discrepancy. First, deep venous drainage may provide a unique vascular flow pattern for brain-stem lesions that somehow increases their risk of hemorrhage.[14] Second, and arguably more plausible, the eloquence of the brain stem may increase the detection of minor hemorrhagic events because symptomatic manifestations occur earlier and are more profound than those involving less eloquent areas of the brain.

Outcome after Hemorrhage

Re-hemorrhage of a brain-stem CM often increases the rate and severity of neurologic deficits and, occasionally, causes death.[11,14,17,29,30] In a study from our institution, 48% of nonoperative patients followed a mean of 35 months were worse neurologically at follow-up compared with their presentation.[18] Similarly, Porter et al. demonstrated that 50% of patients with brain-stem CMs managed conservatively developed devastating and persistent deficits after re-hemorrhage.[17] That these lesions were initially managed nonoperatively suggests that the location is exquisitely eloquent, which may skew the rate of subsequent neurologic decline upward. Nonetheless, it is reasonable to conclude that re-hemorrhage of a brain-stem CMs is associated with a significant risk for worsened neurologic status.

Hemorrhage Clustering

Multiple hemorrhages from a CM may occur in temporal proximity.[20,31] In a series of 96 patients, Wang et al. found that 46.4% of brain-stem CMs that bled more than once re-hemorrhaged within 6 months; 46.4% re-hemorrhaged between 7 months and 4 years later; and the remaining 7.2% re-hemorrhaged after 4 years.[20] Considering CMs of the entire CNS, Barker et al. found that the risk of re-hemorrhage in 63 patients with multiple hemorrhagic episodes was 2% per month for the first 2 years and then decreased to 0.8% per month thereafter.[31] This potentially increased likelihood of re-hemorrhage soon after an initial hemorrhage is an important consideration for the timing of surgical intervention.

♦ Clinical Presentation

Not surprisingly given the eloquence of the region, 81 to 100% of brain-stem CMs that reach a neurosurgical service will be associated with significant clinical manifestations.[11,14–20] The presenting signs and symptoms are caused by the mass effect exerted by the lesion on adjacent neuroanatomic structures. Symptoms can be exacerbated acutely by a hemorrhagic episode or can arise insidiously by slow growth of the CM. Patients often complain of similar past episodes that improved or resolved in the interim. In fact, patients with brain-stem CMs have been diagnosed with multiple sclerosis because of their waxing and waning course.[18,32]

The nature of presenting signs depends on the location of the CM within the brain stem. Based on large series, 14 to 32% of lesions are located in the mesencephalon, 49 to 64% in the pons, 7 to 21% in the medulla, and the remainder in the pontomesencephalic or pontomedullary junction.[14–16,19,20] In a series of 100 patients from our institution, multiple presenting signs were common and included cranial nerve deficits in 69%, ataxia or dysmetria in 43%, sensory deficits in 39%, motor deficits in 38%, speech difficulty in 12%, and an altered level of consciousness in 6%.[18] The most common subjective symptoms were headache in 36%, vertigo or dizziness in 24%, nausea and vomiting in 16%, and trigeminal neuralgia in 4%. Of the symptomatic patients, 38% were deteriorating at presentation, whereas the remaining 62% were stable or improving.

♦ Diagnostic Studies

With the advent of MRI, the radiographic diagnosis of brain-stem CMs has improved significantly. Angiography is nondiagnostic for CMs and only occasionally demonstrates a hint of capillary blush or early venous filling.[33–35] Although computed tomography (CT) is more useful than angiography, it is nonspecific for detecting CMs.[35,36] Hahn et al. reviewed 1361 cases of CMs of the CNS reported between 1854 and 1997. Of these 1361 cases, 1028 (76.6%) were published after 1984 when the use of MRI was becoming widespread.[36a] Their analysis illustrated the utility of MRI in diagnosing brain-stem CMs. Therefore, surgeons must understand the MRI appearance of CMs including the differences on specific MRI sequences.

On MRI, the typical appearance of CMs reflects the presence of hemosiderin and methemoglobin **(Fig. 11–1)**.[34] T2-weighted sequences show a central core of mixed signal intensity with a surrounding rim of hypointensity caused by the peripheral deposition of hemosiderin. Smaller lesions

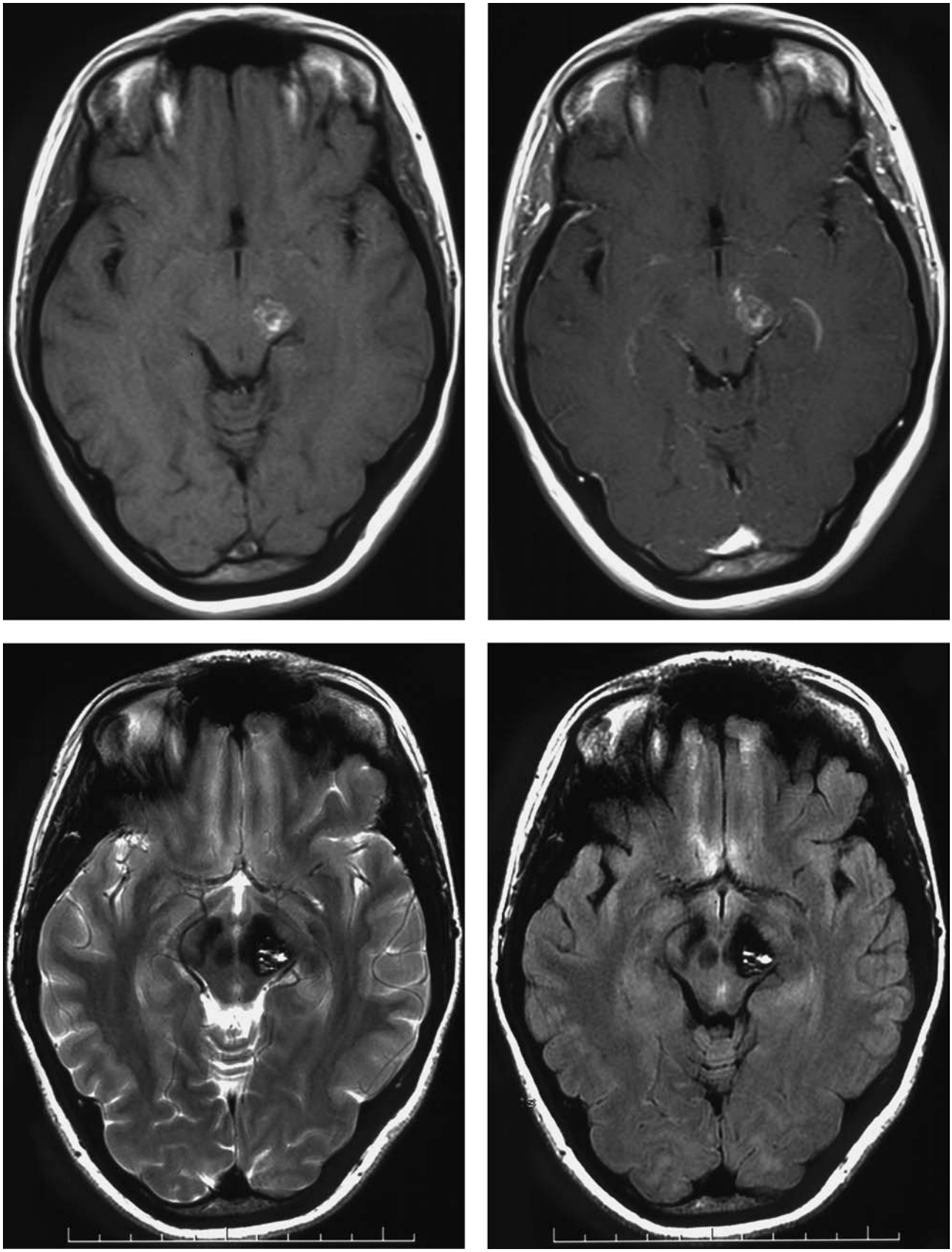

Figure 11–1 Axial T1-weighted magnetic resonance image **(A)** without and **(B)** with contrast. **(C)** Axial T2-weighted magnetic resonance image and **(D)** axial gradient-echo magnetic resonance images show a 1.5-cm left mesencephalic cavernous malformation. Note the marked peripheral hypointensity on the T2-weighted and gradient-echo images reflecting the sensitivity of these sequences to hemosiderin.

show less central heterogeneity and may appear homogenously hypointense. Gradient-echo (GRE) MRI is also useful for diagnosis because it is exquisitely sensitive to hemosiderin; it shows profound hypointensity surrounding the CM. Although T2-weighted and GRE sequences are well suited for diagnosis, both create hemosiderin-related bloom artifact that can obscure the relationship between the CM and surrounding parenchyma.[19] Consequently, T1-weighted imaging, with its more detailed anatomic resolution, should be used for surgical planning.

♦ Surgical Treatment

Indications

Devastating outcomes can occur when patients with a brain-stem CM are managed conservatively; therefore, surgical resection is warranted when appropriate. As with any surgical procedure, the risks and benefits of resection must be weighed against those of nonoperative management. Currently, the indications for resection of these lesions are debated. Bertalanffy et al. noted that most authors agree that symptomatic lesions that abut a pial or ependymal surface can be considered for resection.[14] Conversely, asymptomatic lesions or those deep within the brain stem surrounded by eloquent tissue should be managed nonoperatively. The latter point, however, is arguable. Both Bertalanffy et al. and Bricolo present data on the successful resection of asymptomatic lesions in selected patients.[14,36b]

Some authors believe that surgery should be reserved for symptomatic surface lesions associated with at least two clear hemorrhagic events.[37–39] Others consider resection of symptomatic lesions on a case-by-case basis, with the number of prior hemorrhages being one of several points of consideration. We consider resection of a brain-stem CM if at least one of the following criteria is met. (1) The lesion abuts the pial or ependymal surface or is exophytic. (2) The lesion has produced multiple hemorrhages causing progressive neurologic deficits. (3) Acute hemorrhage extends outside the lesion capsule. (4) Significant mass effect is associated with a large intralesional hemorrhage.[18] However, each situation is unique, and patients must be treated individually based on their clinical history, lesion location, and the surgeon's technical expertise.

Selection of Surgical Approach

This section presents methods for determining the best surgical approach for the resection of brain-stem CMs. Detailed descriptions of each approach can be found elsewhere.

The goal is complete resection of a brain-stem CM with minimal damage to surrounding neural tissue. To optimize outcomes, the most direct route to a lesion usually should be followed to avoid unnecessary parenchymal transection, retraction, or both. The surgeon must consider these factors when selecting a surgical approach.

As described elsewhere, the "two-point" method is a simple yet effective tool for selecting the appropriate approach

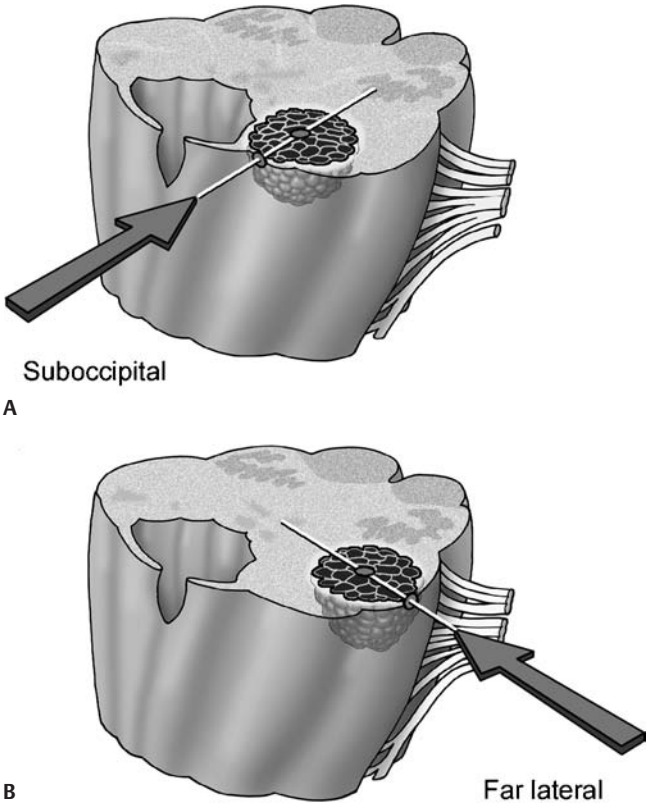

Figure 11–2 Diagrammatic representation of how the two-point method plots **(A)** a suboccipital and **(B)** a far-lateral approach. In these two examples, similarly located lesions suggest quite different approaches, illustrating the importance of where the lesion nears the pial or ependymal surface. (Used with permission from Barrow Neurological Institute.)

to brain-stem lesions **(Figs. 11–2 and 11–3)**.[40] The "two-point" method requires the use of T1-weighted MRI. The appropriate image is selected, and a single "point" is placed at the center of the lesion. A second "point" is then placed at the margin of the lesion where it comes closest to or abuts the pial or ependymal surface. A line connecting the two points is extended superficially and delineates the best approach to the lesion. The surgical approach that most closely mimics the two-point approximation is used to resect the lesion **(Fig. 11–4)**.

In our experience using the two-point method, five approaches have been the workhorses for the resection of brain-stem cavernous malformations: (1) the orbitozygomatic for ventral mesencephalic and high ventral pontine lesions, (2) the retrosigmoid for ventrolateral pontine lesions, (3) the far lateral for ventral medullary lesions, (4) the suboccipital for dorsal pontine (via the fourth ventricle) and dorsal medullary lesions, and (5) the supracerebellar infratentorial for dorsal mesencephalic lesions. Less frequently used are the subtemporal, the transpetrosal, and combined supratentorial-infratentorial approaches.

Regardless of the approach selected, the surgeon must understand the anatomy of the posterior fossa and the safe entry zones into the brain stem, particularly when a lesion

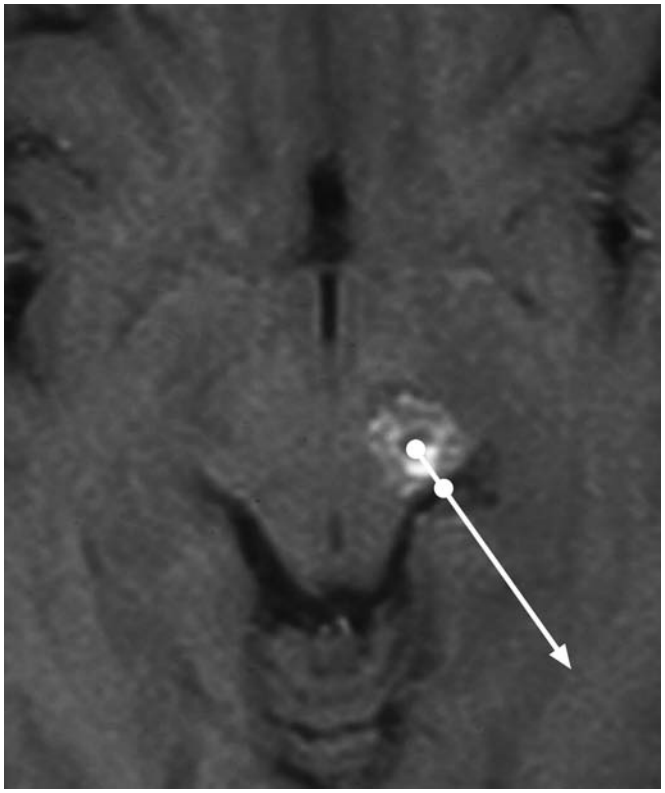

Figure 11–3 Axial T1-weighted magnetic resonance image demonstrating a left mesencephalic cavernous malformation with the two-point method applied. In this case, a left lateral supracerebellar infratentorial approach was selected.

does not reach the surface **(Fig. 11–5)**. For example, dorsal pontomedullary CMs should only be resected through the floor of the fourth ventricle if they directly abut the ependymal surface. If the lesion lies even millimeters below the surface, significant postoperative deficits can be expected if the floor of the ventricle is traversed. In this situation, two more preferable options exist. If the lesion is moderately large and paracentric, it can be reached via an ipsilateral retrosigmoid approach by traversing the middle cerebellar peduncle. More parenchyma is traversed, but it is less eloquent and therefore better tolerated than violation of the fourth ventricular floor. The other option is to avoid surgery until the lesion re-hemorrhages or grows until it abuts the ependyma. At that point, the malformation can be resected safely through the floor of the fourth ventricle via a suboccipital approach.

The surgical approach selected to access a brain-stem cavernous malformation must be as direct as possible and must avoid exquisitely eloquent tissue. Following these principles optimizes neurologic outcomes while minimizing morbidity.

Surgical Technique

When surgery is pursued, every effort must be made to achieve complete resection of a brain-stem CM with minimal damage to surrounding structures. Besides understanding the anatomy of the posterior fossa, two supplementary tools can help maximize outcomes. Both stereotactic image guidance and electrophysiologic monitoring should

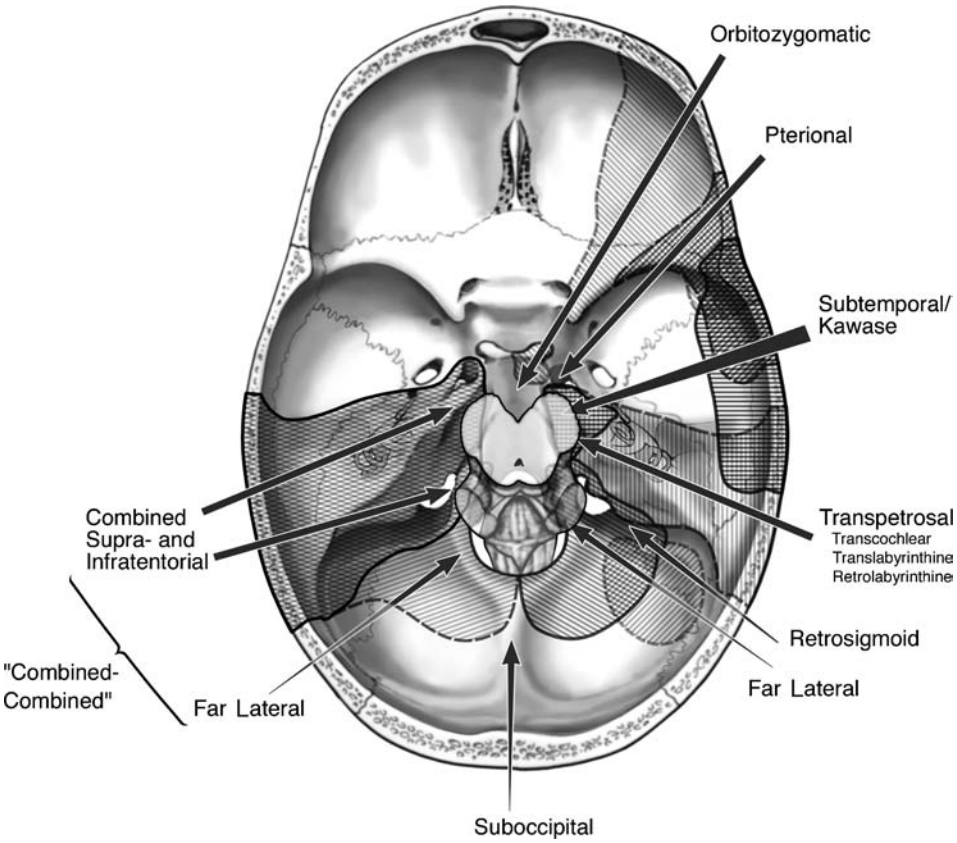

Figure 11–4 Illustration shows surgical approaches to specific locations within the brain stem. (Used with permission from Barrow Neurological Institute.)

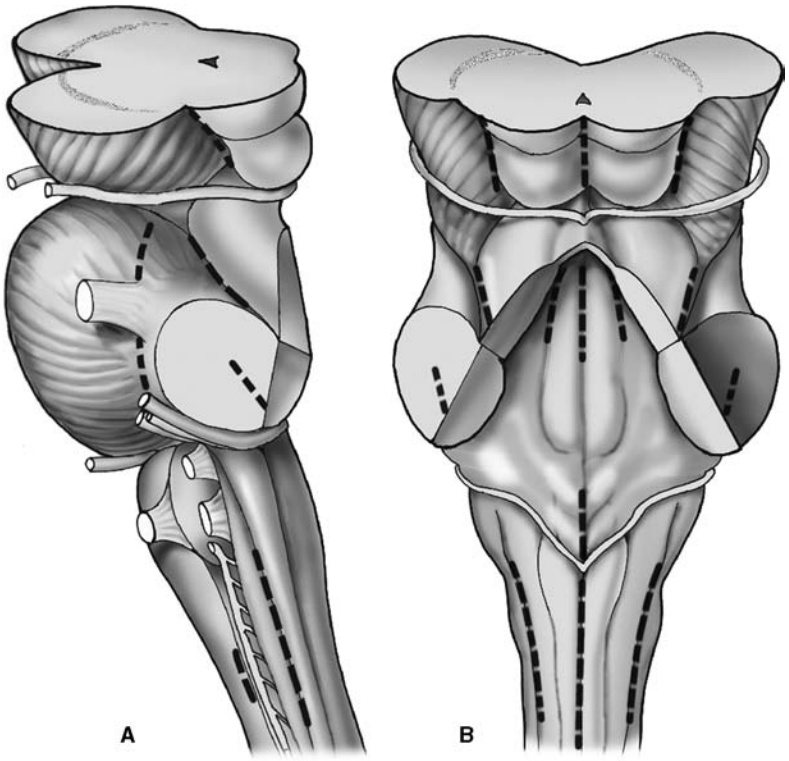

Figure 11–5 Illustration shows the safe entry zones into the **(A)** ventrolateral and **(B)** dorsal aspects of the brain stem. (Used with permission from Barrow Neurological Institute.)

be used in all cases. Image guidance provides real-time anatomic localization to pinpoint the location of the lesion within its investing eloquent tissues, particularly for lesions that lie below the surface. Electrophysiologic monitoring, including somatosensory evoked potentials (SSEPs), brain-stem auditory evoked responses (BAERs), and, when indicated, motor evoked potentials (MEPs), provides feedback when vital structures are encountered. Finally, when a posterior fossa craniotomy is planned, lumbar drainage is frequently necessary to decompress the cisterns and relax the contents of the posterior fossa.

On approach to the brain stem, lesions that abut the pia or ependyma can be identified by their purplish-black appearance or by a thin yellowish hemosiderin-laden gliotic rim that overlies the lesion. For deep CMs not readily apparent at the surface of the brain stem, surgeons must use stereotactic guidance to select the safest and most direct route through the parenchyma to the lesion. In the latter case, the parenchymal entry point is created by bluntly dissecting the neural tissue with a small dissector (e.g., Penfield) to create the smallest possible entrance. The long axis should parallel the direction of the fibers in the tissue being dissected. Once the entry point is made, image-guided blunt dissection with a small dissector and microsuction proceeds deeper until the typical purplish mulberry appearance of the lesion surrounded by the yellowish hemosiderin-laden gliotic rim is encountered. For large, deep lesions, a small self-containing retractor may be placed within the approach corridor for *gentle* retraction.[19,41]

Once the lesion is encountered, resection begins with three goals in mind. First, the entire lesion must be resected. Residual CM creates a persistent risk of hemorrhage and associated neurologic deficits.[42–44] Second, patency of the associated venous anomaly must be maintained. Between 8% and 100% of CMs are associated with venous anomalies.[11,17,18,36,45,46] A venous anomaly must be assumed to drain normal brain; therefore, its patency must be maintained to avoid neural injury.[18] Finally, efforts should be made to keep the surrounding hemosiderin-laden gliotic parenchyma intact.[14] This tissue may remain partially functional, and it need not be resected to prevent further hemorrhage.

The initial step in resection involves aspiration of the contents of the old hematoma to decompress the lesion.[20] Once decompressed, the lesion is freed circumferentially using low-power bipolar electrocauterization and fine microscissors to transect associated vessels. Gentle blunt dissection is used to separate the lesion from its investing gliotic parenchyma.[14,42] The released CM is removed piecemeal using microrongeurs. The intact CM should not be removed in a single maneuver if it stretches the surrounding neural tissue.[14] When the final inspection reveals no further CM, hemostasis is obtained with low-power electrocauterization and a hemostatic agent. Copious irrigation is required to remove all of the hemostatic agent and to ensure meticulous hemostasis. Closure is performed in the typical fashion.

♦ Postoperative Management

Postoperatively, all patients should be maintained on mechanical ventilation in the intensive care unit for a *minimum* of 24 hours. Delayed brain-stem edema can lead to the insidious onset of dramatic respiratory failure. Although typically temporary, such failure is potentially

lethal during the immediate recovery period. For patients undergoing resection of a CM involving the medulla, the lower cranial nerves, or both, preoperative placement of a feeding tube, with or without a tracheostomy, should be considered. Although deficits are typically temporary, airway protection is imperative in the acute and subacute postoperative setting. After a posterior fossa craniotomy, we leave a lumbar drain in place 48 to 72 hours to prevent cerebrospinal fluid leakage.

The postoperative neurologic status of patients may worsen transiently. Consequently, physical, occupational, and speech therapies are started early in the postoperative period. Many patients require a stay in rehabilitation as they convalesce, and early consultation with rehabilitation specialists is advised. Preoperative education of patients regarding their expected postoperative course is imperative. With respect to radiographic follow-up, few data are available. We routinely obtain an immediate postoperative MRI and follow-up MRI at 1- to 3-year intervals depending on our index of suspicion.

♦ Surgical Outcomes

Experienced surgeons using appropriate patient selection criteria can achieve acceptable outcomes for the resection of brain-stem CMs. In the past decade, five studies with more than 20 patients have evaluated surgical outcomes after resection of brain-stem CMs **(Table 11–2)**. All five are retrospective studies that suffer from the problems intrinsic to such a study design. Because outcomes are not assessed uniformly, it is difficult to draw firm conclusions. Nonetheless, these relatively new data provide sufficient information to guide physicians in their treatment planning and patient education.

Bertalanffy et al. ($N = 24$), Porter et al. ($N = 84$), and Steinberg et al. ($N = 57$) present long-term follow-up data based on similar outcome variables.[14,18,19] (The latter study included 15 patients with basal ganglia and thalamic cavernous malformations and 42 brain-stem lesions; specific brain-stem CM outcome data were not provided.) Based on these three studies, at long-term follow-up, 87 to 95% of patients were neurologically stable or better than before surgery, 5 to 10% were worse, and 0 to 4% died. At long-term follow-up in the study by Steinberg et al.,[19] the neurologic condition of 53% of the patients improved relative to their preoperative status.

These studies showed that the neurologic condition of many patients initially worsens before they improve or regain their preoperative neurologic function. In the immediate postoperative period, 29 to 67% of patients were worse than before surgery as opposed to 5 to 10% who were worse at long-term follow-up. This finding demonstrates that convalescence after resection of a brain-stem CM can be prolonged. Consequently, appropriate therapies and rehabilitation efforts must be initiated during the early postoperative period, and patients and their family must be educated about postoperative expectations.

Wang et al. presented their outcome data on 137 cases in a similar fashion and found that 72% of patients were neurologically the same or better after surgery, 28% were worse, and none died.[20] Although these results are less encouraging than those presented above, it is unclear whether the results reflect the immediate postoperative period or long-term

Table 11–2 Summary of Surgical Outcome Data from Large Studies ($N \geq 20$) of Brain-Stem Cavernous Malformations

Author (Year)	Number of Patients	Follow-up (Months)	Surgical Outcomes	Comments
Bertalanffy et al. (2002)[14]	24	5.9	92% neurologically better or same as preoperatively 8% worse than preoperatively 0% mortality	67% had neurologic worsening in the immediate postoperative period
Fritschi et al. (1994)[11]	93	16.4	40% neurointact 44% minimal deficit 15% moderate deficit but independent 1% severe deficit; dependent 0% mortality	No direct comparison with preoperative neurologic status
Porter R. et al. (1999)[18]	84	35	87% neurologically better or same as preoperatively 10% worse than preoperatively 4% mortality	35% had neurologic worsening in the immediate postoperative period 10% had permanent severe neurodeficits
Steinberg et al. (2000)[19]	57*	56.4	95% neurologically better or same as preoperatively 5% worse than preoperatively 0% mortality	29% had neurologic worsening in the immediate postoperative period 52% demonstrated neurologic improvement compared with preoperatively
Wang et al. (2003)[20]	137	52	72% neurologically better or same as preoperatively 28% worse than preoperatively 0% mortality	Unclear if results are from immediate postoperative period or from long-term follow-up

*Includes 42 patients with brain-stem lesions and 15 with thalamic or basal ganglia lesions.

follow-up. If the former, they are consistent with the results of Bertalanffy et al.,[14] Porter et al.,[18] and Steinberg et al.[19]

Finally, Fritschi et al. presented their long-term functional outcomes[11] after the resection of 93 brain-stem CMs. Forty percent of their patients were neurologically intact, 44% had a mild neurologic deficit, 15% had a significant neurologic deficit but functioned independently, 1% had a severe deficit and were dependent, and 0% died. Outcomes were not compared directly with patients' preoperative status, but all patients were symptomatic at presentation. Therefore, at least 40% improved from their preoperative baseline.

♦ Conclusion

Cavernous malformations of the brain stem are rare lesions that can cause profound neurologic deficits when they hemorrhage. Management strategies must weigh the risks of continued observation against surgical resection with the goal of preserving neurologic function and minimizing morbidity. Resection is indicated in symptomatic patients with a hemorrhagic lesion that is deemed to be safe to resect. Asymptomatic patients or those with a CM in an inaccessible location should be observed. Safe and successful resection requires detailed knowledge of posterior fossa anatomy, selection of the appropriate approach, and meticulous surgical technique. When these criteria are met, neurologic function can be preserved or improved after resection compared with most patients' preoperative status. Approximately 85% of patients will be neurologically intact or will have only a minor deficit at long-term follow-up. With mastery of posterior fossa anatomy, refinement of surgical techniques in and around the brain stem, and continued evolution of operative technology, management of these complex, devastating lesions will continue to improve.

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12

Cavernous Malformations of the Spinal Cord

Paolo Perrini, Uygur Er, Robert F. Spetzler, and Giuseppe Lanzino

Cavernous malformations (CMs) of the spinal cord had been considered to be extremely rare until the widespread availability of magnetic resonance imaging (MRI) in the 1980s. Spinal cord CMs were first described in the early 1900s.[1] In 1912, Schultze reported the first successful surgical removal of a cervical CM in a 29-year-old-man. After surgical resection, the patient experienced improvement of his neurologic function.[2] In a literature review conducted in 1929, Globus and Doshay[3] reported this case along with two additional others. Until the mid-1980s, only a few additional anecdotal cases were reported for a total account of 19 cases recorded until 1985.

Because of the widespread use of MRI, spinal cord CMs have been disclosed with increasing frequency, and in 1988, Cosgrove et al.[4] and McCormick et al.[5] reported surgical series of five and six patients, respectively. Since then, several additional series have been reported, and intramedullary CMs have become a recognized potential cause of myelopathy especially in young individuals. CMs affecting the spine and spinal cord display a wide spectrum of pathologic findings to include lesions involving the vertebral body and spinal extramedullary lesions of the intra- and extradural spaces. This chapter, however, focuses only on intramedullary CMs.

♦ Epidemiology

CMs account for 5 to 12% of spinal vascular malformations[5,6] and represent 3 to 5% of all spine lesions in surgical series or autopsy studies. Some authors have reported a slight female preponderance although others have failed to show this.[6–8] More commonly, spinal cord CMs present in the fourth decade, although the age range in the literature varies between 12[9] to 88[1] years. Approximately 10% of all intramedullary spinal cord CMs are observed in the pediatric population.[10] Pediatric patients do not show a gender imbalance and usually present with a more acute episode compared with adults.[10,11]

CMs can occur anywhere along the spinal cord but appear to have a predilection for the thoracic levels followed by the cervical cord. Lesions involving the conus medullaris or cauda equina are less common.[12] Numerous reports suggest that patients with spinal cord CMs are at an increased risk for multiple neuraxis CMs.[13–15] Vishteh et al.[15] reported multiple CMs in almost half of 17 patients with symptomatic intramedullary CMs who had both spinal and brain imaging. On the basis of this data, it is suggested that patients with spinal cord CMs should have a careful family history and screening MRI of the brain. Angiomas of the skin and others organs such as kidney and liver have also been reported in association with intramedullary CMs.[4,5,16,17]

♦ Pathology

CMs present similar gross and histopathologic features whether they involve the brain or spinal cord. The macroscopic features of spinal cord CMs are similar in each case, showing a dark blue-brown mulberry- or raspberry-shaped lesion with surrounding gliosis and hemosiderin staining. The lesions are well circumscribed, but "tongues" of CMs often infiltrate the surrounding gliotic plane. The size of these lesions varies from a few millimeters to centimeters. Due to the slow progressive growth of the malformation, the spinal cord can be completely replaced by the CM without visible enlargement. The cord surface usually presents a typical area of bluish discoloration **(Fig. 12–1)**, but in case of small lesions the spinal surface can present normal appearance. The surrounding parenchymal tissue often shows evidence of repeated hemorrhage with deposition of hemosiderin in the gliotic tissue. Calcification is rare and sometimes can be present as small flecks of bone and focal ossification.[18,19] Cosgrove et al.[4] observed ossification in one of five cases of intramedullary cavernous angiomas, and Ogilvy et al.[18] reported flecks of calcification and focal ossification in only one case of their series. Naim-Ur-Rahman et al.[20] reported a large (2×3 cm) cavitating intramedullary thoracic CM with laminated shell-like pattern of calcification. In this case, the heavily calcified outer shell with spiky projections into the surrounding parenchyma precluded total removal.

De novo spontaneous occurrence of spinal cord CMs has been documented.[21] Appearance of spinal cord CMs after radiation[22,23] has also been observed. In the two reported cases of intramedullary spinal CMs after spinal irradiation,[22,23] the latency period was 5 and 13 years.

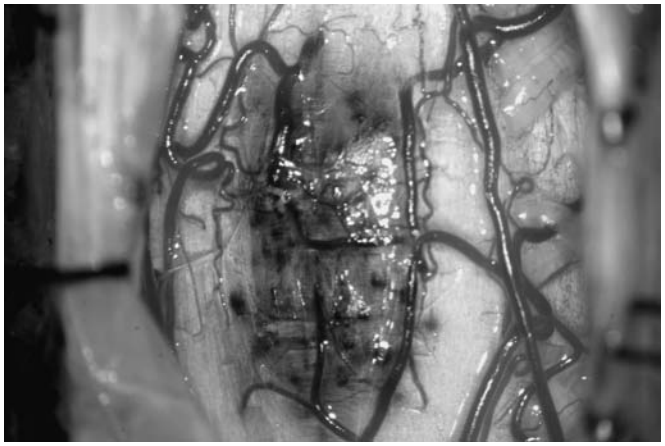


Figure 12–1 Intraoperative microscopic view of a cervical cord CM. The malformation was immediately evident after exposure of the dorsal surface of the cord through a posterior cervical laminoplasty. Under high magnification, the characteristic bluish discoloration of the CM is noted. Brownish discoloration of the cord surface adjacent to the CM is visible. This brownish discoloration is caused by hemosiderin deposition around the CM. (From Lemole GM, Lanzino G, Henn JS, Spetzler RF. Spinal cord cavernous malformations. Operative Techniques in Neurosurgery 2002;5:155–160. Reprinted with permission.)

♦ Clinical Presentation

The clinical presentation of spinal cord CMs is variable. In the past, the intermittent/remittent clinical course, often in young individuals, led to the wrong diagnosis of a demyelinating process or Foix-Alajouanine syndrome.[4] Although the clinical course is unpredictable, the onset of symptoms usually falls into one of three patterns: acute, progressive, or episodic.[4,5,7,12] Acute onset of neurologic symptoms is caused by hemorrhage within or around the lesion. This is supported in surgical cases by the intraoperative findings of recent hematoma within the cord.[5,18,24,25] Patients can present with motor and sensory deficits as well as with bowel and bladder dysfunction. Pain is present in one-half of the patients and usually corresponds with the level of the CM.[26] Although precipitating factors such as trauma, pregnancy, and strenuous activity have been reported, it is unclear whether these associations are coincidental or causative.[5,27] Subarachnoid hemorrhage can occur particularly with lesions of the cauda equina[28,29] and in CMs located on the spinal cord surface.[30] CMs of the cauda are adherent to one or more nerve roots.[31]

A pattern of slow progressive decline in neurologic function has been described in 41% of patients with intramedullary CMs.[12] Various mechanisms can induce this pattern of clinical worsening. Some authors suggested enlargement of the CM due to repeated small hemorrhages or gradual thrombosis.[18] Neurotoxic effect of hemosiderin and compromise of the surrounding microcirculation have been proposed as a possible cause to explain progressive myelopathy.[5] CMs are low-flow shunts, and hemodynamic alterations, such as arterial steal or venous hypertension, are unlikely to play a role in the progressive deterioration.

Episodic and stepwise deterioration have been described in 30% of patients with spinal cord CMs.[12] This pattern can mimic other clinical conditions such as transverse myelitis, multiple sclerosis, and other progressive demyelinating diseases. In these cases, patients present with multiple episodes of neurologic worsening with gradual but usually only partial improvement between events. Multiple hemorrhages from the lesion over several years with subsequent gradual neurologic recovery can explain this clinical pattern. The presence of hemosiderin in the surrounding tissue and blood products of various ages within the lesion is a common surgical finding in such patients.

Hydrocephalus with increased cerebrospinal fluid protein content has been described in a patient with a cavernoma of the cauda equina,[32] probably resulting from subclinical spillage of blood in the subarachnoid space. With the advent of MRI, incidental asymptomatic lesions are encountered, and at this point their natural history is unknown.[16,17] In symptomatic lesions, Zevgaridis et al.[12] estimated an average bleeding rate of 1.4% per lesion per year. This figure, however, was obtained assuming that patients were harboring spinal CMs since birth, but several reports suggest that these lesions can be acquired later in life.[21,22,27]

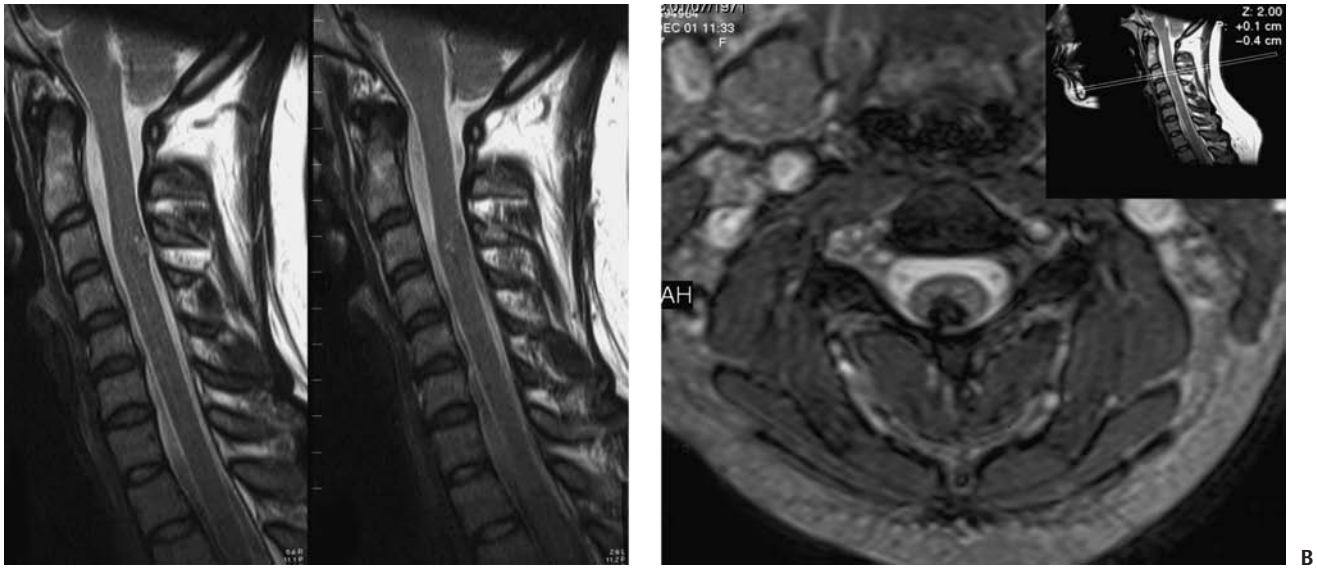
♦ Diagnosis and Indications for Treatment

Symptoms can be present for many years before a correct diagnosis is made. From a pooling of literature data, the overall median duration of pretreatment symptoms is 32 months.[12] The interval between presentation and diagnosis is shorter in more recent series as MRI is currently performed early after initial presentation. As previously mentioned, a history of multiple episodes of stepwise deterioration, slow progression of neurologic signs, or sudden onset of neurologic deficits especially in a young individual should raise the suspicion of a spinal cord CM. Nevertheless, spinal cord inflammatory disease such as multiple sclerosis and transverse myelitis should be excluded.

Computed tomography and myelography have been used in the past for the diagnosis of CMs of the spinal cord but have low sensitivity and are of historical significance. These studies may show evidence of spinal cord widening, suggesting an intramedullary lesion.[4,33,34] Axial computed tomographic scans may also show presence of acute hemorrhage and calcification.

MRI is the procedure of choice in the diagnosis of spinal cord CMs. The MRI **(Fig. 12–2)** characteristics of spinal cord CMs are no different than intracranial CMs[35] and are treated in detail elsewhere in this book. There is usually little if any enhancement on T1-weighted images with gadolinium. T2-weighted images can demonstrate increased signal surrounding the lesion for the presence of the edema as well as a hypointense ring of hemosiderin in the gliotic plane around the malformation. Sometimes in cases of small lesions, spinal MRI can be misleading for surgical planning when trying to estimate where the malformation comes closest to the surface of the spinal cord. Malformation thought on MRI to be located on the surface of the spinal cord can be found deeper only after a myelotomy. Vishteh et al.[36] reported that MRI had a 17.6% false-positive rate in estimating whether a spinal cord CM reaches the pial surface.

Spinal angiography is of little value because cavernous angiomas are angiographically occult, although an associated "tumor blush" has been described.[35,37,38] In some cases,



A B

Figure 12–2 (A) Sagittal and **(B)** axial T2-weighted MRI of the cervical spine shows the typical appearance of a CM involving the dorsal aspect of the cord. This 28-year-old female had presented with paresthesia involving the neck and upper back over 8 months. (From Lemole GM, Lanzino G, Henn JS, Spetzler RF. Spinal cord cavernous malformations. Operative Techniques in Neurosurgery 2002;5:155–160. Reprinted with permission.)

however, spinal angiography is warranted to rule out the presence of a spinal cord arteriovenous malformation because the MRI characteristics of spinal cord CMs are not always clear-cut, especially in small lesions.

As it has been reported that the vast majority of symptomatic patients show a definite progression of their neurologic symptoms,[12] active management is advocated to reduce the neurologic deficit and to stop the progression of symptoms. Surgical removal of the lesion offers protection from future bleeding. The spinal cord presents high eloquence in a small cross-section and is unlikely to tolerate even minor expansion of intramedullary CMs before devastating symptoms occur.[18] Given these considerations, surgery should be recommended to patients with symptomatic lesions reaching the pial surface without waiting for repeated episodes of clinical deterioration.

Much controversy exists about patients with asymptomatic lesions or for those who have experienced only minor and transient symptoms. Because the natural history of asymptomatic spinal cord CMs is unknown, close observation with serial MRIs and clinical exam is recommended. In patients who have already had minor transient symptoms clearly related to the CMs, surgical treatment should be considered especially if the CM comes to the surface of the spinal cord.

Although initial series reported improvement or stabilization of symptoms also after subtotal removal,[4] now it is clear that residual portions of CM left during surgery tend to rebleed and are a well-known cause of progression of symptoms and myelopathy.[12,18,19,36] Therefore, the goal of surgery should be curative resection of the entire CM.

♦ Surgical Treatment

Like the brain stem, the spinal cord presents densely packed and eloquent structures in a small cross-section. As for the treatment of the brain-stem CMs, surgical strategy and point of entry in spinal cord CMs rely on the use of the two-point method.[39] The two-point method defines the best avenue of approach to a CM located within eloquent tissues. Using MRI, axial views of the lesion are obtained before surgery, and a line is dawn connecting the center of the lesion to a point where the lesion is most readily and safely accessed surgically. Usually, the access point is where the lesion reaches the pial surface but may also be where a less eloquent neural tract, such as the dorsal median sulcus or dorsal root entry zone, allows safe entry into the spinal cord parenchyma. When planning surgery and deciding whether or not the CM abuts the pial surface, it is important to rely upon the T1 MRI sequence because on T2 ballooning artifact from the hemosiderin-stained parenchyma can give a false impression of a larger lesion.

For dorsally situated spinal cord CMs, a laminectomy or laminoplasty at the appropriate level is usually sufficient. The proper level is identified radiographically once the patient has been positioned prone on the operating table. For cervical and upper thoracic lesions in young patients, we recommend a laminoplasty to prevent postoperative progressive kyphosis, due to the removal of posterior spinal elements. A laminoplasty may be performed by placing a Midas Rex (Medtronic, Ft. Worth, TX, USA) foot plate below the lamina at the previously made keyhole laminotomy site and drilling cephalad. This maneuver is repeated on the contralateral side, and the entire segment is removed *en bloc*. In a series of 17 patients who underwent resection of intramedullary spinal cord CMs, all lesions were resected posteriorly via laminectomy ($n = 9$) or osteoplastic laminoplasty ($n = 8$).[36]

Lesions located in the ventrolateral surface of the spinal cord are technically difficult and must be approached with greater trepidation given the eloquent motor structures contained therein.

Anterior spinal approaches require a vertebrectomy, and although they provide direct visualization of the ventral surface of the spinal cord on both sides, the operative field

is deep and narrow. Such an approach presents difficulties with the dural closure and requires a cervical fusion and fixation procedure after resection of the intramedullary CM.

Transthoracic approach has seldom been reported in the treatment of intramedullary spinal cord CMs.[7] In the thoracic region, anterior approaches may be provided through thoracotomy with corpectomy. This approach amply visualizes the anterolateral ventral spinal cord, but the utility is limited because the spinal cord exposure is deep and if an absolutely watertight dural closure is not obtained, a spinal-to-pulmonary cerebrospinal fluid fistula can develop. A fistula will be exacerbated if a chest tube is used to re-expand the ipsilateral lung.

Martin et al.[14] reported a modification of the posterolateral approach, in both cervical and thoracic regions, for spinal cord lesions involving the ventrolateral pial surface. The authors reported a patient with an anterolateral spinal cord CM resected through a posterolateral transpedicular spinal approach to the thoracic spine. They combined a linear midline incision with a transverse incision to expose the posterolateral thoracic spine. After a laminectomy with removal of the hemilamina of the side of the pathology and the medial part of the contralateral hemilamina, the facets and pedicles above and below the lesion were removed using a high-speed drill to obtain a flat angle to the lateral and ventrolateral surface of the spinal cord. The dura was opened halfway between the root sleeve and the dorsal midline, and the dentate ligaments were identified and divided several levels above and below the level of the lesion. Traction sutures were placed into the dentate ligament to permit gentle rotation of the spinal cord, bringing its ipsilateral ventrolateral quadrant into view and permitting resection of the anterolateral lesion. Spinal stability is not compromised by the use of the posterolateral transpedicular approach because the anterior and posterior longitudinal ligaments, the disk and the annulus, and the contralateral facet joint are not removed. The limitation of this approach is the inability to visualize the contralateral ventrolateral spinal cord surface. However, bilateral transpedicular approach can be used for lesions that cross the midline that need to be accessed bilaterally. In this case, such aggressive bony resection would necessitate instrumentation and surgical fusion.

From a posterior approach (which is usually sufficient to treat the vast majority of spinal cord CMs), once the bone has been set aside and the underlying ligamentous structures have been removed, the dura is opened sharply in the midline using the operating microscope. The lateral epidural gutters can be packed with hemostatic agents like Gelfoam (Upjohn, Kalamazoo, MI, USA) or Floseal (Baxter, Deerfield, IL, USA) before the dural edges are retracted, usually with stitches. The arachnoid is opened sharply in the midline, and its edges are secured to the ipsilateral dural leaflet. After the dura and the arachnoid are opened, the dorsal surface of the spinal cord is carefully inspected under high magnification looking for the reddish-brown discoloration or bluish discoloration of the parenchyma. In case of grossly exophytic CMs, the lesion may came in view as raspberry- or mulberry-shaped in appearance with multiple venous sinusoidal channels on the surface of the spinal cord. When the only hint of the location of the CM is hemosiderin staining of the overlying spinal cord or when no alteration is visible on the surface of the cord, intraoperative ultrasonography can be useful to locate the lesion and to plan the myelotomy.[12,36,40] Intraoperative ultrasound imaging permits a minimal myelotomy for removal of intramedullary CMs, provides a precise assessment of the size of the lesion, and can confirm the total removal of the malformation.[40]

Dissection is started either directly over the lesion when it approaches the surface or via a midline myelotomy through the dorsal median sulcus for deeper lesions. A lateral myelotomy along the dorsal root entry zone is usually also well tolerated and affords adequate access to deep intramedullary lesions. Care is taken to dissect only around the surface of the lesion in the surrounding plane of gliotic tissue, using sharp dissection, to avoid injury to normal spinal cord tissue. In our experience, gliotic planes are useful to separate the intramedullary spinal cord CM from spinal cord tissue, and during dissection the hemosiderin-stained tissue should not be removed. Resection of the lesion requires meticulous use of microcurettes and gentle suction aspiration. Typically, lesions must be removed piecemeal although sometimes they can be resected *en bloc*. Because of the low pressure of the lesion, bleeding is usually minimal and can easily be controlled with gentle compression and the use of a hemostatic agent. We caution against the use of extensive electrocauterization within the spinal cord. Microfibrillar collagen or absorbable cellulose hemostatic agents are preferable. Anomalous venous channels are actively sought in the intramedullary compartment and, if observed, are carefully preserved because they drain adjacent tissue, and their sacrifice could place those neural structures at risk. Careful surgical inspection reveals cryptic venous malformations in the vast majority of patients with spinal cord CMs. These associated venous anomalies appear as irregular venous channels, deep in the spinal parenchyma, draining into a larger abnormal venous structure.

After resection of the CM, careful inspection of the surgical bed under high magnification is imperative to identify and resect small "tongues" of CM that may extend into adjacent neural tissue **(Fig. 12–3)**. Although it has been reported that incomplete resection can stabilize or improve

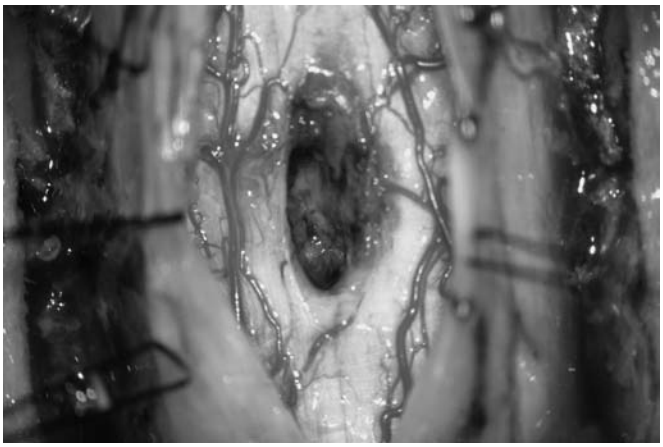


Figure 12–3 Intraoperative view, same case as in **Fig. 12–1** and **Fig. 12–2**. After resection of the CM, the surgical cavity is carefully explored to rule out residual malformation. Residual CM after surgical resection has been reported to cause recurrent postoperative hemorrhages with catastrophic consequences. (From Lemole GM, Lanzino G, Henn JS, Spetzler RF. Spinal cord cavernous malformations. Operative Techniques in Neurosurgery 2002;5:155–160. Reprinted with permission.)

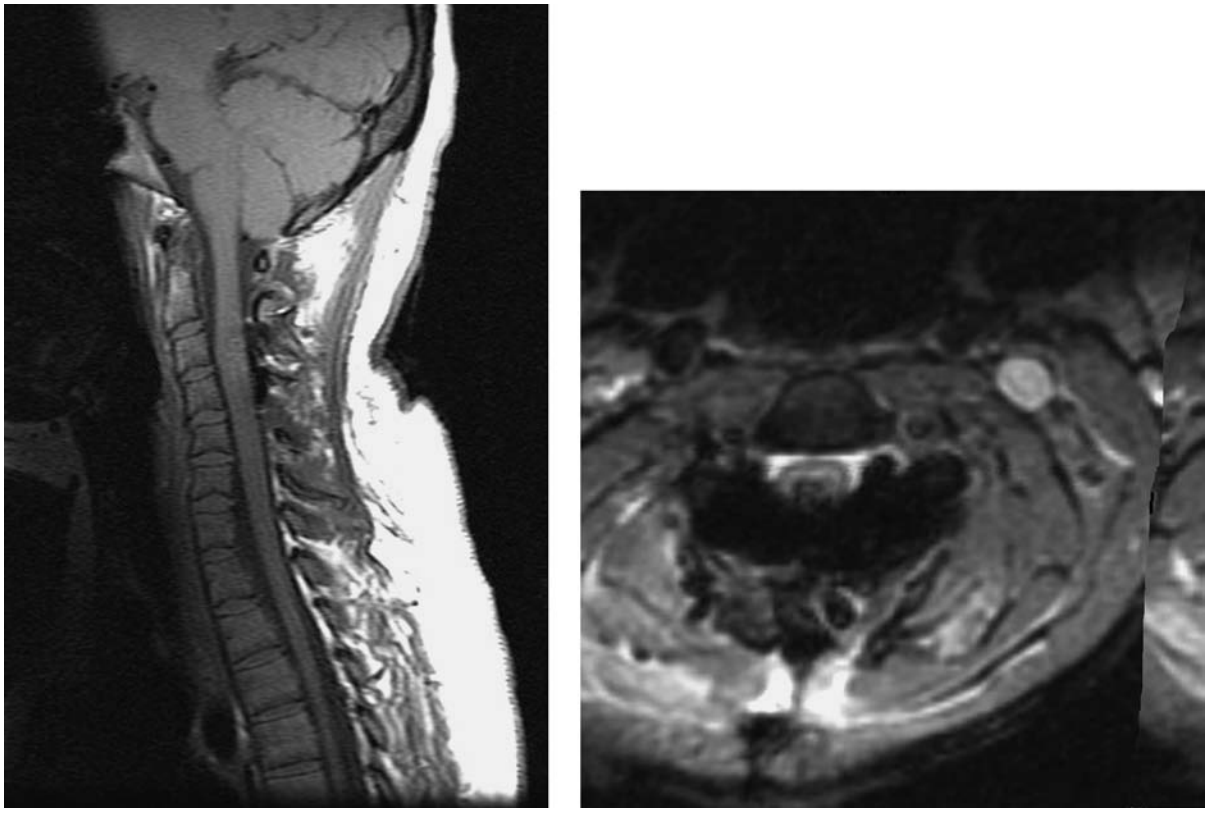


Figure 12–4 Postoperative **(A)** sagittal T1-weighted and **(B)** axial T2-weighted MRI indicates complete surgical resection of the CM. On postoperative imaging, it is very difficult to rule out any residual CM especially in the spinal cord. Therefore, we recommend obtaining an immediate (within 24 hours) MRI study to establish a neuroimaging baseline. Future MRI studies can then be compared with the immediate postoperative one.

symptoms,[4] other authors have observed a high risk of regrowth of the lesion with recurrent hemorrhages and symptoms.[36] In a series of 17 operated patients,[36] three patients presented delayed complications resulting from incomplete resection. These patients presented with new neurologic symptoms, MRI revealed new hemorrhage at their previous surgical bed, and they underwent successful resection of their residual CMs.

After careful hemostasis, the dura is closed in a watertight fashion. A Valsalva maneuver can help in identifying areas of leakage. The dura may be reinforced with fibrin glue, and the laminoplasty piece is replaced with sutures to avoid artifacts in the follow-up MRI studies. The paraspinous musculature and fascia are closed along with the subcutaneous tissues and skin in a meticulous fashion.

Immediately after surgical resection of spinal cord CMs, transient neurologic worsening is not unusual.[36] Close observation in the immediate postoperative period is recommended, and we recommend routine admission of these patients to the intensive care unit after surgery. In the reported surgical series, long-term improvement or stabilization of symptoms are observed in 66% and 28% of patients, respectively. Postoperative permanent deterioration is unusual (6% of cases).[12] The degree of neurologic recovery after surgical treatment is related to a patient's preoperative level of neurologic status and is strongly influenced by the length of symptoms duration before surgery. The majority of patients (76%) with symptoms of less than 3 years improve after surgery, whereas when symptoms are present for more than 3 years, the rate of symptomatic improvement decreases significantly (52%).[12] An immediate postoperative MRI **(Fig. 12–4)** is recommended to establish a neuroimaging baseline. Further serial MRI studies can then be compared with the immediate postoperative one. Because of the risk of recurrent hemorrhage with incomplete resection and of possible delayed spinal cord tethering, we recommend long-term follow-up MRI be performed 12 to 24 months postoperatively, in addition to early postoperative MRI. Tethering of the spinal cord after resection of intramedullary spinal cord CMs has been reported,[36] and when the radiologic appearance of the cord tethering is associated with development and progression of new symptoms, operative intervention is indicated.

♦ Conclusion

Because of the widespread availability and use of MRI, intramedullary spinal cord CMs are now a commonly recognized cause of spinal myeloradiculopathy. The clinical presentation can mimic that of other neurologic diseases such as multiple sclerosis, but MRI is usually pathognomonic showing a mixed-density signal lesion with popcorn-like appearance. Surgical resection should be considered for all symptomatic patients, especially if the lesion is superficial. In asymptomatic incidental lesions, surgical indication should be based on the lesion's proximity to a surgically accessible surface and the patient's wishes. Most spinal cord CMs are readily approached through a posterior approach. Complete resection is the goal of surgery because incomplete

resection is associated with high risk of recurrent hemorrhage. Transient neurologic deterioration after surgey is common, but most of the patients return to their preoperative level of neurologic function or improve. Long-term clinical and neuroradiologic follow-up is mandatory after successful surgical resection.

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13

Giant Cavernous Angiomas of the Cavernous Sinus

Atul Goel and Trimurti D. Nadkarni

Cavernous angioma of the cavernous sinus is an uncommon lesion accounting for ~2% of all cavernous sinus tumors.[1–5] This benign tumor is a neurosurgical challenge because of the high vascularity, location within the cavernous sinus, and relationship to the intracavernous internal carotid artery and cranial nerves.

Cavernous angiomas of the cavernous sinus are vascular malformative lesions, analogous to the intraaxial cavernous angioma. Some authors feel that the correct term for extracerebral cavernous (hem)angiomas is *cavernoma*, or venous vascular malformation of the cavernous type.[6] The term *hemangioma* should be avoided and reserved for the vascular tumors commonly seen in infants.[6] Cavernous angiomas in the cavernous sinus are anatomically and physically different from cavernomas or cavernous angiomas of the cerebral parenchyma. Histologically, cavernous angioma involving the cavernous sinus is similar to intracerebral cavernous angioma but is a distinct clinical entity, and the management issues are vastly different from those located within the cerebral parenchyma and other extracerebral locations. Histology reveals that cavernous angiomas of cavernous sinus are vascular malformations composed of large vascular channels lined by flat endothelium and separated by fibroconnective tissue stroma. Ohata et al. have described the cavernous angioma to be a cluster of sinusoidal cavities, the size of which depends on the systemic blood pressure.[7] Katada et al. suggest that growth mechanism of cavernous angioma could be progressive ectasia of vessels or their autonomous development at the edges of the lesions.[8]

Cavernous angiomas involving the dural confines of the cavernous sinus frequently reach giant size before diagnosis. Radiation treatment has been successful.[9–11] However, the general consensus favors radical surgery as the primary and the only modality of therapy for these benign tumors. Understanding of the anatomic location and relationships and the vascular pattern of the tumor can lead to a successful resection even through a small exposure. As the surgical principles involved in the treatment are different from all other brain lesions, an experience in the surgical resection of these tumors is of great help during surgery.

♦ Epidemiology, Clinical Presentation, and Treatment at King Edward Memorial Hospital: Clinical Experience

Fifteen patients with cavernous angiomas of the cavernous sinus, 10 females and 5 males aged from 15 to 55 years (mean, 30 years), were treated in our unit from 1992 to 2003. The duration of symptoms at the time of presentation ranged from 7 days to 2 years (mean, 40 days). All patients were treated with radical surgery and followed up from 8 months to 9 years (mean, 45 months).

The principal clinical features are shown in **Table 13–1**. All patients presented with symptoms of headache. Thirteen patients had sudden onset of single or multiple cranial nerve pareses, and the symptoms were progressive in three of these patients. Four patients had visual deficits on the side of the tumor, one of which had visual deficits on both sides, worse on the side of the tumor. The visual deficits were progressive in all patients. Six patients had moderate to severe pain in the face on the side of the tumor. Two patients had no cranial nerve deficit at presentation; one presented with an episode of generalized convulsions and headache, and the other had only headache.

Table 13–1 Presenting Clinical Symptoms

Symptoms	No. of Patients	Percent of Patients
Headache	15	100
Retroorbital and facial pain	6	46.2
Visual impairment	4	30.8
Impaired corneal reflex	9	69.2
Decreased sensation over face	10	76.9
Wasted temporalis/masseter muscle	8	61.5
Sixth cranial nerve paresis	12	80
Third cranial nerve paresis	11	73.3
Seizures	2	15.4

All patients were investigated with magnetic resonance imaging (MRI) and computed tomography (CT). CT showed the lesion as hypodense to isodense with marked enhancement after contrast administration. On T1-weighted MRI, the lesion was moderately hypointense, and on T2-weighted MRI, the lesion was highly hyperintense. The size of the lesion ranged from 28 to 73 mm in maximum dimension (mean, 44 mm). All cavernous angiomas irrespective of size were located entirely within the dural confines of the cavernous sinus and had extensions toward the petrous apex, superior orbital fissure, and the sella **(Figs. 13–1 to 13–4)**. All lesions encased the internal carotid artery circumferentially during its course through the cavernous sinus.

Angiography was performed in five patients. These lesions were angiographically relatively "occult" despite the intense vascularity encountered during surgery **(Figs. 13–2 and 13–3)**. There was a relatively minor vascular blush in

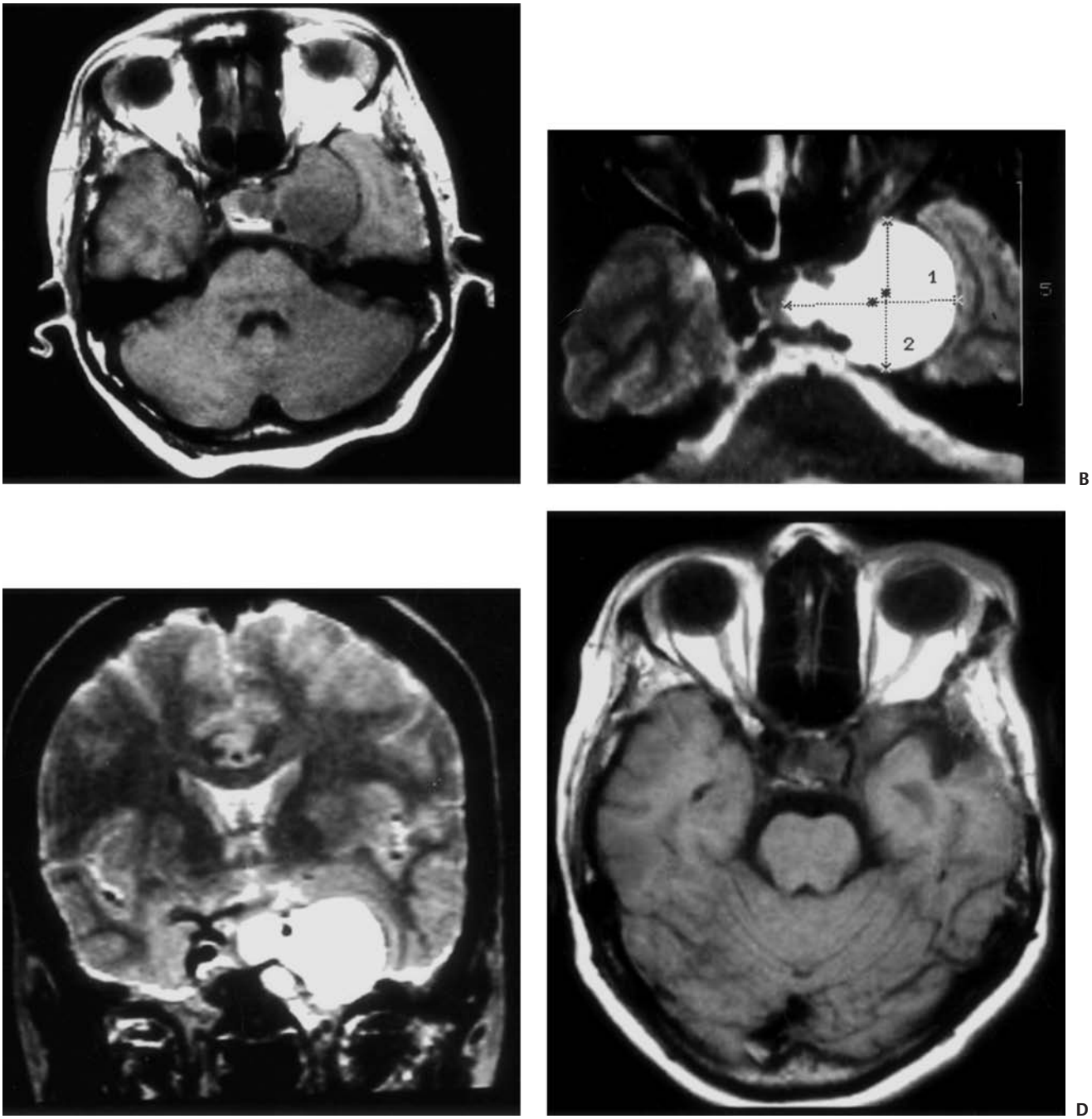

Figure 13–1 A 40-year-old woman presented with headaches associated with third, sixth, and fifth cranial nerve dysfunction. **(A)** Axial T1-weighted image showing an isointense left cavernous sinus angioma with a sellar extension. **(B)** Axial T2-weighted magnetic resonance image showing the hyperintense left cavernous tumor. **(C)** Coronal T2-weighted image shows the carotid artery to be encased by the tumor. **(D)** Postoperative T1-weighted axial image demonstrates complete excision of the cavernous sinus mass.

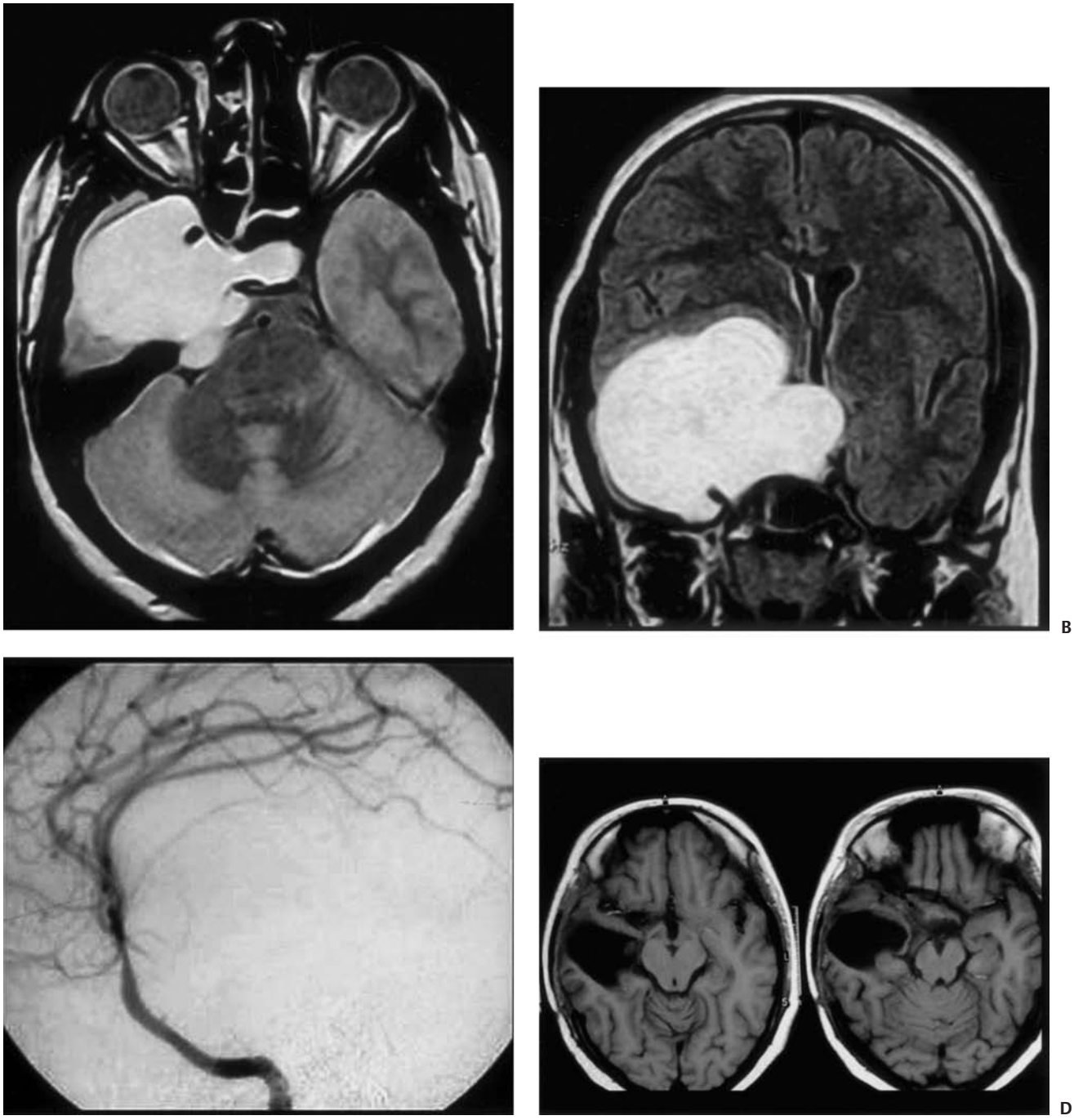

Figure 13–2 A 15-year-old girl presented with diminution of vision in both eyes for 6 months. She had right eye ptosis and diplopia for a fortnight. On examination, she had only perception of light in the right eye and finger counting vision in the left eye at 3 feet. There was total ophthalmoplegia of the right eye. The right fifth nerve demonstrated motor, sensory, and corneal affection. **(A)** Axial proton density magnetic resonance image demonstrated a large hyperintense right intracavernous sinus tumor. **(B)** Postcontrast T1-weighted magnetic resonance image showed the tumor to enhance and the carotid artery to be encased. **(C)** Right internal carotid angiogram demonstrated no tumor blush. **(D)** Postoperative axial T1-weighted magnetic resonance images showing complete excision of the tumor.

all cases. Small leashes of vessels arising from the internal carotid artery fed the cavernous angioma. The cavernous angioma was also fed by larger vessels such as the inferolateral trunk in four cases and from the region of the McConnell capsular artery in two cases. Preoperative embolization was not possible in any of our series as the feeding vessels were too small. One case of huge cavernous angioma incorporated a large aneurysm in the intracavernous segment of the internal carotid artery associated with evidence of intralesional bleeding **(Fig. 13–3)**. There was no evidence of hemorrhage in any other lesion. No case showed any calcification or necrosis.

Orbitozygomatic osteotomy, basal pterional craniotomy, and an intradural approach to the lesion were performed in our first case.[12] Intraoperative control of the internal carotid artery in the neck was performed in this patient. A basal zygomatic bone–based temporal craniotomy was performed with the patient in a lateral position in all other cases. Proximal control of the internal carotid artery in the neck or in the petrous apex was not obtained in these

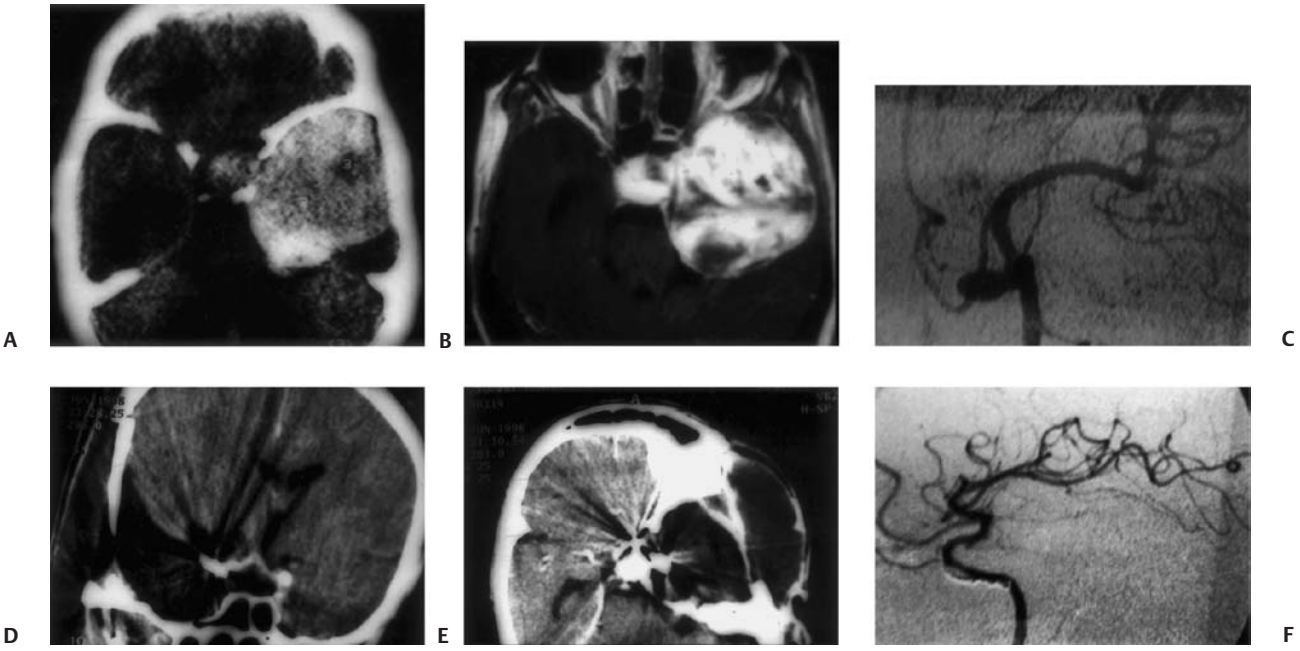

Figure 13–3 A 50-year-old female presented with acute onset of ophthalmoplegia 5 days prior to admission. **(A)** Axial computed tomography (CT) with contrast shows a massive cavernous sinus mass that occupies nearly the entire middle cranial fossa. **(B)** Postcontrast axial T1-weighted magnetic resonance image showing enhancement with extensions into the sella, superior orbital fissure, and the Meckel cave. **(C)** Left internal carotid angiogram showing a large aneurysm on the anterior ascending segment of the artery. The tumor demonstrates no significant blush. **(D)** Postoperative coronal (CT) scan shows complete excision of the tumor with clip artifacts. **(E)** Axial CT demonstrates complete excision of the tumor. **(F)** Postoperative left carotid artery angiogram shows the aneurysm to be completely excluded from circulation.

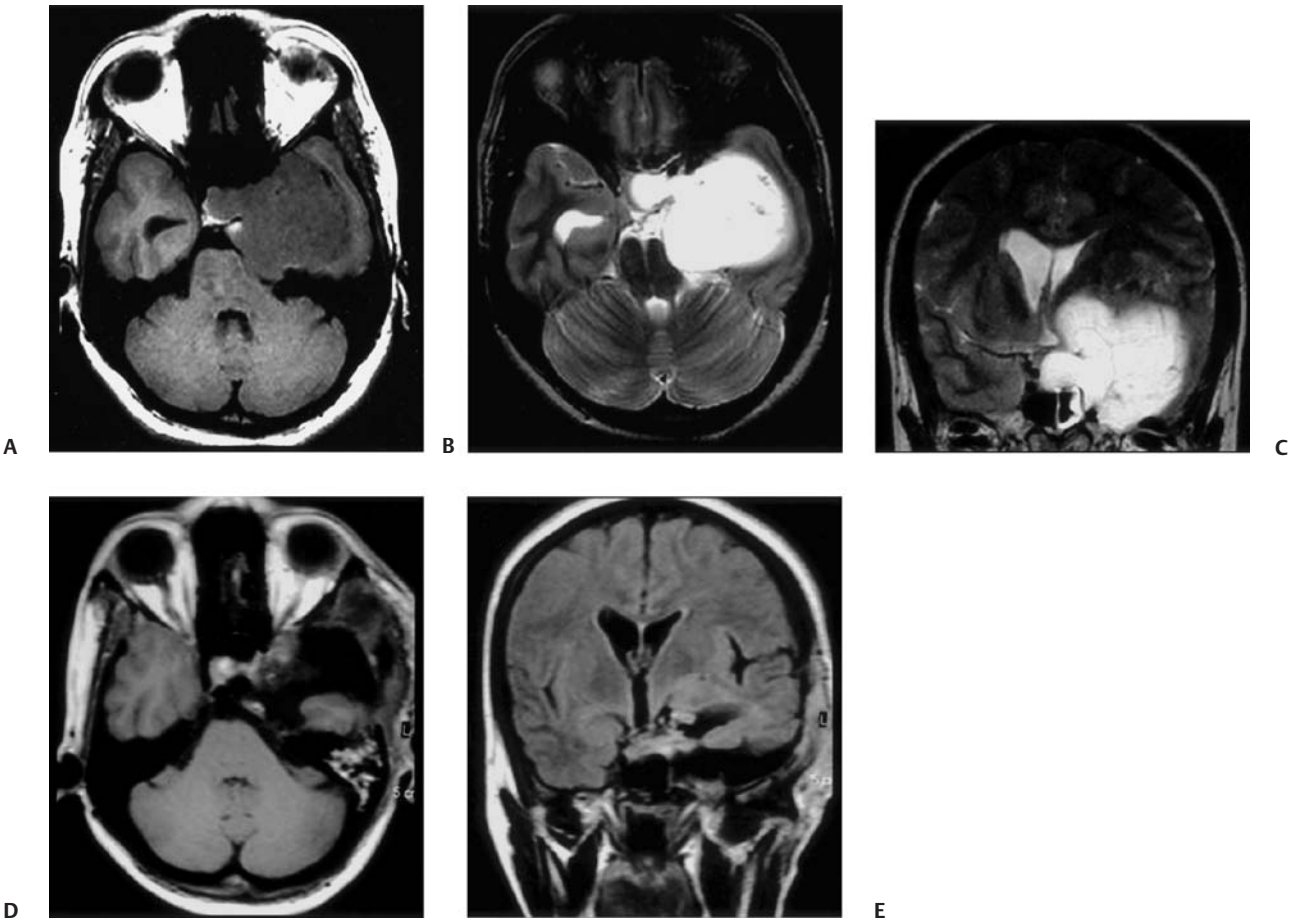

Figure 13–4 A 43-year-old woman presented with one episode of generalized seizure but without any neurologic deficit. **(A)** Axial T1-weighted magnetic resonance image shows a hypointense cavernous sinus tumor. **(B)** Axial T2-weighted magnetic resonance image demonstrates the tumor to be hyperintense. **(C)** Coronal T2-weighted magnetic resonance image showing the large dimensions of the tumor. **(D)** Postoperative axial T1-weighted image and **(E)** coronal T1-weighted image shows complete excision of the giant cavernous angioma of the cavernous sinus.

patients. Lumbar drainage of the cerebrospinal fluid was performed during surgery. Exposure of the lesion extradurally was attempted in the latter 14 cases but was possible only in 11 cases, whereas the extradural approach was adopted but an additional intradural approach was used to facilitate resection and to confirm the completeness of removal in the other three cases. A large part of the lesion lateral to the carotid artery was removed *en bloc* by careful dissection from the adjoining structures in two cases of relatively small cavernous angiomas. However, the lesion was large and required piecemeal resection in the other cases. Total resection was achieved in 14 patients and partial resection was achieved in one patient.

The surgical strategy was to expose the region by an extradural route from an inferior perspective. The lesion bulk was then exposed by working between the laterally displaced fifth cranial nerve fibers. Most of the cavernous angiomas were soft and friable and were compressible. An initial attempt was made to dissect the lesion circumferentially from the adjoining structures. However, wherever an excessive bleeding was encountered, a rapid debulking of the cavernous angioma using relatively powerful, graded, and controlled suction was performed to remove the bulk of the lesion, to expose the sixth cranial nerve near the petrous apex, and to coagulate the feeders arising from carotid artery early in the operation. Once the bulk of the lesion was removed and the branches from the major feeding channels were obliterated, hemostasis was largely spontaneous and relatively simple. Two patients suffered a puncture hole injury in the carotid artery in the region of the inferolateral trunk during resection. The bleeding could be stopped by local coagulation and gentle pressure for a period in both cases.

The sixth cranial nerve could not be identified in its course within the cavernous sinus in seven patients. The sixth cranial nerve was identified in eight patients and could be completely preserved in five patients. In the immediate postoperative phase, none of the patients showed recovery of function of any cranial nerve. Extraocular movements completely recovered in five patients ~12 months after surgery. One patient who had intact preoperative function of all cranial nerves developed sixth cranial nerve paresis after surgery, but the third cranial nerve remained normal. At follow-up after 18 months, she showed complete recovery of all extraocular movements. Nine patients had moderate to severe dysfunction of the extraocular movements, and both the third and the sixth cranial nerves were affected. Six patients showed partial recovery of third cranial nerve function. All patients were relieved of the headaches after surgery. During the follow-up period, no recurrence or regrowth of the residual cavernous angioma was found, and all patients are leading active lives.

♦ Literature Review of Epidemiology, Clinical Presentation, and Treatment

Cavernous angiomas of the cavernous sinus are frequently seen in the fourth and fifth decades of life.[12,13] Nearly half of the reported cases were of Japanese origin.[13] Ninety-four percent of the reported cases occurred in women.[2] In our series, 67% were females. Symptoms have been reported to first appear or to worsen with pregnancy.[1, 14] Considering that females in their youth or middle age are more common victims of this lesion, the origin may be hormonal.[14,15]

Clinical presentation is usually in the form of symptoms related to the acute or subacute dysfunction of the nerves traversing the cavernous sinus and the optic nerve. Hemorrhage within the cerebral cavernous angiomas is a common feature but is relatively uncommon in cavernous angiomas located in the cavernous sinus.[13,16] Despite the acute nature of clinical presentation in 10 cases, only 1 case had evidence of bleeding.[17,18] In the absence of a bleed within the lesion, it appears that the acute cranial nerve symptoms may be a result of an ischemic insult. In our series, one patient had no affection of any cranial nerve and presented with the primary symptom of severe headache. The rest of the patients had deficit involving cranial nerves coursing through the cavernous sinus. Vision was affected in four patients. The cause of the visual affection could be due to a vascular steal phenomenon as in high-flow arteriovenous malformations. Headache, which varied in intensity from moderate to severe, was present in all patients and was the most disabling clinical feature. Two patients had generalized seizures. No other hemisphere-related symptoms occurred in any patient. Pituitary hypofunction has been reported with these lesions[2,18] but was not encountered in our series. An acute cavernous sinus syndrome, manifesting as retroorbital pain, blepharoptosis of the eye, diplopia, and sensory disturbance of the face similar to the Tolosa-Hunt syndrome, has been reported.[8] Yamamoto et al. have reported amenorrhea and hyperprolactinemia in a 34-year-old female as presenting symptoms.[19] Exophthalmos, trigeminal neuralgia, and hemi- or monoparesis are the other reported symptoms at the time of presentation.[2]

Improvement in the diagnosis after the introduction of computer-based imaging had led to an increased rate of diagnosis of cavernous angiomas in intracerebral and extracerebral locations. Identification of the lesions as *cavernous angioma* within the cavernous sinus on the basis of preoperative clinical findings and radiologic parameters is crucial for planning of the surgical strategy. Radiographically, cavernous angiomas of the cavernous sinus have a characteristic pattern of extension toward the sella, superior orbital fissure, and the Meckel cave, which was observed in all our cases and in the majority of reported cases with radiography of the lesion.[2,3,13] Cavernous angioma is the only primary intracavernous sinus tumor. Irrespective of the size, the tumor has never been found to protrude out of the anatomic dural confines of the cavernous sinus. The extension toward the sella appears to be through the enlarged intercavernous sinus. Extension into the other tributaries of the cavernous sinus such as the superior and inferior petrosal sinuses has not been encountered. Erosion of the bones of the middle fossa floor, sphenoid wing, and the temporal squama and wasting of the temporalis and masseter muscles in some cases suggest the slow growth and progression of these lesions.[10]

Cavernous angioma is hyperdense on CT with brilliant enhancement after contrast administration. Extraaxial cavernous angiomas differ from intraaxial ones on MRI in that the hemorrhagic variant is less frequent, hemosiderin ring is rare, the signal characteristics are different, and

contrast enhancement is the rule.[20] The lesion is hypointense on T1-weighted MR images and highly hyperintense on T2-weighted images.[21,22] The lesion encased the internal carotid artery during its entire course in the cavernous sinus in all our cases. Cavernous angioma is usually angiographically "occult" despite the extensive vascularity,[10,13] although a mild blush is frequently seen.[2,13,23–26] This blush has been observed to have flecked, pooling, or lake-like appearance in the late venous phase.[2] As in our cases, the inferolateral trunk,[15,23,27] meningohypophyseal trunk,[10,11,18] accessory meningeal artery,[18,26] and middle meningeal artery[2,9–11] have been identified as major feeding vessels. In two of our cases, there was a relatively large feeder from the region of the McConnell capsular artery. Preoperative embolization of the lesion has been reported,[2,9,12,18] but this could not be done in our series because of the small size of the feeding vessels. An aneurysm of the internal carotid artery was seen in one of our cases.[28] Although likely, it is difficult to confirm whether this associated aneurysm was due to high-pressure blood flow in the cavernous angioma simulating the aneurysm seen on feeding vessels of intracranial arteriovenous malformations.

Thallium-201 (201Tl) single photon emission computed tomography (SPECT) shows low uptake in cavernous sinus angiomas, and technetium-99m–human serum albumin–diethylenetriamine penta-acetic acid SPECT reveals high uptake within tumor. 201Tl SPECT usually shows very high uptake in meningiomas and malignant tumors. Thus, SPECT is useful for distinguishing cavernomas from other cavernous sinus tumors.[29]

Selection of the operative route for cavernous sinus–related lesions, the extent of exposure necessary, the need for operative control of the carotid artery, and feasibility and need of radical resection depend on the histologic nature of the lesion. The age and sex of the patient, principal presenting signs, size of the lesion, extent of cranial nerve and carotid artery involvement, imaging characters, and other such features are helpful in estimating the consistency and vascularity of the lesion, site of origin, and direction of its spread and the extent and nature of cavernous sinus involvement. Evaluation of the histology of the lesion on the basis of radiologic and clinical parameters and the impact on decision regarding the surgical strategy is paramount.[30]

Surgical excision is the most acceptable therapy for cavernous angiomas of the cavernous sinus considering the benign nature of the lesion and potential curability.[2,10,11,23,26,31–34] Smaller lesions and those with mild symptoms can be clinically and radiologically observed. The main difficulty during surgery for cavernous angioma is the vascularity of the lesion.[2,11,27] Surgical resection carries the risk of extensive and uncontrollable bleeding. Surgical misadventures have resulted in high morbidity and mortality.[2,14,18] Preoperative radiation treatment as a modality to reduce lesion vascularity has been suggested.[2,11,25,35] Direct puncture and injection of sclerosing agents (alcohol, fibrin glue, plastic adhesive material) in the lesion has produced good results.[36–38] Induced hypotension and hypothermia may be useful adjuncts for surgery.[7]

In our first case, we performed an orbitozygomatic osteotomy and basal frontotemporal approach.[12] However, we observed that the brain in these cases was lax and the tumor was soft and compressible, so elaborate skull base exposures could be safely avoided. In the later part of our series, we performed a basal temporal craniotomy based over the entire zygomatic bone. The lateral aspect of the lesser wing of the sphenoid bone was removed. Bone work in the extradural space was restricted to prevent avoidable blood loss. We observed that extradural exposure was the most appropriate approach for these essentially intracavernous sinus lesions. The lateral dural wall of the cavernous sinus could be stripped in a relatively bloodless field from the inner dural layer containing the splayed out cranial nerves.[39] The incision in the inner layer was taken toward the base to avoid injury to the first division of the fifth cranial nerve. Extradural surgery avoided handling of the temporal brain and reduced the possibility of postoperative seizures.

In our earlier report on this subject,[12] we recommended *en bloc* excision of the cavernous angioma. Other authors have also favored an *en bloc* tumor excision.[2] *En bloc* resection of these lesions is most suitable for small, moderate, and even large cavernous angiomas. Although, identified by some,[2,3] a pseudocapsule providing an opportunity for surgical dissection plane was not observed in our series. Most of the cavernous angiomas were very large or giant in our series, so we preferred an alternative method of dissection. The lesion was first dissected from its surface in an *en bloc* manner. However, during this dissection whenever the cavernous angioma bleeding was significant and excessive, a debulking of the lesion was performed by working within the mass. The red, extensively vascular lesion was soft and contained thin vascular channels and could be debulked and decompressed using relatively powerful and controlled suction. Avoiding sharp dissection in the cavernous sinus while working in a bloody field was useful to preserve the internal carotid artery and the cranial nerves. We observed that hemostasis was achieved spontaneously after a large part of the lesion was resected, and the residual cavernous angioma could be resected under vision from the corners. The technique of minor resection and then hemostasis before further tumor resection and maintaining a bloodless field may not be applicable in these cases. Such a procedure is associated with greater overall blood loss than if a relatively quick resection is performed. Partial or subtotal resections are not recommended and can lead to difficulty in control of bleeding during surgery and could be associated with an increased incidence of postoperative hemorrhage.

The initial direction of debulking the lesion mass was toward the petrous apex to identify the sixth cranial nerve as the site of its entry into the cavernous sinus. The nerve was then followed distally. The feeding vessels from the intracavernous sinus carotid artery were coagulated as soon as significant debulking was completed and wide exposure of the carotid artery was achieved. The third cranial nerve is located on the dome of the cavernous angioma and is securely placed within the dural walls. The dissection of the lesion in the region of the dome was performed later in the region of the surgery after a large portion of the cavernous angioma had been removed from within the cavernous sinus and the bleeding from the lesion was under control.

Radical resection of cavernous angiomas located within the cavernous sinus is possible by an entirely extradural route. Rapid decompression of the lesion after wide exposure can

lead to successful resection. The outcome for extraocular movements is excellent after surgery on small or moderate-size cavernous angiomas. However, the outcome of extraocular movement was poor in our series after surgery in giant cavernous angiomas. Recurrence rates after successful resection are extremely low.[13,40] There was no recurrence or regrowth in any of our patients.

Radiotherapy has been demonstrated to show complete disappearance of cavernous sinus angioma or a significant reduction in size of the tumor. There has been symptomatic relief and recovery of cranial nerve function. Radiation has been used in doses of 30 to 40 grays.[19,41–45] Radiotherapy should be considered for patients with incomplete tumor excision or for patients who are too ill to undergo surgery.[2] Radiosurgery has also shown similar results.[46–50] Radiosurgery could be beneficial in the treatment of small cavernous angiomas[47] and could be a modality of therapy for smaller residual lesions.

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14

Management of Atypical Cavernous Malformations

Vivek R. Deshmukh and Robert F. Spetzler

Cavernous malformations are considered vascular malformations, a designation that they share with arteriovenous malformations, capillary telangiectasias, and venous malformations. Cavernous malformations are angiographically occult. Histologically, they appear as compact, thin-walled, dilated capillary spaces without intervening brain tissue. Their reported incidence is 0.3 to 0.5%.[1–3] These lesions occur in sporadic and familial forms. Most are found in the supratentorial compartment (80%) followed by the infratentorial compartment (15%) and spinal cord (5%), a relative predilection that reflects the volumes of the central nervous system compartments. These lesions may become symptomatic with headache, hemorrhage, seizures, and progressive neurologic deficits.

Atypical cavernous malformations are lesions located in atypical locations, including the ventricular system and extraaxial space. The latter can afflict the dura and cranial nerves traversing the subarachnoid space. These atypical cavernous malformations pose unique diagnostic and surgical challenges.[4]

♦ Intraventricular Cavernous Malformations

The third ventricle is the most common location within the ventricular axis, followed closely by the lateral ventricles **(Fig. 14–1)**. Fourth ventricular cavernous malformations are exceedingly rare. Patients usually exhibit symptoms related to mass effect. In the contemporary literature, 24 third ventricular cavernous malformations have been reported.[5,6] There is a female predilection. Presenting symptoms may be the result of hydrocephalus or local mass effect. The onset of symptoms is usually insidious. It has been theorized that ventricular cavernous malformations undergo more rapid growth than cavernous malformations in other locations. Repeated extralesional microhemorrhages can cause superficial siderosis (hemosiderin deposition in subpial or subependymal lining). Suprachiasmatic lesions can cause field defects and endocrine disturbances. Those located at the foramen of Monro can cause hydrocephalus. Short-term memory loss in particular may result from third ventricular wall involvement. The floor of the third ventricle can be impinged, and hypothalamic dysfunction can be profound as a result.[7,8]

The fourth ventricle is the least common intraventricular location for cavernous malformations. Dandy first reported the excision of a fourth ventricular cavernous malformation in 1928 **(Fig. 14–2)**.[9] Symptoms in these patients are the result of cranial nerve dysfunction, obstructive hydrocephalus, and midline cerebellar deficits.[10,11]

Intraventricular cavernous malformations should be treated aggressively. The significant deficits that they cause and their rapid growth rate justify gross total resection. However, a solitary lesion that is clinically quiescent may be observed. The interhemispheric transcallosal approach

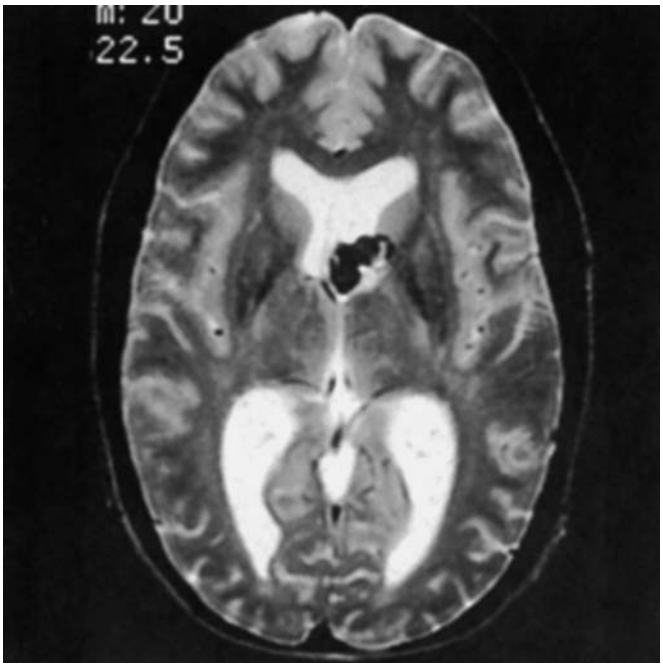

Figure 14–1 T2-weighted magnetic resonance image shows a cavernous malformation involving the left caudate and thalamus. An exophytic portion extrudes into the left lateral ventricle. (From Deshmukh VR, Spetzler RF. Cavernous malformations of the brain and spinal cord. Operative Techniques in Neurosurgery 2002;5(3):167. Reprinted with permission from Elsevier, Inc.)

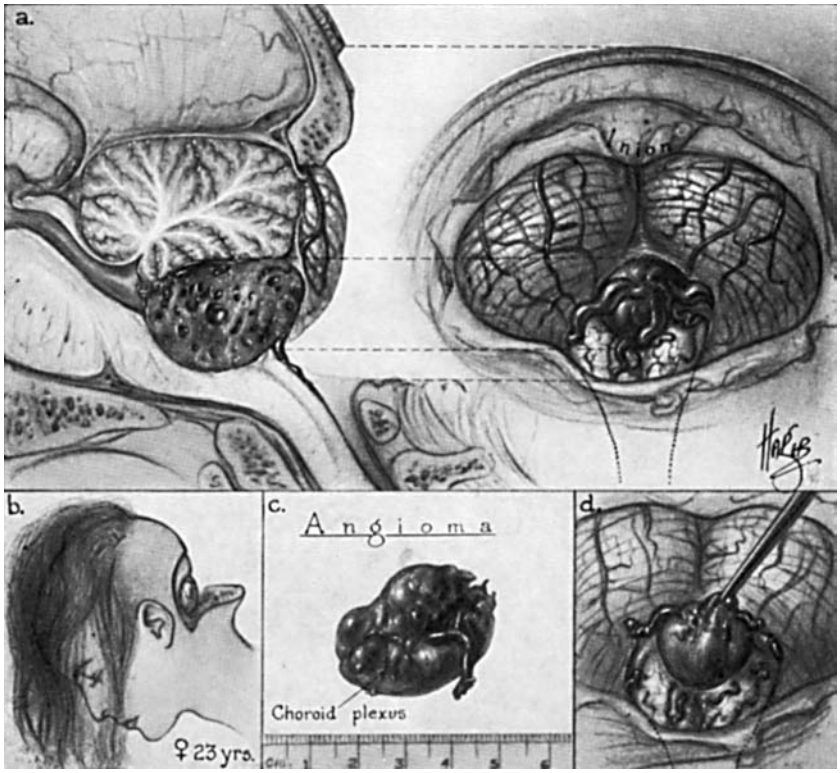

Figure 14–2 Illustration of the removal of a fourth ventricular cavernous malformation by Dr. Walter Dandy, the first such reported case. (Drawing from the Dorcas Hager Padget Collection, Brödel Archives, Department of Art as Applied to Medicine, Johns Hopkins University. Reprinted with permission from Johns Hopkins University.)

can be used for lesions within the third and lateral ventricle. A transcortical route via the superior parietal lobule should be considered for lesions within the trigone. Septal and caudate nucleus lesions can be approached through either a transcortical or interhemispheric transcallosal approach. For these cases, the interhemispheric approach is preferred because it minimizes the amount of brain injury and offers an elegant corridor through noneloquent existing tissue planes. Fourth ventricular lesions can be excised through the suboccipital approach.

♦ Cranial Nerve Cavernous Malformations

Cavernous malformations involving the cranial nerves are extremely rare, but several case reports and series of cavernous malformations involving the optic nerve and chiasm, the vestibulocochlear nerve complex, oculomotor nerve, trigeminal nerve, and hypoglossal nerve have been reported. These lesions must be recognized in a timely manner and surgically excised if cranial nerve function is to be preserved.

Twenty-three cases involving the optic pathways have been described.[12–22] Most of these patients became symptomatic with acute chiasmal syndrome or chiasmal apoplexy. Sudden onset headache, visual deterioration, and signs of meningeal irritation characterize this apoplectic event. Typically, magnetic resonance imaging (MRI) shows a focal suprasellar lesion involving the optic pathways with heterogeneous signal intensity. A hyperintense signal suggests recent hemorrhage. If present at all, postcontrast enhancement should be minimal **(Figs. 14–3, 14–4, and 14–5)**. This clinical scenario of acute visual deterioration represents a

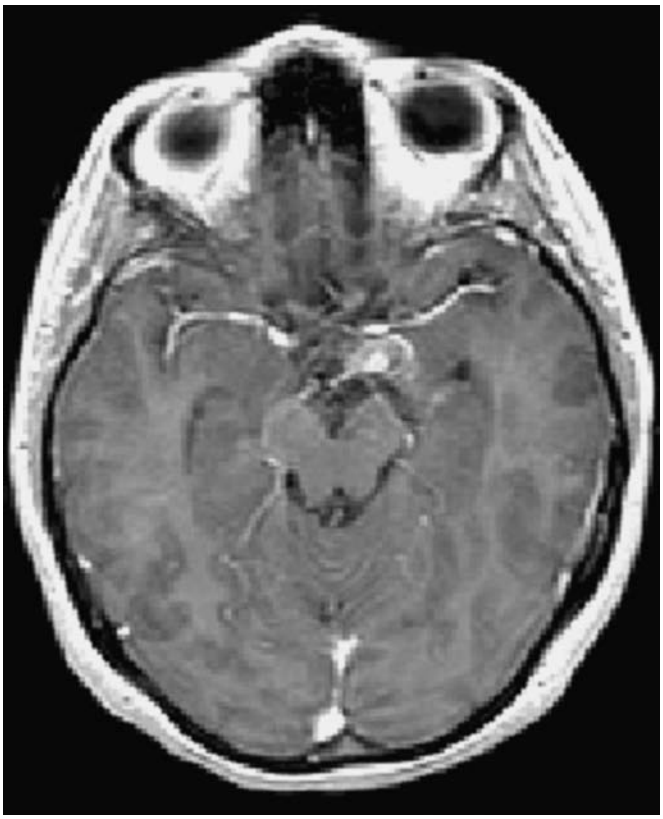

Figure 14–3 Axial T1-weighted postcontrast magnetic resonance image shows a large cavernous malformation, within the left optic apparatus involving the surrounding structures. (From Deshmukh V, AIbuquerque FC, Spetzler RF. Surgical management of atypical cavernous malformations. Operative Techniques in Neurosurgery 2002;5(3):168. Reprinted with permission from Elsevier, Inc.)

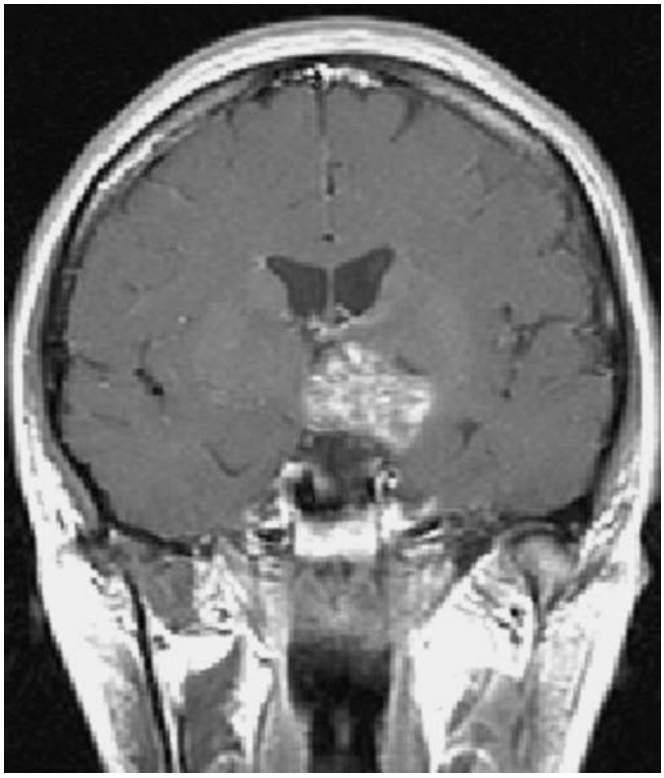

Figure 14–4 Coronal T1-weighted image shows the rostral extent of this cavernous malformation, which originates within the optic apparatus. (From Deshmukh V, Albuquerque FC, Spetzler RF. Surgical management of atypical cavernous malformations. Operative Techniques in Neurosurgery 2002;5(3):168. Reprinted with permission from Elsevier, Inc.)

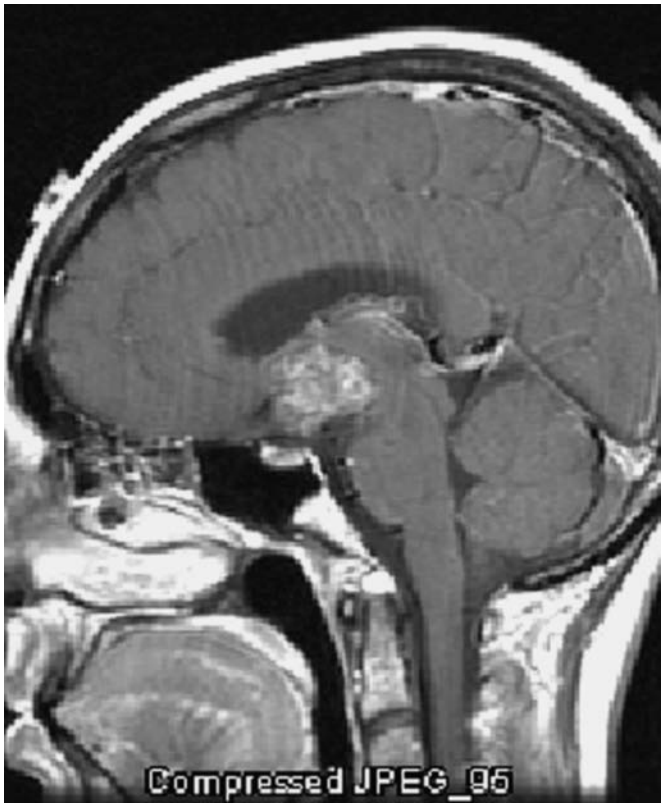

Figure 14–5 Sagittal T1-weighted image shows heterogenous signal intensity and the posterior extent of the cavernous malformation. (From Deshmukh V, Albuquerque FC, Spetzler RF. Surgical management of atypical cavernous malformations. Operative Techniques in Neurosurgery 2002;5(3):168. Reprinted with permission from Elsevier, Inc.)

surgical emergency. Such patients should undergo emergent craniotomy and excision of the cavernous malformation.

The preferred surgical approach is a pterional craniotomy combined with an orbital roof and lateral wall osteotomy to obtain adequate exposure of the optic apparatus. An eyebrow key-hole craniotomy also has been used successfully.[22] The optic apparatus will be edematous with evidence of hemosiderin staining **(Figs. 14–6 and 14–7)**. Removal of the hematoma alone leads to significant decompression. The lesion must then be resected completely because residual

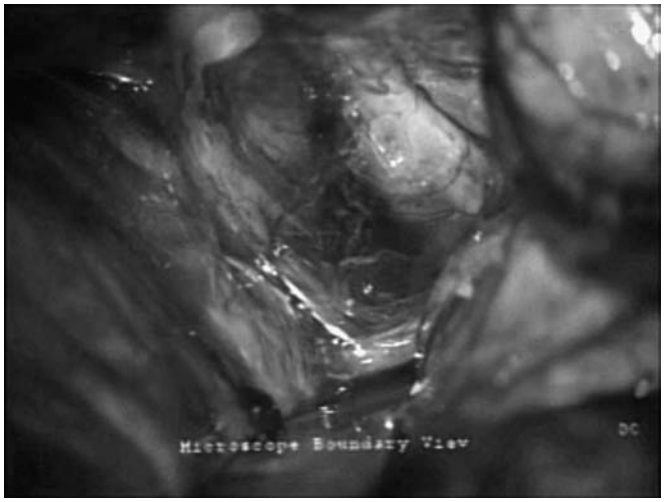

Figure 14–6 Intraoperative image of an edematous optic nerve and chiasm with evidence of hemosiderin staining suggests prior hemorrhagic episodes. (From Deshmukh V, Albuquerque FC, Spetzler RF. Surgical management of atypical cavernous malformations. Operative Techniques in Neurosurgery 2002;5(3):168. Reprinted with permission from Elsevier, Inc.)

Figure 14–7 The cavernous malformation is removed in a piecemeal fashion. (From Deshmukh V, Albuquerque FC, Spetzler RF. Surgical management of atypical cavernous malformations. Operative Techniques in Neurosurgery 2002;5(3):169. Reprinted with permission from Elsevier, Inc.)

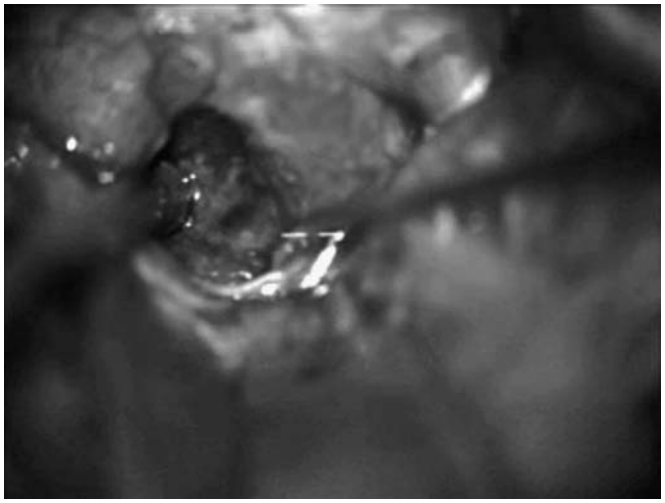

Figure 14–8 The hemosiderin-stained tissue that is not part of the cavernous malformation need not be resected. The resection cavity must be examined thoroughly. (From Deshmukh V, Albuquerque FC, Spetzler RF. Surgical management of atypical cavernous malformations. Operative Techniques in Neurosurgery 2002;5(3):169. Reprinted with permission from Elsevier, Inc.)

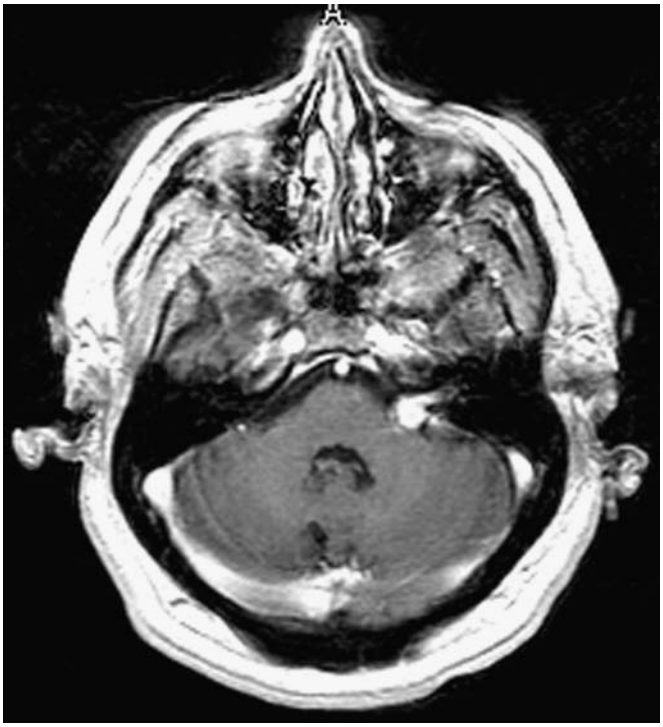

Figure 14–9 Axial postcontrast T1-weighted magnetic resonance image shows a lesion involving the left cerebellopontine angle extending into the porus acusticus. (From Deshmukh V, Albuquerque FC, Spetzler RF. Surgical management of atypical cavernous malformations. Operative Techniques in Neurosurgery 2002;5(3):169. Reprinted with permission from Elsevier, Inc.)

cavernous malformation recurs and leads to progressive symptoms. The hemosiderin-stained tissue should not be resected because it is not part of the malformation; its resection would injure eloquent tissue **(Fig. 14–8)**. Most patients' preoperative symptoms or deficits improve after resection. Patients who have suffered multiple hemorrhagic events will have persistent deficits after surgery, and this possibility should be emphasized during preoperative counseling.

Eighteen cavernous malformations involving the vestibulocochlear nerve complex have been reported.[23–31] Presenting symptoms include acute onset of hearing loss often accompanied by facial nerve paresis. The sensorineural hearing loss and facial weakness are disproportionate to the size of the lesion. Imaging studies show a hyperintense lesion without postcontrast enhancement. Before surgery, most reported patients were erroneously thought to harbor acoustic schwannomas. The rapidity of the onset of symptoms and severe deficits, however, should suggest the diagnosis of cavernous malformation. The hyperintense appearance on MRI without enhancement also makes schwannoma a less likely diagnosis **(Fig. 14–9)**. All patients with this clinical picture should undergo urgent excision of the cavernous malformation.

The suboccipital-retrosigmoid approach is ideal. An edematous and hemosiderin-stained vestibulocochlear nerve complex is common. Like lesions involving the optic pathways, the entire cavernous malformation must be excised without resection of hemosiderin-stained tissue. Facial nerve function improves in most patients, but the recovery of hearing is less uniform.

Four cases of cavernous malformations within the oculomotor nerve have been described.[32,33] These patients usually present with headache, diplopia, and third cranial nerve dysfunction. Multiple cranial nerves may be involved if the lesion is large. In two cases, the oculomotor nerve required transection to achieve gross total resection. In a third case, a subtotal resection was performed and the oculomotor nerve was preserved. Two patients were diagnosed with Roberts syndrome, a genetic abnormality associated with multiple cutaneous and central nervous system vascular lesions among other constitutional findings. A cavernous malformation involving the trigeminal nerve manifested with trigeminal neuralgia,[34] and a single case of hypoglossal nerve cavernoma has been reported.[35] The tenets of management and surgical resection of cavernous malformations also hold true for lesions involving the oculomotor, trigeminal, and hypoglossal nerves.

♦ Extraaxial Cavernous Malformations

Most extraaxial lesions are found within the cavernous sinus, torcula, petrosal sinus, cerebellopontine angle, and calvarium. There appears to be a female predominance. Patients with cavernous sinus malformations often develop multiple cranial neuropathies, visual deterioration, and headaches. Imaging studies reveal bony erosion rather than hyperostosis. Clearly delineated from surrounding structures, the lesions appear isointense on T1-weighted MRI **(Fig. 14–10)** and markedly hyperintense on T2-weighted MRI. Angiography may show feeding arteries. Whether extraaxial cavernous malformations are distinct clinicopathologic entities is a point of contention.

These lesions are difficult to manage surgically, and their natural history remains unknown. Cavernous malformations

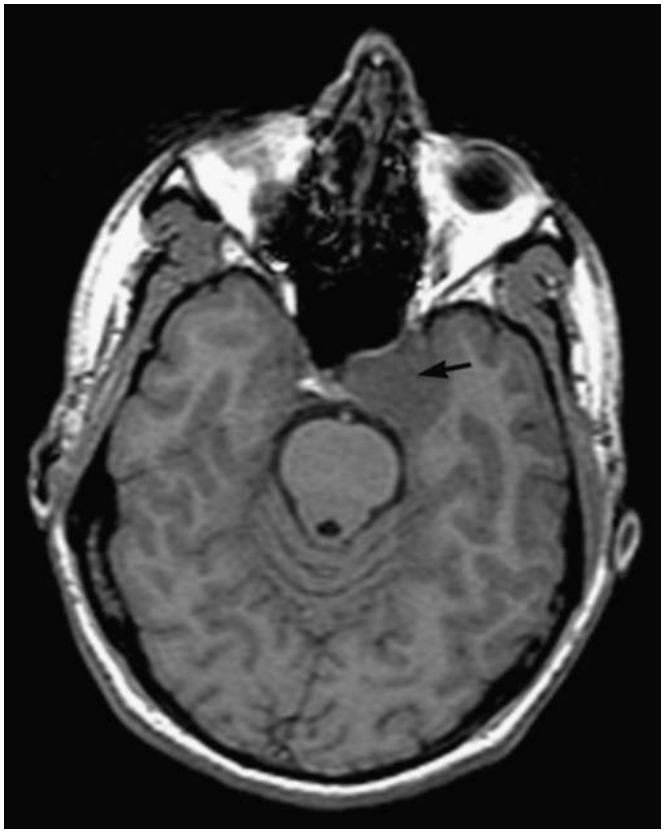

Figure 14–10 Axial precontrast T1-weighted magnetic resonance image shows a hemangioma in the left cavernous sinus. The patient underwent biopsy followed by Gamma Knife radiosurgery.

within dural venous sinuses are highly vascular tumors. Historically, surgical resection has been associated with a high mortality rate related to massive intraoperative hemorrhage. If resection is to be attempted, embolization of feeding vessels should be considered. Recently, hemangiomas involving the cavernous sinus have been excised successfully.[36–38] Nonetheless, conservative management is advisable for asymptomatic patients. An attempt at gross total resection is associated with a high rate of cranial neuropathy. The extradural approach may offer a higher likelihood of a gross total resection.[38] Radiosurgery is a viable option in treating these lesions, particularly after subtotal resection.[38–41]

♦ Conclusion

Atypical cavernous malformations are challenging lesions. Their manifestations and behavior are protean and primarily depend on their location. Surgical excision is the preferred treatment modality for these lesions with the exception of those involving the cavernous sinus. Outcomes tend to be excellent.

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15

Cavernous Malformations and Seizures: Lesionectomy or Epilepsy Surgery?

Giovanni Broggi, Paolo Ferroli, and Angelo Franzini

Cavernous malformations (CMs) are an increasingly recognized cause of partial epilepsy. These benign, mulberry-like vascular lesions may occur at any site within the CNS, as well as in other organs such as the liver, bone, or skin. Histologically, they consist of ectatic, endothelium-lined channels without mural muscular or elastic fibers within a matrix of collagenous tissue lacking any neuronal elements. Typically, although not invariably, gliosis and hemosiderin deposition can be found in the surrounding neural parenchyma.[1] Supratentorial CMs present with epileptic seizures, less often with hemorrhage or with signs and symptoms of space-occupying lesions.[2–6] The diagnostic incidence of CMs has dramatically increased in the magnetic resonance imaging (MRI) era. It is not uncommon to see patients with incidentally diagnosed, asymptomatic CMs.[7–9]

Epileptic seizures caused by CMs are often medically refractory[10,11] as is often the case for partial seizures secondary to other space-occupying lesions.[12,13] Even in patients who present with seizures as the first clinical manifestation, MRI often shows the presence of microhemorrhages. The presence of microhemorrhages in patients with CMs who present with seizures at the first clinical manifestation has been confirmed by postoperative histologic analysis.[8,9,14] Epileptic seizures are thought to be the consequence of hemosiderin deposits or the presence of gliotic scars secondary to the microhemorrhages.[14,15] Surgical treatment of CMs presenting with seizures is usually recommended, not only to prevent future bleeds but also to prevent future seizures.[16] However, surgical indications and optimum management of CMs causing epilepsy still remain controversial.[11,16–24] In cases of intractable epilepsy with concordant clinical, electrophysiologic, and neuroimaging findings, the indication for surgery is clear. There are no accepted guidelines for the management of patients with CMs and recent onset of seizures or with medically controlled seizures. The best surgical strategy in patients with CMs presenting with seizures (i.e., simple lesionectomy versus "epilepsy surgery"), is also debated.

♦ Surgical Treatment at Instituto Nazionale Neurologico Carlo Besta

Of 191 patients (111 men, 80 women) with intraparenchymal hemispheric CMs who underwent surgical treatment at our institute between 1988 and 2003, 163 (85.3%) presented with seizures. The mean age at the time of surgery was 33.4 ± 14.2 years (range, 17 to 63 years). The mean duration of illness was 4.5 ± 7.6 years (range, 15 days to 43 years). Ninety-nine (60.7%) patients had a history of chronic epilepsy and a longer mean duration of illness (10.2 ± 9.1 years). Sixty-four (39.3%) patients had only single or sporadic seizures, and an immediate diagnosis of CM and surgical treatment, so that the mean duration of illness was much shorter (1.2 ± 1.7 years).

Preoperative Assessment

In patients with chronic epilepsy, the aim of the preoperative investigation was to identify a possible correlation between electroclinical and anatomic data. Data from detailed clinical histories, neurologic examinations, MR images, and scalp electroencephalograms (EEGs) were collected and examined. Seizures were divided into simple partial, complex partial, and secondary generalized seizures according to the International League against Epilepsy classification. Scalp EEGs with hyperventilation and photic stimulation are obtained by use of 16- or 18-channel bipolar recordings according to the International 10–20 system. In some cases, sleeping and waking EEGs were recorded. Only a few patients required video-EEG recording. EEGs were classified as normal; nonspecific, when nonfocal waves were present; or focal, when slow waves, sharp waves, spikes, rapid activity, or any combination of these abnormalities were restricted to one or two adjacent channels.

All patients underwent preoperative MRI (0.5 or 1.5 T). Magnetic resonance images consisted of multiplanar spin echo sequences using T1- and T2-weighted images and, also,

in most patients, gradient echo T2-weighted images. Functional MRI data were collected in patients with CMs in eloquent areas treated more recently. When a correlation between cavernoma location and electroclinical data was found, patients underwent lesionectomy without any other investigation. Only patients with incongruent data (multifocal seizures, multiple cavernomas, suspected dual pathology, etc.) were considered candidates for further invasive studies.

Surgical Technique

When lesionectomy alone was performed, this was accomplished by a minimally invasive transsulcal approach under high magnification. Before neuronavigation became available, the entrance sulcus was chosen with the help of a stereotactic frame. A guidance catheter was inserted to guide the surgeon only when approaching deep lesions. Frameless image-guidance with different neuronavigation systems has been employed since 1995. Functional MRI data fused with conventional neuronavigation MR images and direct cortical mapping data collected during awake surgery were used for surgical planning in case of eloquent location. Short linear skin incisions (6 to 8 cm) were generally used. The diameter of the craniotomy (2 to 4 cm) was chosen according to the amplitude of the arachnoidal incision planned to reach the lesion. The larger and deeper the lesion is, the longer the arachnoidal incision. This strategy was adopted to avoid any traction at the edges of the arachnoidal incision and to minimize compression on the cortical surface exposed within the sulcus. Retractors were generally avoided; when used, care was taken to keep them loose. The cortical surface within the sulcus is protected with unsticky cottonoids. Sharp incision of the superficial arachnoidal layer and underlying arachnoidal bands under high magnification is used (the tip of a 22-gauge needle used as a knife and microscissors). Any damage to the pial surface of the surgical corridor to the lesion is carefully avoided, until the pial surface covering the lesion is reached and incised using bipolar low-current coagulation. Particular care is taken to avoid damage to the vessels at the bottom of the sulcus. The surgical strategy is lesionectomy, limiting the removal to the CM and covering cortex, as clear evidence is lacking that better outcomes result from removing the hemosiderin-stained gliotic perilesional tissue.

Postoperative Follow-up

Postoperative follow-up included similar clinical, neuroradiologic, and electroencephalographic examinations used in the preoperative assessment. Antiepileptic drugs in patients with seizures were withdrawn after at least a 1-year seizure-free follow-up period. Three patients required reoperation because of recurrent seizures due to residual CM **(Fig. 15–1)**. The mean duration of follow-up was 48 months (range, 0.5 to 14 years).

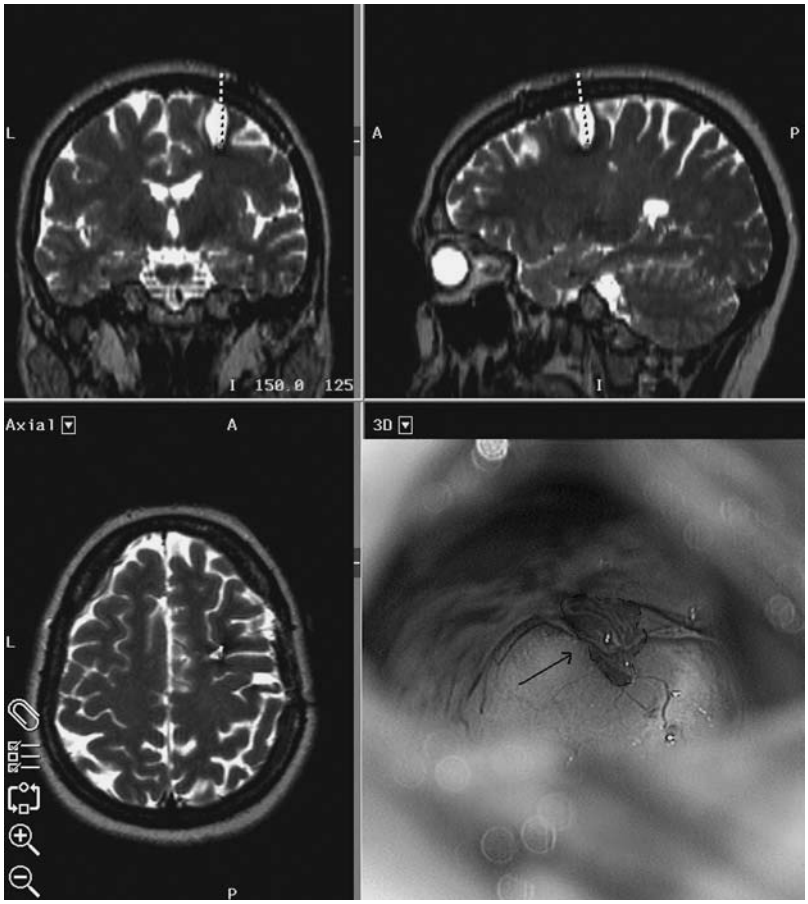

Figure 15–1 Surgical plan and intraoperative view of a case of residual cavernoma (*arrow* and *dotted line*) that required surgery for seizure persistency. After repeated surgery, the patient was seizure-free.

Clinical History, Preoperative Neurologic Examination, and Cavernous Malformation Location

None of the patients had any risk factor for epilepsy. Preoperative neurologic examination was within normal limits in 139 patients. The other 24 had focal neurologic signs. In one patient who had suffered seizures since the age of 13, mild hemiparesis had become apparent in the early months of life: this was believed to be secondary to the presence of a giant motor strip CM. Two patients suffered intracerebral bleeding after having presented with seizures.

Mesiotemporal, temporolateral, or insular cavernomas were more commonly observed in patients with chronic epilepsy (mesiotemporal, 19.2%; neocortical temporal, 34.3%) than in those with occasional seizures (mesiotemporal, 7.8%; neocortical temporal, 17.2%); the most frequent location in this latter group being the frontal region (57.6%, versus 19% of the patients with chronic epilepsy). The CM was subcortical in 52.1%, cortical in 19.6%, and corticosubcortical in 12.3% of cases. There were no significant differences in cortical or subcortical location in patients with chronic epilepsy when compared with those with occasional seizures.

The size of the lesions ranged from 0.5 to 4 cm, although in one patient, the CM was unusually large (6 cm) and mimicked a hemorrhagic tumor. The MRI findings reproduced the typical picture of CMs previously reported.[9,19] The core of the malformation was commonly found to have a high signal in both T1- and T2-weighted images, thus indicating the presence of extracellular methemoglobin. In some patients, mixed areas of decreased and increased intensity were observed, the result either of different stages of hemorrhage or of interspersed areas of calcification. In all of the patients, T2-weighted images revealed peripheral marginal or ring-like hypointensity caused by hemosiderin drift. Eleven patients had evident radiologic signs of previous bleeding with intraparenchymal hematoma, for which three of them had undergone surgery in the years preceding the excision of the CM. An associated developmental venous anomaly was commonly observed. Mass effects and surrounding edema were found in 14 patients. Twenty-two patients had multiple CMs (13.5%). In the 99 patients with chronic epilepsy, seizures were completely controlled by antiepileptic drugs in only 36 patients.

Thirty-seven of the 163 patients had exclusively generalized tonic-clonic seizures. Twenty-two patients had usually generalized tonic-clonic seizures with focal onset. Simple partial seizures were reported in 64 patients and partial complex seizures in 35 patients, with simple onset in 11. In two patients with multiple CMs, two different types of seizures were reported. The results were normal or nonspecific in 40.9% of those who had waking EEGs; 61.1% of the patients also had sleep EEGs, which were normal in 45.4% and revealed focal abnormalities in 54.6%. Overall focal electroencephalographic abnormalities were found in 68.2% of the total patient population.

Epilepsy Outcome after Lesionectomy

Among the 99 patients with chronic epilepsy, 68 (68.7%) are completely seizure-free (20 of 68 [29.4%] still under AEDs [antiepileptic drugs]), 10 (10.1%) have only sporadic seizures, and 17 (17.1%) still have seizures despite surgery and therapy. Four patients were lost to follow-up. In patients with preoperative drug-resistant epilepsy, only 60% were seizure free at follow-up. As previously mentioned, three patients required reoperation because of seizures due to residual CM (**Fig. 15–1**). Sixty-three of the 64 (98.4%) patients without chronic epilepsy (single or sporadic seizures) were completely seizure free (28% still waiting for definitive withdrawal of AEDs, which usually occurs 2 years after surgery). One patient was lost to follow-up. A longer clinical history of chronic epilepsy was found to be related to a poorer prognosis. No clear correlation between CM location and outcome could be found even though there was a trend for mesiotemporal CMs to have poorer prognosis in terms of seizure control.

Mortality and Morbidity

Postoperative focal neurologic signs (sensorimotor defects and homonymous hemi- or quadrantopia) appeared in 12% of patients. Most of these signs were transient and had completely disappeared or were greatly reduced at subsequent clinical examinations. Only in three (1.8%) patients was a partial residual deficit found at long-term follow-up. These consist of slight hand paresis in a patient with a CM under the motor hand area; right inferior limb paresis with a slight gait impairment in a patient with a CM of the mesial prerolandic cortex; and hemianopsia in a patient harboring a CM in the depth of the calcarine scissure who required emergency surgery for evacuation of a postoperative hematoma. There was no mortality. Postoperative MRI was available in 122 cases and showed a complete CM resection in all patients (in three after repeated surgery). Hospital stay and duration of surgery progressively shortened as image-guided minimally invasive techniques became available. Mean surgery duration in the last 50 cases was around 2 hours and the mean hospital stay 4 days.

♦ Epileptogenesis in Patients with Cavernous Malformations

The underlying mechanisms causing seizures in patients with CMs are complex and still not completely understood. Given the lack of intralesional brain tissue, CMs per se are clearly not epileptogenic.[25] Furthermore, the mass effect does not explain the high epileptogenicity of this vascular malformation. Other lesions of larger size such as diffuse growing malignant tumors are less commonly associated with medically refractory epilepsy,[26,27] and epileptogenic mechanisms seem to be different.[28] Awad and Robinson compared the seizure incidence in patients harboring a CM with that of patients with arteriovenous malformations (AVMs) or gliomas and found an incidence of 50 to 70% in cavernomas, 20 to 40% in AVMs, and 10 to 30% in gliomas.[29] In our series, 99 of 163 (60.7%) patients operated on for a CM were affected by chronic epilepsy. Seventy-seven of 99 (77.7%) were drug resistant. Del Curling et al. estimated the risk of developing seizures at 1.51% per person/year and 2.48% per lesion/year for those with multiple lesions.[30] According to Cohen et al., 41 to 59% of symptomatic CMs will present with seizures,[31] and around 4% of refractory partial epilepsies are thought to be symptomatic of CMs.[32]

Williamson et al. recently reported the results of intracellular recording from neurons adjacent to intracerebral neoplasms and CMs.[28] Neurons adjacent to CMs were found to have a greater propensity to show large, complex, spontaneous synaptic events than neurons adjacent to tumors. Both spontaneous excitatory and inhibitory events were recorded. Neurons neighboring CMs displayed more excitable responses to synaptic stimulation, with multiple action potentials riding on prolonged excitatory postsynaptic potentials being evoked (71% vs. 32% of neurons from the tumor group). In studies using hippocampal tissue, these authors noted a similar pattern of spontaneous activity in tissue adjacent to CAs, suggesting that a common synaptic mechanism should be hypothesized for both neocortical and hippocampal CMs. The prevalence of epileptiform responses appeared to correlate only with the proximity of the lesion.

The underlying cause for CM epileptogenicity is thought to be the presence of chronic, clinically silent microhemorrhages[25,33] secondary to fragility of the capillary sinusoidal wall and lack of tight junctions. This results in deposition of iron-containing blood breakdown products such as hemosiderin, a probable degradation product of ferritin, as well as hemin, a globin breakdown product, in the adjacent brain tissue. Iron salts are proven potent epileptogenic agents when applied on the rat cortex.[32,34,35] Iron may generate epilepsy by different mechanisms. As an electron donor, iron is implicated in the production of free radicals and lipid peroxides, which interact with receptor activity, calcium channels, cellular transport proteins, intracellular second messengers, and neurotransmitter (glutamate and aspartate)-mediated excitotoxicity.[33,36,37] Von Essen et al. found a marked increase in the levels of serine (fivefold), glycine (10-fold) and ethanolamine (20-fold) in the peripheral zone of cerebral CMs.[38] In addition, iron deposition seems to inhibit glutamate uptake. Such biochemical abnormalities in the marginal zone of CMs may cause excessive activation of excitatory transmission. Studies using a ferrous chloride model of epilepsy demonstrated that gliosis and neuronal loss can occur[39] presumably because of the generation of free radicals and subsequent lipid peroxidation.[40,41] Iron-triggered cellular alterations are more likely and more significant the longer the duration of epilepsy. As a consequence, the tissue adjacent to CMs becomes increasingly epileptogenic.[42] This can explain why the longer the history of epilepsy, the poorer are the results of pure lesionectomy.

Iron-laden epileptogenic tissue may cause independent secondary epileptogenic foci in experimental animals by kindling. However, it is controversial whether or not such secondary foci are found in humans. One indicator of secondary epileptogenesis in humans is the finding of dual pathology, that is, hippocampal neuronal cell loss in some patients harboring extrahippocampal lesions such as brain tumors, cortical dysgenesis, or vascular malformation.[27,43–45] In patients with CMs, dual pathology has rarely been found.[28,43,46] In these patients, lesionectomy did not result in seizure control, and subsequent resection of the mesial temporal lobe structures became necessary to achieve satisfactory seizure outcome.[43,46,47] In summary, as far as epileptogenesis of CMs is concerned, it can be speculated that the hemosiderin deposition near CMs results in impaired glutamate uptake as well as injury-induced synaptic reorganization, which may subsequently allow neuronal hypersynchronization in focal regions. This can then propagate activity to more distant regions.

♦ Indications for Surgical Treatment

Surgical indication should arise from the comparison between the risks of surgery and the risks related to the natural history of these lesions. As far as CMs are concerned, there has been in the recent past a growing tendency to recommend resection of supratentorial CMs for the following reasons:

- *Risk of bleeding:* Supratentorial CMs, although rarely, may cause large intracerebral hematomas and irreversible neurologic deficits.[48] The estimated risk of bleeding for supratentorial CMs is ~0.7% per patient per year.[49]
- *Risk of CM growth:* CMs have been recently recognized to be dynamic lesions that may arise after birth and grow.[50]
- *Risk of developing seizures:* This risk has been estimated to be as high as 1.5% per person per year.[30]
- *Low surgical risk and effectiveness of CM removal in preventing bleedings and seizures:* Minimally invasive, image-guided supratentorial CM resection has been shown to be safe and effective even in eloquent areas (in our series: 1.8% permanent morbidity, no mortality, 98.4% of cases seizure-free when patients undergoing surgery after one or sporadic seizures are considered, 98% incidence of complete removal after surgery).

It is our policy to recommend surgery for all symptomatic supratentorial CMs.

♦ Lesionectomy or Epilepsy Surgery?

Many retrospective studies reported a good outcome after CM resection in patients with seizures (**Table 15–1**). Seizure outcome of lesionectomy alone is excellent with improvement of seizure control in 92% of cases, amounting to abolishment of seizures in 84%.[51] No data are available to clearly demonstrate a different outcome if lesionectomy includes the perilesional hemosiderin-stained tissue. In our opinion, there is no significant difference in seizure outcome whether lesionectomy alone or a "seizure operation" is performed. Literature data suggest that seizure history and length of clinical history are the main prognostic factor. This confirms what Olivecrona and Riives stated as early as 1948: ". . . the prognosis of epilepsy is best in the case of the younger person with a short history of epilepsy, while in cases of inveterate disease with a long history of epilepsy the outcome is poor." In our series, all patients who underwent lesionectomy after the first seizure or who presented only with sporadic seizures remained seizure-free at long-term follow-up, whereas 40% of patients with a clinical history of chronic epilepsy (often drug-resistant) still had seizures after lesionectomy. Early lesionectomy seems therefore to be the best way to avoid the development of chronic epilepsy. The fact that the duration of epilepsy at time of surgery

Table 15–1 Seizure Outcome after Lesionectomy in Recent Patients' Series with More Than 10 Reported Cases

Author (Year)	Number of Cases	Outcome
Lonjon et al. (1993)[3]	16	14/16 seizure-free 2/16 improved
Giulioni et al. (1995)[16]	11	Improved seizure control in 100% Seizure-free without therapy: 18%
Zevgaridis et al. (1996)[23]	168	88.3% seizure-free 6.5% marked reduction in seizure frequency
Braun et al. (1996)[17]	14	10/14 complete relief 2/14 improved
Cappabianca et al. (1997)[18]	35	Less than five preoperative seizures:100% seizure-free More than five preoperative seizures: 62.5% seizure-free
Moran et al. (1999)[51]	33	Improvement in seizures in 92%
Mahla et al. (1999)[4]	31	Alleviation of epilepsy: 21/31 Seizure-free without medication: 4/31
Current series (2004)	163	Preoperative chronic epilepsy: 68/99 (68.7%) seizure-free Preoperative only sporadic seizures: 63/64 (98.4%) seizure-free

has a negative influence on seizure outcome underscores the importance of early CM resection. It is our policy to recommend surgery after the first seizure. What to do when a chronic, often drug-resistant epilepsy develops still remains under debate. Lesionectomy obviously holds the greater theoretical benefit of removing the smallest amount of nonpathologic cerebral parenchyma by means of a straightforward, low-risk, minimally invasive surgery, requiring a few days of hospitalization. Such a minimal resection, however, may not provide the desired complete relief from seizures. Conversely, localization and removal of the epileptogenic zone may provide a higher rate of cure than lesionectomy alone. The price of real epilepsy surgery may include invasive electroclinical investigations such as stereoelectroencephalography, corticography, and strips recording of brain parenchyma outside the lesion. The surgical resection may be tailored according to electroclinical data and may result in a considerably wider resection than pure lesionectomy. In our series, lesionectomy alone allowed for the control of seizures in 60% of epileptic patients, avoiding potential complication of invasive studies, subsequent resection of brain parenchyma, along with added time and equipment costs. These considerations led in our institute to the institution of a two-step surgery for CM-related chronic epilepsy. Patients and families are fully informed, and during the first operation only the lesion is removed. Twelve to 24 months later, if drug-resistant seizures are still present (despite MRI demonstration of radical resection), second surgery is performed with the goal of removing some of the surrounding hemosiderin-stained brain often with the guidance of invasive electrophysiologic data.

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16

Cavernous Malformations in Children and Adolescents

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One-fourth of central nervous system cavernous malformations (CMs) occur in the pediatric age group. CMs represent one of the main causes of intracerebral hemorrhage in children, together with ruptured arteriovenous malformations.[1,2] Although magnetic resonance imaging (MRI) has improved the diagnosis and understanding of the evolution of CMs in children and adults, the natural history of cerebral CMs is still poorly understood in children. In the pediatric age group, the rate of hemorrhage is higher than in adults, and this fact often justifies a more aggressive surgical approach. This chapter is based on an analysis of the literature and on the experience of the authors.[3]

♦ Epidemiology

Incidence

The prevalence of CMs is estimated to be between 0.37% and 0.53% in children.[4–9] Mazza et al. reported an incidence varying between 1.7% and 18% of all vascular malformations.[10] Herter et al. reported a prevalence of 42% of all vascular malformations in the general population, with 25% of CMs found in children.[11] Simard et al. reported a pediatric incidence of 23% of all the vascular malformations.[12] In the most recent literature, the incidence of pediatric CMs has been reported at about one-fourth of the total number.[13,14]

Two peaks of incidence are reported: one in early childhood, the other in adolescence.[15–18] Our experience[3] confirms this age-related distribution, with a peak below 3 years and a second peak after 11 years (age range, 9 months to 17 years). The explanation for this finding remains unclear. The occurrence of cerebral CMs in the prenatal and neonatal period is very low.[4,19–22] Gangemi et al. reported on 11 cases from the literature and described 2 additional cases below the age of 1 year.[20] We have not observed any case of fetal or neonatal cerebral CMs in our area, but Guibaud et al. reported on three cases of capillary telangiectasia of the cerebellum in fetuses.[23]

Familial Cerebral Cavernomas

Familial forms of cerebral CMs account for ~20% of pediatric cases.[24–26] The pattern of inheritance, in studies dealing with familial forms, is consistent with an autosomal dominant pattern with incomplete clinical penetrance and is sometimes associated with de novo mutations.[24] A mutation has been reported on the 7q chromosome in Hispanic Americans but the genetic heterogeneity of inherited cerebral CMs has been demonstrated.[27–30] Familial CMs are characterized by a higher incidence of multiple lesions and are more frequent in children.[31,32] Systematic screening for multiple CMs has been advocated and is facilitated by MRI. This screening is mandatory because hemorrhagic risk is higher in cases of familial and multiple lesions. In our experience, a familial pattern was found in 15.5% of cases, but we could not demonstrate a higher rate of hemorrhage compared with the sporadic form. A systematic MRI follow-up may also be useful to assess lesion growth from clinically silent hemorrhagic modifications, which may aid in surgical decision-making.

Associated Diseases

Pediatric CMs are generally not associated with other pathologic conditions. There is no need to screen for other visceral locations. In our experience, only one case presented with neurofibromatosis type 1. Another patient presented with a concomitant tectal plate glioma discovered after the surgical removal of a CM responsible for a hemorrhage in the ventricular atrium. In one additional patient, a thalamic CM responsible for a hemorrhage was associated with a giant hemispheric arachnoidal cyst.

Cranial irradiation seems to represent a potential risk factor for the development of cerebral CMs. Two cases of cerebral CMs have been observed months after irradiation, performed for a cerebral tumor in one case and a leukemia in another case.[33] The development of cerebral CMs after radiotherapy remains controversial, but a growing number of reports sustain this theory. The follow-up of these postirradiation lesions showed growth and hemorrhagic potential as reported by Edwards[34] and confirmed by our own experience.

Neuropathology

The neuropathologic characteristics of pediatric CMs are not different from those in adult patients. CMs are made

up of vascular spaces of varying size, lined with a single layer of endothelial cells.[35] The blood-filled vascular spaces are separated by collagenous walls of varying thickness that are typically devoid of smooth muscle and elastin, and the histologic features of arteries, veins, or capillaries are usually missing.[36–40] The vascular space (caverns) does not demonstrate intervening brain tissue. In children, macroscopic cystic spaces are observed more frequently, presumably due to the higher hemorrhagic rate. The brain around the CM exhibits features of astrocytic gliosis with different thickness and various patterns: a necrotic or an atrophic area with hemosiderin, associated with a zone of cerebral atrophy, calcium, and iron deposits. These perilesional changes could be the substratum for epileptic foci and may be more pronounced when patients are operated on weeks and months after the initial hemorrhage. Collagen fibers arising from the core of CMs with densely proliferating granulation tissue and partially re-endothelialized hemorrhage suggest a possible mechanism for CM growth. In children, and especially before the age of 3 years, microsatellite malformations such as small CMs, capillary telangiectasia, and pseudoangiomatous dysmorphic vessels are found in the surrounding cerebral parenchyma more frequently than in adults.[9,39,41–44] This phenomenon led Barrow and Awad to consider an association between various types of vascular malformations and CMs.[43–46] The higher risk of hemorrhage could be due to these associated anomalies.[43] The association with venous anomalies, frequently reported in adult patients, is less common in children, being reported in only 7.3% of children explored by MRI.[4,47–49] We observed this association in only 2 of 47 surgically treated children. The typical cavernous structure can be almost completely obscured by hemorrhage. A capsule is sometimes described with a structure similar to that of a chronic subdural hematoma in giant cystic lesion.[50–52] The presence of a capsule can facilitate surgery and can explain the frequent imaging finding of an "encapsulated hematoma."

Location

The location of CMs in children is not very different from that in adult patients. A supratentorial location is more frequent than a posterior fossa location, which accounts for only 20% of cases.[53,54] Brain-stem lesions seem more frequent in children than in adults, and the pontine region is the most commonly involved.[34,54] CMs are rarely located in the hypothalamic region, the basal ganglia, or the ventricular system. In our experience, the supratentorial location was found in 72% of cases and the frontal region was the most frequently involved, followed by the temporal, the parietal, and the occipital lobes. Spinal CMs are rare in children, and we have observed only one such case. Spinal CMs represent 5 to 12% of intraspinal vascular tumors and 3 to 16% of all vascular malformations.[55–59]

Lesion Number, Size, and Growth

Follow-up MRI studies have established that CMs can vary in number and size over time, and so they have to be considered as dynamic lesions. In our series, the number of CMs varied at diagnosis from 1 to 12, and small, new lesions were observed during follow-up in three children. MRI is superior to computed tomography (CT) scans for the screening of small lesions. The size of the main lesion is often larger in children, with an average diameter of 6.7 cm, whereas in adults, the average diameter is between 2 mm and 3 cm. In our series, diameters varied from 2 to 3 mm to 11 cm, with an average of 4.5 cm. No clear correlation can be demonstrated between size, risk of bleeding, and late neurologic deficits. According to Awad et al.,[60] lesion growth is related to repeated microhemorrhages. The extravasation of red cells outside the vessels of the CMs could stimulate an angiogenic factor that is responsible for the formation of coalescent vessels.[44,61–63] Larger hemorrhages usually cause acute neurologic symptoms and are frequently responsible for discovery of the lesion in the pediatric age group.

♦ Clinical Presentation

The clinical picture of pediatric CMs is variable.[18,46,64] They can be asymptomatic or can manifest with acute or progressive clinical symptoms related to hemorrhage, mass effect, or epileptic manifestations. Based on the current literature, it is somewhat difficult to determine the exact proportion of these clinical manifestations in children because hemorrhagic lesions are reported either as responsible for raised intracranial pressure, isolated neurologic focal deficits, and/or seizures. According to Simard et al.,[12] the three modes of presentation were equally represented. Seizures, occurring in 25 to 50% of patients, are reported as the primary complaint warranting clinical evaluation.[65,66] Vaquero reported epilepsy in 70% of cases, a mass effect presentation in 20% of cases, and a hemorrhagic event in 10% of cases.[67] In our experience, seizures frequently are an expression of acute hemorrhage from supratentorial cortical and/or large white matter lesions. The rate of hemorrhage in children is estimated to be between 36% and 78% of symptomatic cases,[10,34,63,68,69] whereas in adults, it is between 8% and 37% of cases. We reported a hemorrhagic event in 80% of pediatric cases, and we observed a shorter delay between clinical onset and diagnosis compared with other authors, who reported diagnostic delays up to 20.5 months.[34] The higher incidence of hemorrhage in children is responsible for the high rate of acute clinical onset. The typical clinical picture of hemorrhagic CMs located within the brain stem or basal ganglia is associated with coma and focal neurologic deficits.

♦ Imaging Findings

Calcified cerebral CMs can be an incidental finding on skull X-ray views performed for other reasons, such as trauma. Angiography is not useful and should be performed only if there are doubts as to the presence of a true arteriovenous malformation after MRI.[70] CMs are no longer "occult" or "cryptic" in the MRI era.[2,71–73]

CT scans performed in children presenting with acute symptoms usually show a typical hemorrhagic, hyperdense, well-limited lesion with a spherical shape and no or limited surrounding edema. The CM itself is often seen as a smaller area with a different density within the hematoma.

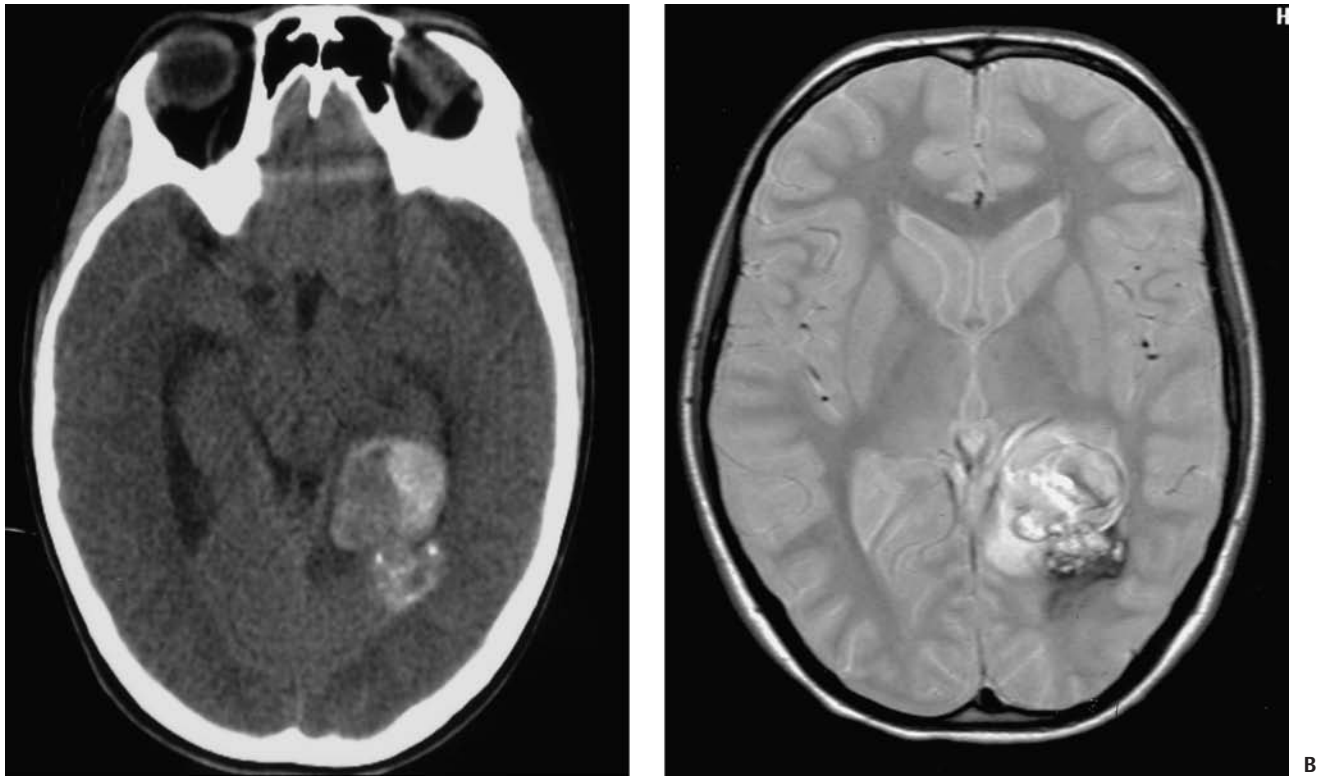


Figure 16–1 A spherical-shaped, well-limited intracerebral hematoma should make one consider the diagnosis of CM, as in this patient with left ventricular CM in the region of the internal wall of the atrium who presented with bleeding. **(A)** CT scan and **(B)** MRI.

CT scans are easy to obtain in emergent situations and are rarely negative in the acute clinical setting. Multiple small lesions, however, are commonly overlooked with CT, unless they are calcified.[74–77] MRI is the preferred imaging modality for the diagnosis and follow-up of pediatric CMs. MRI, in addition to the lack of ionizing radiation, is far more sensitive and specific than CT **(Figs. 16–1 and 16–2)**.[75,78–80] Gradient echo T2*-weighted sequences are sensitive to magnetic susceptibility artifacts produced by hemoglobin-derived blood products located within and/or around the lesion. Deoxyhemoglobin accounts for the dark signal of acute hematomas on T2*-weighted images, whereas hemosiderin deposits persist after occult or overt hemorrhage. This accounts for the high sensitivity of MRI for the detection of small lesions.[3,30,74,81,82]

An intracerebral hemorrhagic lesion with a spherical shape and no intraventricular rupture, occurring in an otherwise healthy child or adolescent, should always make one consider the diagnosis of a hemorrhagic cerebral CM **(Fig. 16–1)**.[71, 81,83] A hemorrhagic true cerebral arteriovenous malformation (AVM) is the main differential diagnosis at neuroimaging. In this setting, hematoma is more likely to present with an irregular and elongated shape and hemorrhagic extension to the ventricles. We emphasized the usefulness of these morphologic characteristics in a comprehensive imaging classification system.[3,84,85]

The classic radiologic classification proposed by Zabramski et al. does not demonstrate a strict correlation between CMs and their potential hemorrhagic risk.[86] A simple classification that takes into account both imaging and especially surgical features is herein described:

- Type I CMs of small size (<1 cm), multiple, and located in superficial or deep areas, with no clear surgical indication.
- Type II large hemorrhagic CMs of spherical shape, located superficially (type II A) in functional (A1) or nonfunctional

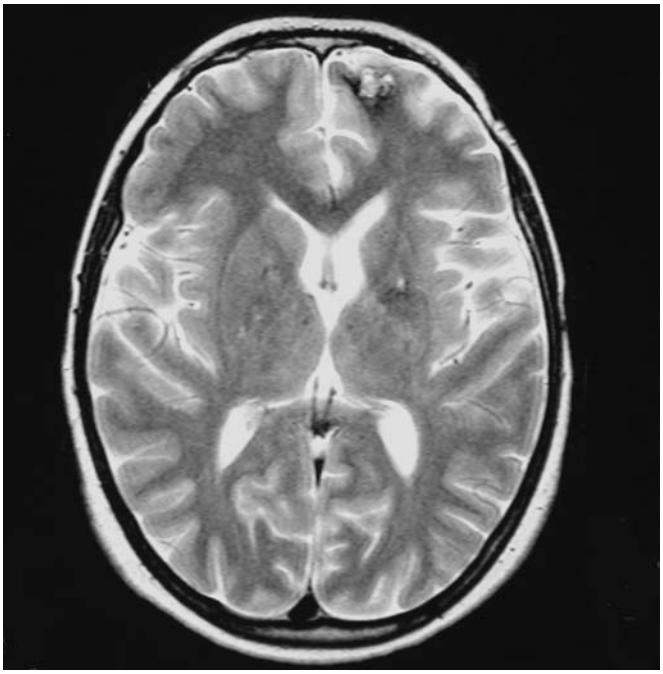


Figure 16–2 MRI is more precise than CT scan to display lesions of small volume as in this postirradiation CM of the left frontal region following irradiation of a chiasma-hypothalamic tumor.

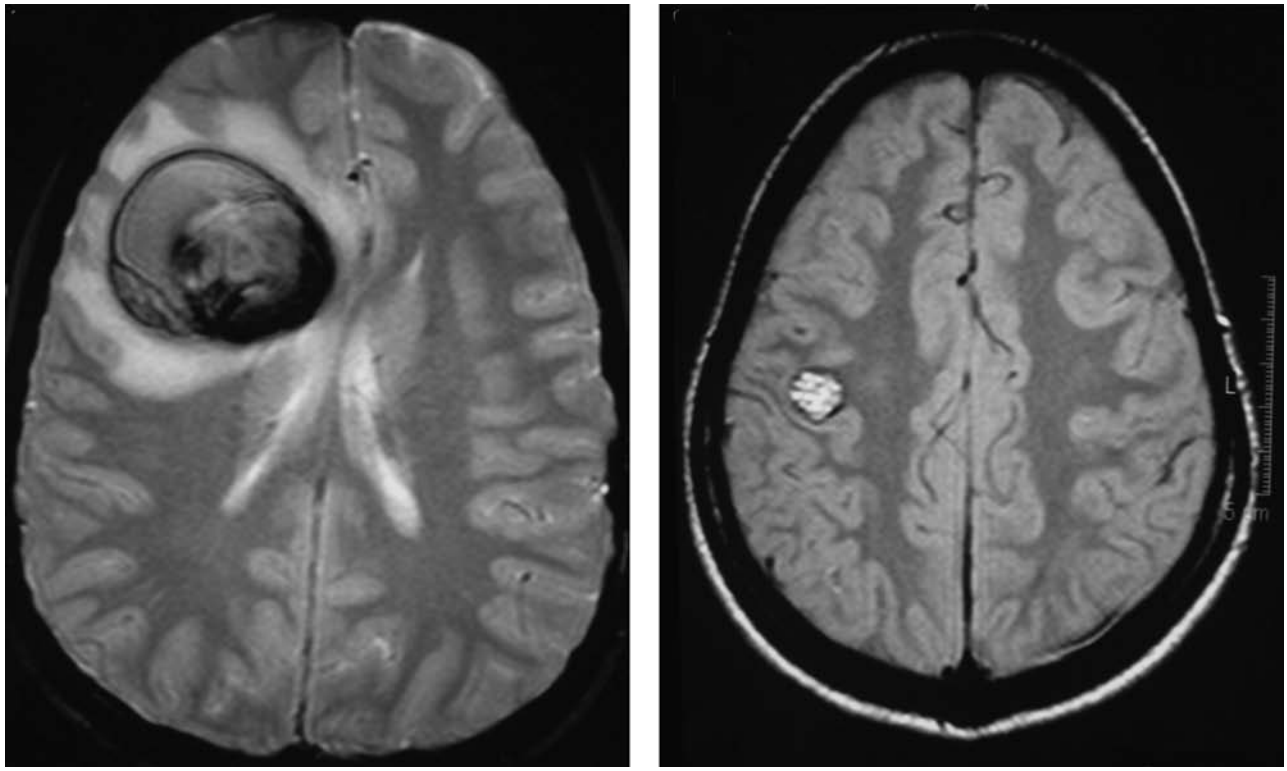


Figure 16–3 Generally in children, CMs are more frequently responsible for hemorrhage. **(A)** Encapsulated CM in right frontal lobe with signs of old hemorrhages (type II A1); **(B)** a lesion in the prerolandic area (type III).

areas (A2) or deeply (type IIB) in functional (B1) or nonfunctional (B2) areas, requiring surgical excision **(Fig. 16–3A)**.

- Type III CMs without signs of overt hemorrhage, responsible for epilepsy, or asymptomatic, with demonstrated growth on imaging and/or clinical deterioration at follow-up. Surgical excision can be considered according to lesion location **(Fig. 16–3B)**.

♦ Differential Diagnosis

In children, huge CMs can be misdiagnosed with CT scans as cerebral tumors such as oligodendrogliomas or ependymomas.[49,87] MRI usually allows the correct diagnosis. Cerebral cysticercosis associated with hydrocephalus and epilepsy can be confused with a radiologic picture of multiple CMs. Positive serologic studies and/or parasitic soft tissue calcifications may contribute to the diagnosis of cysticercosis. A focal hyperechoic cerebral mass at antenatal imaging, consistent with a CM complicated by hemorrhage, has been reported in a 23-week-old fetus.[88] Fetal capillary telangiectasia is a clinically relevant differential diagnosis because this entity seems to have limited bleeding potential, and should lead to a conservative management of the pregnancy.[23]

♦ Treatment

The management strategy for CM in the pediatric population must be carefully considered, keeping in mind the risks of their natural evolution and the risks of their surgical removal.[9,16, 36, 63,86,89–93] As suggested in the literature, the management strategy must take into account age, sex, location, and the efficacy of medical treatment to control seizures in epileptic cases.

Surgical Treatment

In children, CMs are more frequently symptomatic, and, considering the long life expectancy and the elevated risk of hemorrhage, surgery should be considered regardless of location. The increased risk of further hemorrhage is a strong motive for removal of symptomatic posterior fossa lesions.[54,94] A difficult question is the time of surgery. After diagnosis of a hemorrhagic CM, some surgeons prefer to delay lesion removal because this delay might provide a way to obtain a better resection plane around the lesion. Other teams prefer an early surgery because the absence of gliosis could facilitate removal. We think that a delayed surgical procedure is usually safe because the brain is slack, but in many cases the presence of a hematoma is not well tolerated, and thus, early surgery is necessary to reduce intracranial hypertension. As for other neurosurgical entities, intracranial hypertension in children can have a rapid evolution with an increased risk of mortality. When located in the brain stem, the surgical removal of a CM is a challenge, especially when located far from the ependymal plane.[95,96] Some authors have emphasized the possible entry zone avoiding the anatomic localization of the nuclei of the cranial nerves and of the reticular system.[97,98] The inferior losange of the floor of the fourth ventricle is particularly rich in sensory and motor nuclei. When located in the bulbar and the pontine region, the surgical approach has to

safeguard these nuclei to avoid irreversible deficits of deglutition, phonation, and taste.

In children with repeated seizures despite medical treatment, surgery plays an important role to cure epilepsy definitively. The indication for surgical removal of CMs with epilepsy should be discussed for each case and requires a thorough evaluation with long-duration electroencephalogram (EEG) recording and video EEG. Invasive investigations may be mandatory to assess the true localization of the epileptic focus, which can sometimes be distant from the CM, especially in the case of mesial lobe epilepsy.[99] A point of surgical controversy is the removal of the hemosiderin capsule located around the lesion that can represent an irritating element.[100] The epileptogenicity of these lesions has been credited to the ongoing deposition of iron and blood breakdown product in the periphery of the lesion as reported by Maraire and Awald.[63] The management of CMs presenting with seizures is detailed elsewhere in this book. The difficulty in differentiating lesion from compressed or atrophic tissue[55] leads some surgeons to remove only the CM. Removing the surrounding brain tissue may also generate a deleterious vasogenic reaction, which can increase the risks of sequelae, especially if the lesion is located near a functional area. We think that it is sufficient to remove only the CM, sparing the resection of the parenchyma around the lesion. In case of multiple CMs, only bleeding or symptomatic lesions should be removed and only if the lesions show imaging evidence of fresh hemorrhage or lesion growth. If the localization spares functional areas, we recommend systematic removal.

Technically, the removal of CMs in children is not different from that in adults, but, in children, particular care must be exercised, especially in very young patients, to avoid significant blood loss. The complete removal of the lesion is the main goal of surgery, because, as reported by Scott et al.,[21,22] residual lesions are associated with a high incidence of hemorrhage and a high risk of neurologic deficits. We agree with other studies that indicate that if the removal is not total, the residual nodule should be the subject of a second-look surgery.[54] In children, basal approaches involving orbito-zygomatic osteotomies, as used in adult patients, should be avoided, especially in children younger than 5 years.

The use of neuronavigation (in children more than 3 years of age) allows the best trajectory, as well as easy localization for small and deeply located lesions **(Fig. 16–4)**. Because of the use of neuronavigation, we are able to make a small linear skin incision and a small spherical-shaped bone flap located at the level of the projection of the lesion on the skull. When the lesion is located in a functional area, we try to achieve a trajectory that will avoid severe deficits. Thus, surgery through the cerebral sulcus is possible to reach the lesion, sparing the removal of the cerebral parenchyma. Finally, the use of neuronavigation has rendered obsolete stereotactic procedures for localizing the lesion. If a cortectomy is necessary because the lesion is deeply located, the entry point can be established to avoid functional areas. Cortical stimulation can help the surgeon when the lesions are located in or near the motor area **(Fig. 16–5)**.[101]

Surgery under local anesthesia is difficult in children, and so lesions located in the language area (frequently an indication to perform surgery under local anesthesia in adults) have to be removed using general anesthesia. In this

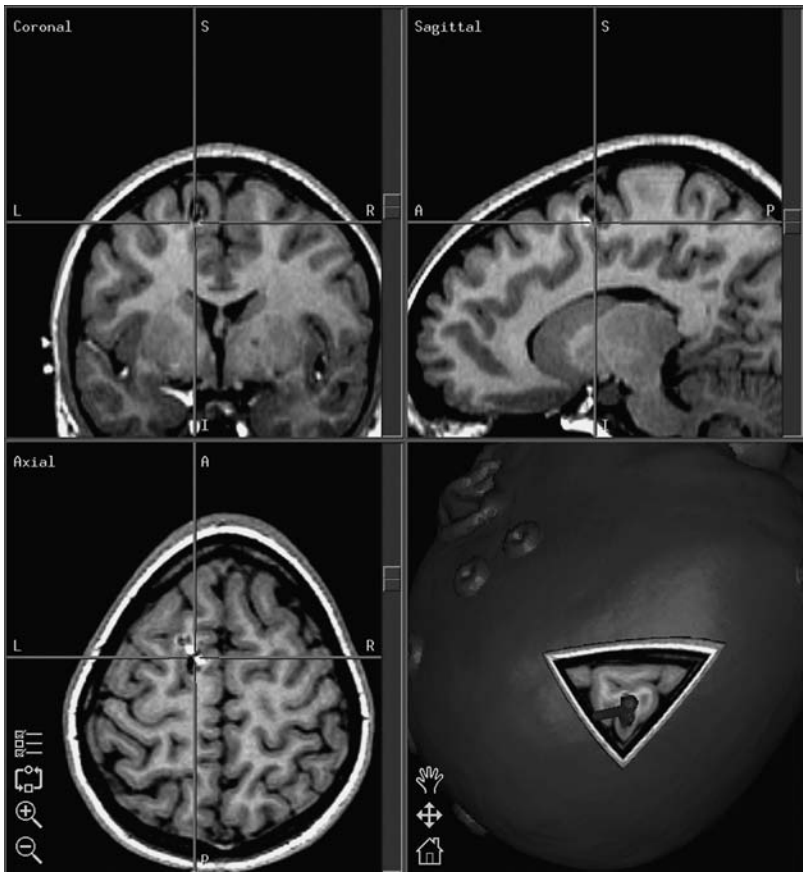


Figure 16–4 The neuronavigator is helpful in localizing lesions of small size and deeply located. Location of the lesion has to be established before opening the dura because errors appear after CSF outflow with consequent brain shift. The illustration shows an example of left prerolandic CM localized with frameless steretotaxy.

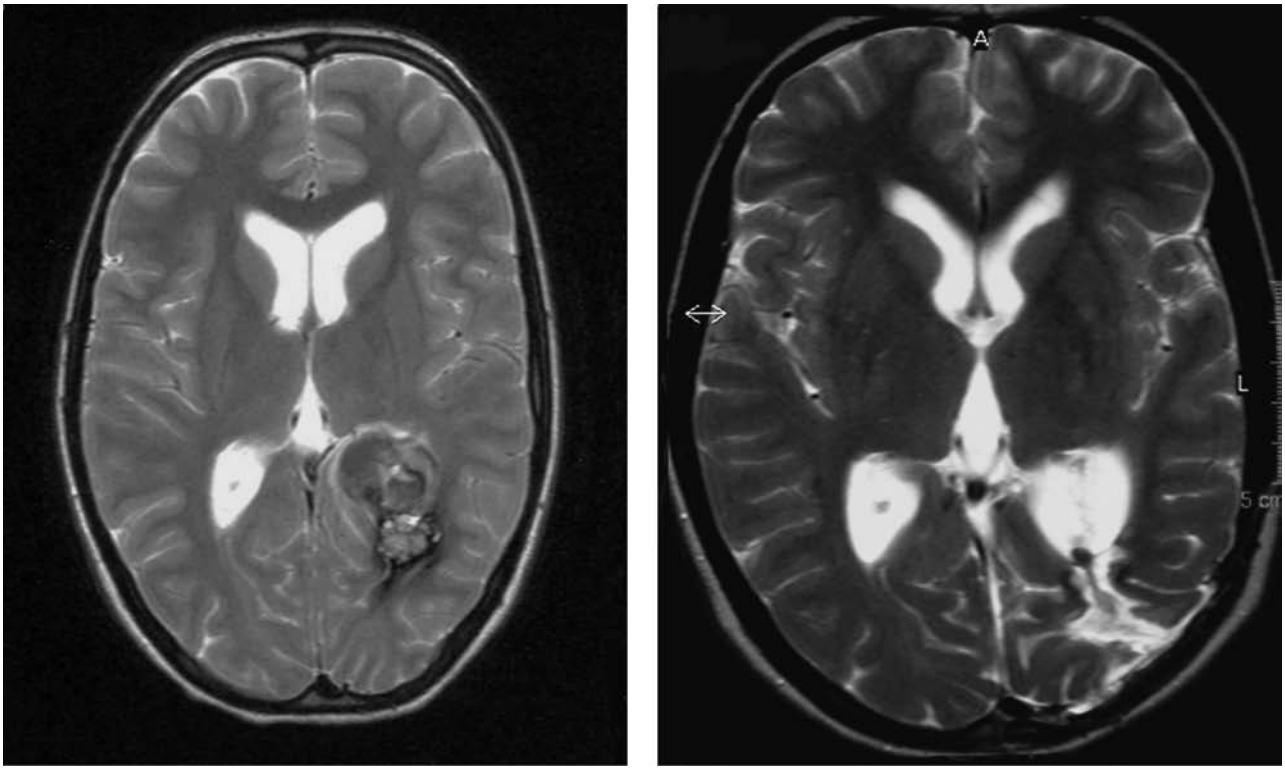
Figure 16–5 Cortical stimulation is useful to avoid complications when resecting CMs located in critical areas. Intraoperative view of a motor region stimulation for a prerolandic left CM. It is critical to avoid compromising the cortical veinous drainage system.

critical location, in older children, the fusion of morphologic and functional MRI data, coupled with neuronavigation, can be useful for the surgical removal; however, the interpretation of pediatric functional MRI can be problematic.[102] Sparing arteries and veins is particularly important in functional regions. The use of microscopic techniques has improved the results and decreased the incidence of complications after surgery in such critical areas. In our opinion, it is better to remain outside the lesion to ensure complete removal. If the surgeon invades the lesion, there is a small risk of an uncontrollable hemorrhage and it can be difficult to find an adequate plane to remove the CM completely. We usually do not remove the lesion using a piecemeal technique or by using the ultrasonic aspirator. The use of a cottonoid to push the lesion slightly allows visibility of the small afferent arteries and allows following of the yellow-reddish plane that is indicative of the true limits of the lesion. The microscope also allows visualization of satellite veins that must be spared to avoid cerebral infarcts. We do not think that a staged surgical procedure is useful for giant lesions, and we do not use the laser beam for the removal of such lesions.

Vaporization of the lesion with a laser could theoretically be useful, but the morphologic modifications induced by this method can prevent the recognition of the easier resection plane. For these reasons, we do not advocate the laser beam to practice a delicate opening of the brain-stem surface or the vaporization of the lesion when located adjacent to critical structures. In case of associated malformations, the aim of the surgeon should be complete removal to prevent late hemorrhagic recurrences.[92,103] Preoperative evoked auditory potentials are useful for the management of brain-stem lesions. The entry zone should be precisely planned for brain-stem CMs.[96,97] For lesions located in the pontine area or at the level of the floor of the fourth ventricle, we prefer an approach through the fourth ventricle. In two cases with a lateral location in the pons, we successfully used a subtemporal, transtentorial approach behind the fourth nerve.[104] In these cases, cutting the tentorium behind the passage of the fourth nerve facilitates the exposition of the lateral portion of the pontine region.[104,105] Access to a CM located in the floor of the fourth ventricle is easier when the lesion is near the ependymal surface, or when the hemorrhage permits direct access through the ventricle. The main problem at the level of the floor of the fourth ventricle is to preserve the anatomic and functional integrity of the nuclei of the sixth and seventh cranial nerves and the fibers of the medial longitudinal fascicle. When the CM is located in the tectal plate, the pineal region, or the thalamic area, we prefer the suboccipital transtentorial approach modified by Lapras.[106,107] This approach permits a large vision of the quadrigeminal and pineal region, of the thalamic area in the right and left side, and if necessary permits one to control also the superior part of the fourth ventricle. Surgery has to be done under the venous arch of the Galen vein and of the basilar veins.[106] Monitoring of the auditory evoked potentials and direct recordings inside the collicular body are helpful in avoiding severe neurologic deficits. The removal of large lesions inside the tectal plate, with preservation of at least one colliculus, avoids complete deafness. Dissection that avoids the plane of the aqueduct prevents lesions of the reticular substance, allowing lesion removal. We believe that precise hemostasis is of critical importance during surgery for pediatric CMs. Hemostatic agents should not be left in place because these agents may obscure interpretation of follow-up neuroimaging. Advancements in neuronavigation systems, as well as neuroanesthesia and neurointensive care therapy, have rendered almost no CM inoperable, even when considering very young patients **(Figs. 16–6 and 16–7)**.[10,108]

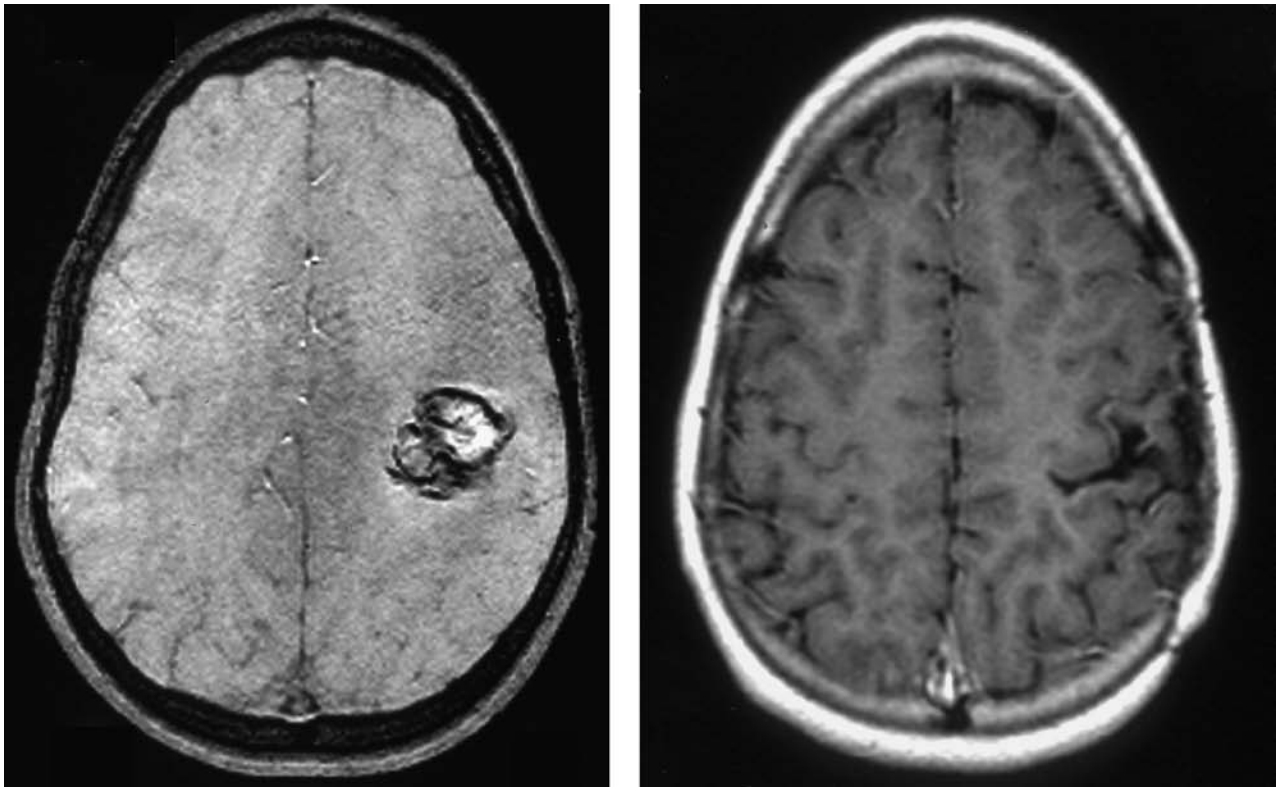
Radiosurgical Treatment

Radiosurgery has been proposed, with contradictory results,[109] but may be a possible therapeutic alternative in difficult cases.[44,110,111] The main indication for Gamma Knife surgery is when CMs are located in functional areas that are considered high-risk regions for surgery. Some problems for the generalization of previously published results are related to the methods of hemorrhagic rate assessment and interpretation of radiologic images after treatment. As with true AVM malformations, complete therapeutic efficacy (i.e., the prevention of bleeding) is expected after a latency period of about 2 years. Kondziolka et al. reported a rate of hemorrhage of 1.1%, 2 years after the treatment.[112] Kjelleberg et al.[109] reported a reduced incidence of hemorrhage with a fall in the rate of hemorrhage from 22.4% in the first 2 years to 4.5% after the treatment. This reduction of the rate of hemorrhage does not mean that the risk of hemorrhage can be eliminated. Weil reported a high rate of complications for CMs located in the brain stem and affirmed that no therapeutic benefit was seen after stereotactic radiosurgery (50%).[113] Kondziolka et al.[112] reported a 26% complication rate, with permanent deficits in 4%. The complication rate for radiosurgery seems higher for CMs than for AVM when a similar regimen is used. This elevated rate of complications occurred more frequently in association with lesions in the brain stem or deep lesions.[109,112] We



A B

Figure 16–6 Magnetic resonance images of a deep-seated CM **(A)** before and **(B)** after surgical removal. The lesion was reached through a cortical sulcus of the posterior parietal region.



A B

Figure 16–7 Magnetic resonance images of a CM located in the right prerolandic region **(A)** before and **(B)** after surgical excision.

do not advocate radiosurgery as the therapeutic modality of choice for pediatric CMs, even when lesions are located in critical areas or in the brain stem.

♦ Treatment Experience of the Authors

From 1985 to 2002, we treated 47 children from 9 months to 17 years of age, some of whom have been the subject of a previous publication.[3] The median age was 9.7 years. All patients except one were treated for a cerebrally located CM, and only one was operated on for a CM located in the dorsal spinal cord. Of this series, 18 patients were female and 29 patients were male, with 34 (72%) patients presenting with clinical signs related to hemorrhage and 12 (36%) patients presenting with seizures. A partial seizure was reported in 46.1% of cases and generalized epilepsy was reported in 53.9%. There were 45 patients who presented with signs of increased intracranial hypertension with headache, vomiting, nausea, and bradycardia associated with loss of consciousness. The localization was supratentorial for 38 (81%) patients and infratentorial in 9 (19%) patients. The supratentorial location was frontal in 56% of cases, temporal in 11%, and parietal in 4.5%, whereas in the other 25% of cases, the location was in the thalamoventricular region. In the infratentorial location, the brain stem was involved in most cases, with a preference for the pontine region. The hemispheric cerebellar location involved only three patients. The patient with a spinal cord lesion had a CM in the dorsal region at the level of T9. Eight (18%) patients presented with multiple CMs, and only the lesions responsible for the symptomatology were treated initially, whereas in six successive patients, another CM, not located in a critical area and presenting signs of radiologic evolution, was operated on. All patients were operated on using a microscopic technique, and, in the past several years, the neuronavigator and cortical stimulation were used for lesions located in or near a functional area or in a deeply seated region. For supratentorial locations, the approach to the lesion was generally through a linear skin incision centered on the lesion to reach the CM in the shortest distance from the convexity. For lesions of the pineal and tectal plate, or those located in the posterior fossa, the surgical procedure was performed in a sitting position. For lesions located in the ventricular system, we used a transcallosal approach, and for pineal and tectal plate locations, a suboccipital transtentorial approach. Two patients with lesions in a lateral pontine location were addressed through a right subtemporal transtentorial approach. Three patients required a shunt for a posthemorrhagic hydrocephalus, in one case before the direct treatment of the CM. The removal was judged total in 45 patients (96% of cases) after the study of the postoperative MRI obtained at 6 months from the surgical procedure. The clinical results were judged good in 43 patients (81% of cases): 13 patients had no neurologic deficits and excellent school performances; 30 patients were judged to have a good result with mild deficits, but functional; 3 patients had a poor result with motor deficits and limited neuropsychological capacity and severe functional limitations. With regard to epilepsy, two patients presented with late seizures that required medical treatment. Of all patients who presented with seizures at the time of diagnosis, medical treatment was continued for at least 1 year and stopped progressively if the EEG showed no comitial activity. The only patient operated on for a spinal cavernoma did not recover after the surgical treatment and has a paraplegia that required surgical treatment for spasticity.

♦ Conclusion

CMs in children and adolescents carry a higher rate of hemorrhage, and most require early surgical treatment. Microneurosurgical removal, with the help of neuronavigation and cortical stimulation, provides good results for the large majority of pediatric cases and renders single lesions operable in almost all cases. In the setting of multiple CMs, we believe that after the treatment of the symptomatic lesion, the child should be followed clinically and by MRI, and, if evolution can be documented, the surgical treatment of another lesion should be considered. CMs are dynamic lesions in children and adolescents, but their natural history is not yet fully elucidated and will require further assessment to optimize the therapeutic strategy. Radiotherapy and radiosurgery are ineffective and, in our opinion, are contraindicated in this age group.

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17

Radiosurgery for Cavernous Malformations

Douglas Kondziolka, John C. Flickinger, and L. Dade Lunsford

Stereotactic radiosurgery is used for patients with deep-seated, high-risk cavernous malformations of the brain. If resection is judged to be high risk, we perform radiosurgery for patients with multiple, symptomatic, imaging-confirmed hemorrhages. This chapter examines the long-term results after radiosurgery.

Management of brain cavernous malformations (angiographically occult vascular malformations, cavernous angiomas, cavernomas) remains controversial. Since the mid-1980s, there has been improved understanding of their natural history,[1–9] as well as increased experience with surgical resection.[10–16] In the case of arteriovenous malformations (AVMs), the elimination of the angiographically identifiable anatomic shunt can be demonstrated on imaging and correlates highly with cure. Unfortunately, imaging cannot confirm cure of a cavernous malformation after radiosurgery, as they cannot be defined by angiography. Some patients have cavernous malformations that are not amenable to surgical resection with acceptable risk. When such malformations repeatedly bleed, they warrant management.

Stereotactic radiosurgery is a safe intervention that provides a reduction in hemorrhage risk after an initial latency interval for patients with these high-risk cavernous malformations.[17–26] These observations confirm the hypothesis that radiosurgical intervention reduces subsequent bleeding rates. The microvasculature of a cavernous malformation ultimately responds to radiosurgery in the same way AVMs respond.[27,28] Without an imaging correlate of risk elimination, clinical follow-up remains the standard by which radiosurgery must be judged.

♦ Clinical Experience of the Authors

Epidemiology

High-risk cavernous malformations were managed with stereotactic radiosurgery at the University of Pittsburgh between 1987 and 2003 in a total of 110 patients. There were 58 male and 52 female patients with a mean age of 39 years (range, 4 to 81 years). Almost all patients had multiple hemorrhages (range, 2 to 9), and some suffered a single hemorrhage but had a subsequent stepwise decline in neurologic function. A hemorrhage was defined as a symptomatic, ictal event that consisted of new neurologic symptoms or deficits and imaging confirmation of new blood on magnetic resonance imaging (MRI) or computed tomography (CT). Patients were selected for radiosurgery when the malformation caused functional deterioration due to hemorrhage. Four patients had seizures. In general, the lesions tended to be located in critical brain regions as demonstrated in **Table 17–1**. Prior to radiosurgery, 30% of patients had surgical interventions that included attempted malformation resection, clot evacuation, biopsy, or shunt placement. One patient had proton beam irradiation and Gamma Knife radiosurgery prior to treatment at our center.

Table 17–1 Locations of 110 Cavernous Malformations Selected for Radiosurgery

Location	Number
Pons/midbrain	60
Thalamus	18
Medulla	3
Temporal lobe	6
Parietal lobe	7
Basal ganglia	7
Frontal lobe	4
Cerebellum	3
Occipital lobe	1
Other	1

♦ Radiosurgical Treatment

Radiosurgical Technique

Prior to radiosurgery, all patients underwent MRI to ensure that the lesion was a typical cavernous malformation. Typically, MRI showed mixed signal change within an outer hemosiderin ring of low signal intensity **(Fig. 17–1)**.[28–30] If there was any question about the diagnosis, angiography was performed to exclude an AVM or associated venous malformation.

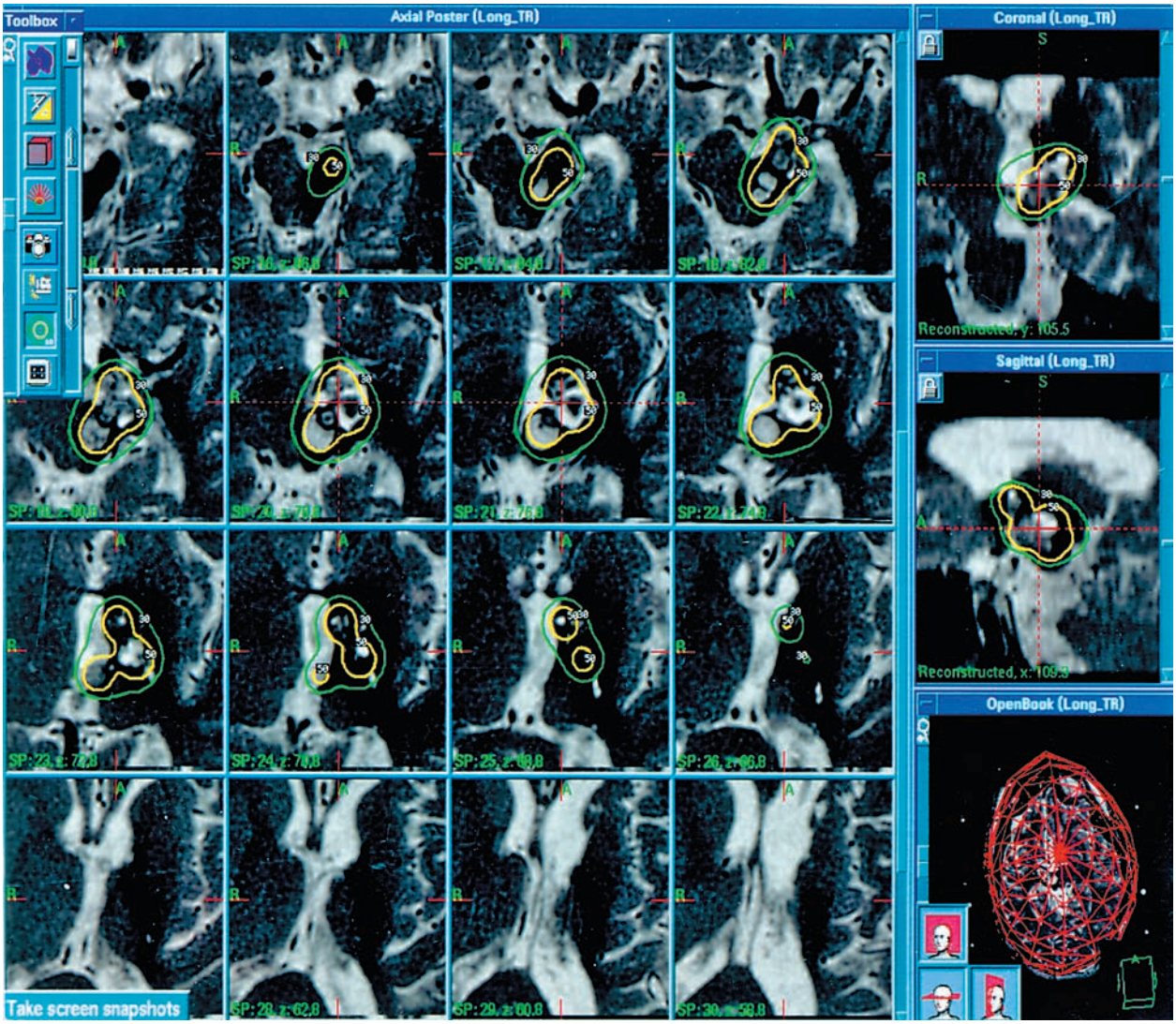

Figure 17–1 Axial magnetic resonance scan at the time of radiosurgery showing a left thalamic and superior midbrain cavernous malformation. This 22-year-old man had five prior symptomatic hemorrhages and three prior subtotal resections. Radiosurgery was planned with seven 8-mm isocenters. A margin dose of 14 Gy and a maximum dose of 28 Gy were administered. Six months later, the lesion was smaller as much of the blood had been resorbed.

Radiosurgery was performed with the use of the Leksell model G stereotactic frame (Elekta Instruments, Atlanta, GA, USA). The frame was applied after mild sedation and local anesthesia was administered. General anesthesia was reserved for patients under 12 years of age. After frame application, all patients had stereotactic imaging. CT was used for planning in all patients prior to 1990. Patients treated from 1988 through 1992 had both CT and MRI. Since 1992, stereotactic MRI alone has been utilized because MRI is superior to CT in defining cavernous malformations and is equally accurate. A sagittal short-repetition time (TR) scout image acquisition was obtained, followed by axial short- and long-TR images obtained at 3-mm image intervals. Finally, repeat axial and coronal short-TR images with volume acquisitions (1 to 1.5 mm slices) and contrast enhancement were obtained.

Images were transferred to the dose planning workstation of the Gamma Knife (GammaPlan; Elekta Instruments). A team composed of a neurosurgeon, radiation oncologist, and medical physicist selected the target and composed the dose plan. Single or multiple isocenter (range, 1 to 9) plans were constructed to give a conformal irradiation volume for the cavernous malformation margin **(Fig. 17–2)**. The mean number of isocenters was 3.2. The target nidus was defined as the region characterized by mixed signal change within an outer hemosiderin ring, typically of low signal intensity. Hematoma eccentric from the malformation was excluded from dose planning. In all patients in this series, the 50% isodose or greater was used for the target margin. The radiosurgical dose selection was set just below that advocated for angiographically identifiable vascular malformations and was, therefore, dependent on the location and volume of the cavernous malformation.[20,22] The volume was calculated as the sum of the voxels within the isodose used to envelop the malformation margin. The mean volume was 1.36 mL (range, 0.12 to 9.5), and the mean maximum and marginal doses were 30 Gy (maximum = 40) and 15.7 Gy (maximum = 20 Gy), respectively.

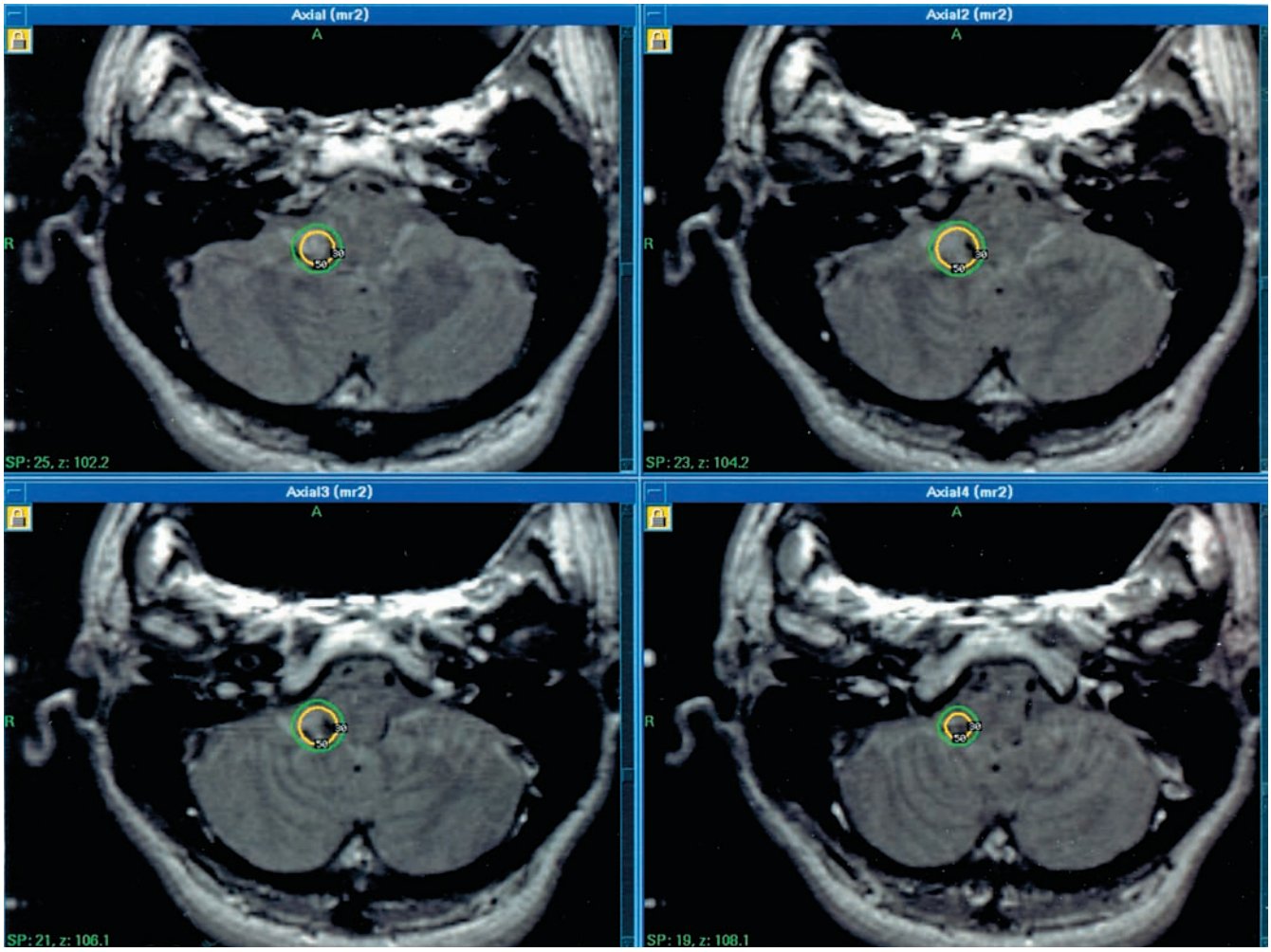

Figure 17–2 This 33-year-old patient presented with multiple hemorrhages (vertigo and vomiting) in association with a cavernous malformation of the right inferior cerebellar peduncle. Radiosurgery was performed with one 8-mm isocenter to deliver a margin dose of 14 Gy.

Radiosurgery was performed with a 201-source cobalt-60 Leksell Gamma Knife, models U, B, or C (Elekta Instruments). After radiosurgery, all patients received 40 mg methylprednisolone and were discharged from the hospital within 24 hours.

Follow-up

Clinical follow-up data was obtained from either the patients or their referring physicians if they lived at a distance from Pittsburgh. Where necessary, patients were contacted by telephone to update their outcome for the purposes of this study. Imaging follow-up was requested at 6-month intervals for the first 2 years after radiosurgery, and then annually. The following equation was used to determine hemorrhage rates:

$$\text{Rate} = \frac{\text{Total hemorrhages observed}}{\text{Total patient-years observed}}$$

Hemorrhage rates were compared before and after radiosurgical intervention using a paired *t*-test. A hemorrhage was defined as a new neurologic symptom or sign associated with new blood detected on MRI.

Hemorrhage Rates before Radiosurgery

Patient observation before radiosurgery began with the first symptomatic, image-documented hemorrhage and ended with radiosurgery. At our last comprehensive review, a total of 354 patient-years were observed by this definition, giving a mean observation time of 4.33 years per patient (range, 0.17 to 18 years). During this period, 202 hemorrhages (2.46 per patient) were observed. Multiple hemorrhages were documented in 76 patients (range, 2 to 7), whereas six patients had one hemorrhage. The first hemorrhage of the 202 hemorrhages was excluded, leaving 120 subsequent hemorrhages observed in 354 patient years. This gave an annual hemorrhage rate of 33.9%, a rate that remained fairly stable over five separate annual observations. After the first bleed, the annual hemorrhage rates in years 1 through 5 were 52%, 35%, 39%, 24%, and 32%, respectively.

Hemorrhage Rates after Radiosurgery

The mean follow-up after radiosurgery was 4.89 years per patient (range, 0.42 to 12.08 years), with 57 patients having at least 2 years of follow-up and a total of 401 patient-years of follow-up. During this period, 19 hemorrhages

(0.22 per patient) were identified in 15 patients. Of these hemorrhages, 17 occurred in 13 patients during the first 2 years after radiosurgery, representing 138 patient-years of observation, for an annual hemorrhage rate of 12.3% per year. After the expected latency period, two hemorrhages were identified during 262 patient-years of observation, giving an 0.76% per year hemorrhage rate from years 2 to 12.[20] One patient had neurologic deterioration accompanied by increased edema on T2-weighted MRI and increased high signal on T1-weighted MRI, suggestive of new blood, at 5 years. The other patient's bleed was asymptomatic, but follow-up imaging at 10 years showed an increase in size and high signal intensity in T1-weighted imaging. There was no significant difference between the maximum dose received, the margin dose received, the number of isocenters, or the number of hemorrhages prior to treatment between the group who hemorrhaged after radiosurgery and those who remained hemorrhage free.

The mean number of hemorrhages per patient was significantly reduced after radiosurgery (2.43 vs. 0.22, $P < 0.0001$) as well as after the 2-year latent interval (0.19 vs. 0.02, $P < 0.01$). We compared a group of 52 patients who had their first hemorrhage more than 2 years before radiosurgery (group 1) with 30 patients who had their first symptomatic bleed within 2 years of radiosurgery (group 2). During the 2 years after radiosurgery, the annual bleeding rates were 16.6% and 4.2% for groups 1 and 2, respectively. Two years after radiosurgery, the rates were 1.1% and 0%. This data indicated that the hemorrhage rate after radiosurgery was independent of the time from the first hemorrhage.[20]

Morbidity of Radiosurgery

Twelve patients (12.4%) had new neurologic symptoms without hemorrhage after radiosurgery. Such new symptoms are suspected to be adverse radiation effects (AREs). AREs have been uncommon since 1992, when we instituted lower margin doses and switched exclusively to MRI-based targeting. Seven of the new deficits were minor and six of these were temporary. Complications were seen with 8 of 51 lesions located in the pons or midbrain, 2 of 13 in the thalamus, and 1 of 7 in the medulla. All radiosurgical complications were seen within a year of radiosurgery. Patients with AREs received a small, but significantly higher marginal dose (17.45 vs. 16.05, $P < 0.03$), delivered by a lower number of isocenters (1.64 vs. 3.06, $P < 0.01$), and tended to have more previous hemorrhages (3.18 vs. 2.32, $P < 0.001$). There were more complications observed with malformations in the brain stem or diencephalon compared with other sites.

Patients were chosen for radiosurgical management because they had progressively symptomatic cavernous malformations, located in areas that are associated with unacceptable surgical risk of morbidity. In general, they did not present at a pial or ependymal surface. Morbidity after radiosurgery is higher when the malformation is located in an area of critical brain function. We suspect that AREs are related to the hemosiderin ring surrounding the malformation, corresponding with a region of normal brain stained with iron pigment, which is a potential radiation sensitizer.

♦ The Goal of Radiosurgery: Reduction in Hemorrhage Risk

We believe that radiosurgery on such high-risk, cavernous malformations must improve outcomes compared with the natural history of these lesions. Any treatment modality must rely on clinical follow-up to demonstrate its effectiveness and justify its use. Studies of the natural history of asymptomatic cavernous malformations have suggested that they have a relatively low yearly risk of hemorrhage.[1–9] A study at the University of Pittsburgh concluded that the overall annual risk of hemorrhage was 2.6%.[5] However, when these patients were stratified into those who had previously suffered a hemorrhage and those who had not, the former group appeared to be at higher risk. Patients with one previous hemorrhage had a yearly 4.5% risk of hemorrhage, whereas those without had a 0.6% yearly risk. Patients with two or more hemorrhages had a bleeding rate of ~30% per year.[23] It was for this reason that the patients with prior hemorrhage were chosen for radiosurgery. It follows, then, that their results may differ from the former groups at lower risk. Barker et al. hypothesized that symptomatic cavernous malformation hemorrhage may occur in a pattern of temporal clustering.[31] They noted a 2.4-fold decline in the hemorrhage rate after 2.5 years and suggested that this alone may be responsible for the reduced bleeding rate seen after radiosurgery. These data were derived from a series of 141 patients who had resection or proton beam irradiation of their malformation over an 18-year period. However, only 63 patients had a second hemorrhage. This series is different from ours in that most patients were not observed to see if they would rebleed without treatment.

We believe that the observed 33.9% yearly risk of hemorrhage prior to radiosurgery in our series warranted intervention. Within 2 years of radiosurgery, this risk of hemorrhage was reduced by one-third to 12.3% per year. After the anticipated 2-year latency interval, the yearly risk of hemorrhage was further reduced to 0.76%. This risk approximated the 0.6% yearly rate of hemorrhage seen in patients who harbor asymptomatic cavernous malformations.[5] Radiosurgery was associated with a greater than 30-fold reduction in the baseline risk of symptomatic bleeding.

♦ The Radiobiological Effect of Radiosurgery

It is not clear why the risk for hemorrhage is reduced after radiosurgery. Our hypothesis is that the endothelial-lined channels undergo progressive hyalinization leading to thickening and eventual luminal closure, perhaps via the chronic inflammatory response typical of radiation-induced vasculopathy.[3,23,32] Unfortunately, there are few reports about the histology of cavernous malformations after radiation. Gewirtz et al. reported pathologic changes in 11 patients who underwent surgical resection after irradiation.[33] Of these lesions, eight were identified as cavernous

malformations, one was identified as a true AVM, and two were not identified adequately. No malformation was completely thrombosed; this is not surprising as most had rebled necessitating surgical resection. Six lesions showed a combination of marked vessel fibrosis, fibrinoid necrosis, and ferrugination. In addition, Karlsson et al. showed a cavernous malformation specimen that was treated with Gamma Knife radiosurgery, revealing that more than 70% of the lesion had been obliterated.[21]

Chang et al. reported 57 patients with surgically inaccessible cavernous malformations treated by helium ion or linear accelerator radiosurgery.[18] They found an annual hemorrhage rate of 9.4% was reduced to 1.6% after 36 months elapsed after radiosurgery. Complications included symptomatic radiation edema (7%), necrosis (2%), and increased seizure frequency (2%). Amin-Hanjani et al. reported 95 patients with 98 cavernous malformations who were treated with stereotactic Bragg-peak proton beam therapy.[10] They found that the annual hemorrhage rate was reduced from 17.3% before treatment to 4.5% after a latency period of 2 years with a 16% incidence of permanent neurologic deficit and a 3% mortality rate. Karlsson et al. reported a hemorrhage rate after radiosurgery of 8%, but they cautioned on the use of this technique because of side effects (27%).[21] Some of their patients were treated without MRI guidance and at doses that currently would be considered excessive.[21] Some may have had associated venous anomalies.

In contrast, Steinberg et al. reported results after microsurgical resection in 56 patients with 57 deep angiographically occult vascular malformations (AOVMs).[15] They also reported a long-term neurologic morbidity rate of only 5% and a complete lesion resection of 93% after the initial planned resection. This figure may have been overestimated because two of their patients had rebleeding despite postoperative MRI that suggested complete resection. Compared with surgical resection, the obvious disadvantage of radiosurgery is the latency interval necessary to achieve a reduction in the bleeding rate. This disadvantage is outweighed by the lower risk of radiosurgery for hemorrhagic malformations completely located within critical brain parenchyma. Although Pollock et al. reported a reduction in the bleeding rate after radiosurgery in their series of 17 patients (reduced from 40% before radiosurgery to 2.9% two years later), they found a radiation-related morbidity rate of 41%.[26] This may have been due to the high median margin dose of 18 Gy.

It is still unclear whether radiosurgery should be offered to a patient after one symptomatic hemorrhage. Good clinical decision-making is difficult in this group because their overall yearly hemorrhage rate is ~4 to 5% per year.[5] Any intervention for this group must have a lower overall morbidity associated with it and offer a clear benefit. Perhaps the best patient for radiosurgery after a single bleed is a younger patient whose first hemorrhage caused disabling symptoms. Because the morbidity of radiosurgery for cavernous malformations may be much lower than previously thought, and the rate of hemorrhagic risk reduction dramatic, we think that after a single-bleed, radiosurgery is reasonable for selected patients. A decision analysis model should help to elucidate the crossover points of morbidity and hemorrhage rate that would make radiosurgery an appropriate treatment strategy for patients with a first hemorrhage from a cavernous malformation.

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