

Neoplasm

Multiple dynamic cavernous malformations in a girl: long-term follow-up[☆]

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Abstract

Background: Cavernous malformations have generally been viewed as fairly benign vascular lesions with low potential for causing massive hemorrhage.

Case Description: We present an interesting case of multiple CMs, several of which were formed de novo and exhibited aggressive biological behavior resulting in recurrent episodes of intracranial hemorrhage over a 10-year period. This case illustrates a dynamic and aggressive form of CMs. Recent advances in our understanding of the molecular pathogenesis of CMs implicate genetics as an important pathogenic factor, which is the most likely etiology of this patient's presentation.

Conclusion: Special challenges exist in managing young children with multiple, highly aggressive CMs.

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Keywords:

Cavernous malformation; Natural history; Hemorrhage; De novo formation; Vascular malformation

1. Introduction

Cavernous malformations are low-flow, benign vascular lesions that affect 0.4% to 0.8% of the population [10,11]. However, their potential for a more aggressive course has also been recognized. We will describe this unique case of multiple hemorrhages of CMs by outlining the patient's initial presentation, radiologic findings, and histopathologic findings over a 10-year follow-up period. We will conclude with a discussion of recent advances in their potential for serious complications.

Abbreviations: AVM, arteriovenous malformation; CECs, cavernous malformation endothelial cells; CMs, cavernous malformations; CT, computed tomography; DSA, digital subtraction angiography; MR, magnetic resonance; VEGF, vascular endothelial growth factor; VM, venous malformation.

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2. Case Report

2.1. History and operative interventions

In May 1996, when this patient was a 6-month-old baby girl, she was transferred to our hospital for evaluation of inconsolable crying and vomiting. Emergency CT scan of the head revealed 2 small hematomas in the left parietooccipital lobe, which were thought to be CMs. The patient recovered well after conservative therapy. Two months later, the patient's symptoms recurred and a repeat CT scan showed rebleeding of the same CMs. This was also treated conservatively.

Two years later, this patient presented with a more severe, third episode of intracranial hemorrhage that was associated with somnolence and required admission to our neurosurgical intensive care unit. In addition to the enlarging hematoma in the left parietooccipital lobe, CT scan also demonstrated a separate, expanding hematoma in the left cerebellum as well as a smaller hemorrhage originating from the right frontal lobe. Despite significantly elevated intracranial pressure, there was no imminent threat of herniation; hence, con-

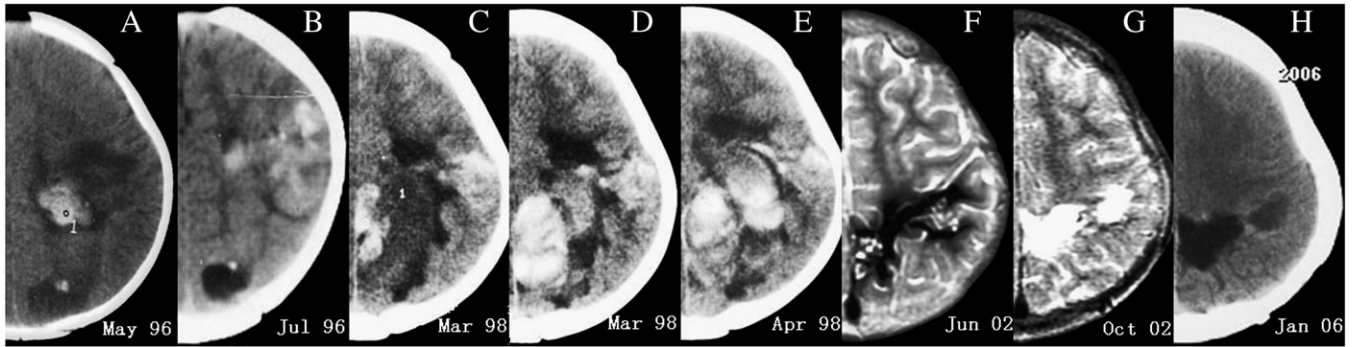


Fig. 1. CT (A–E, H) and MR (F, G) manifestations of 2 hemorragic CMs in the left parietooccipital lobe. Initial CT scan (A) revealed 2 small hematomas in the left parietooccipital lobe, with the parietal one enlarging 2 months later (B). Rehemorrhage of this CM occurred 2 years later (C). At that time, continuous enlargement of the occipital lesion was found (D, E). MR (F) was performed after absorption of the hematoma. Postoperative MR (G) and CT (H) showed complete resection of the CMs.

servative therapy was once again followed. The patient eventually recovered well except for mild gait ataxia.

Further investigations were pursued once the patient was stabilized from her acute illness. Digital subtraction angiography of the brain was unremarkable. Von Hippel-Lindau disease was effectively ruled out by a normal abdominal CT scan, as well as a normal dilated fundoscopic examination. A familial cause was also explored but denied.

The left cerebellum CM was resected in March 2001. This was followed by resection of the remaining 2 CMs in the parietooccipital lobe in July 2002 under neuronavigation. In January 2006, however, this patient underwent episode of brain hemorrhage derived from a suspected CM in the left frontal lobe that was not seen in previous CT or MR images. After the hematoma was absorbed, a third operation was recommended to the patient's family, although the patient's family remains hesitant and will likely opt for continued surveillance and follow-up.

The patient is currently 11 years old, developmentally normal, and otherwise well except for mild gait ataxia. She presents almost all forms of CM biological behavior, including the de novo formation of the left frontal CM, the concurrent overt hemorrhages of the CMs in the left parietooccipital lobe and left cerebellum, and the dynamic changes from de novo formation, maturation, to total calcification of the right frontal CM. Serial CT and MR images of the 5 lesions over a 10-year period are presented in chronological order (Figs. 1–4, Table 1).

2.2. Histopathologic findings

The pathologic specimens of the left parietooccipital and left cerebellar vascular lesions revealed CMs with typical histopathologic features. These specimens were composed of dilated, thin-walled vascular channels consisting of endothelium and collagen, filled with blood and thrombi, without intervening neural parenchyma within the bulk of lesion. We did not find any significant difference in

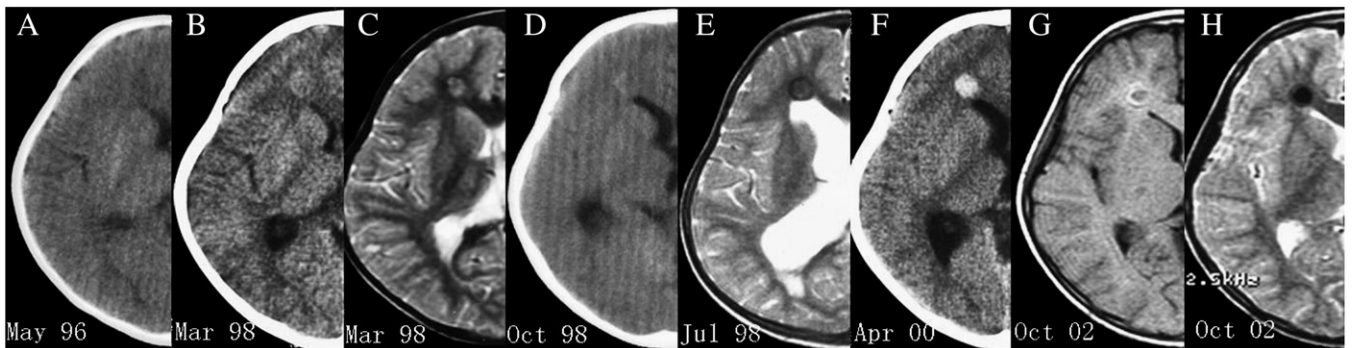


Fig. 2. The formation and signal change of a CM in the right frontal lobe on CT and MR images. Nothing abnormal was found in the right frontal lobe on initial CT scan (A). Two years later, a lesion of slightly high density was found near the anterior horn of the lateral ventricle (B). The MR (C) confirmed this finding, but this lesion did not demonstrate features consistent with a typical CM. After the absorption of the small hematoma, the lesion becomes unclear as to its identity on CT scan (D), although T2-weighted MR images (E) show a lesion with a low-signal ring, which is typical of CM. The CT (F) shows several intralésional hemorrhages. Obvious low-signal change is found both on T1- and T2-weighted MR images (G, H), which we believe is due to intralésional calcification, a consequence of the lesion aging.

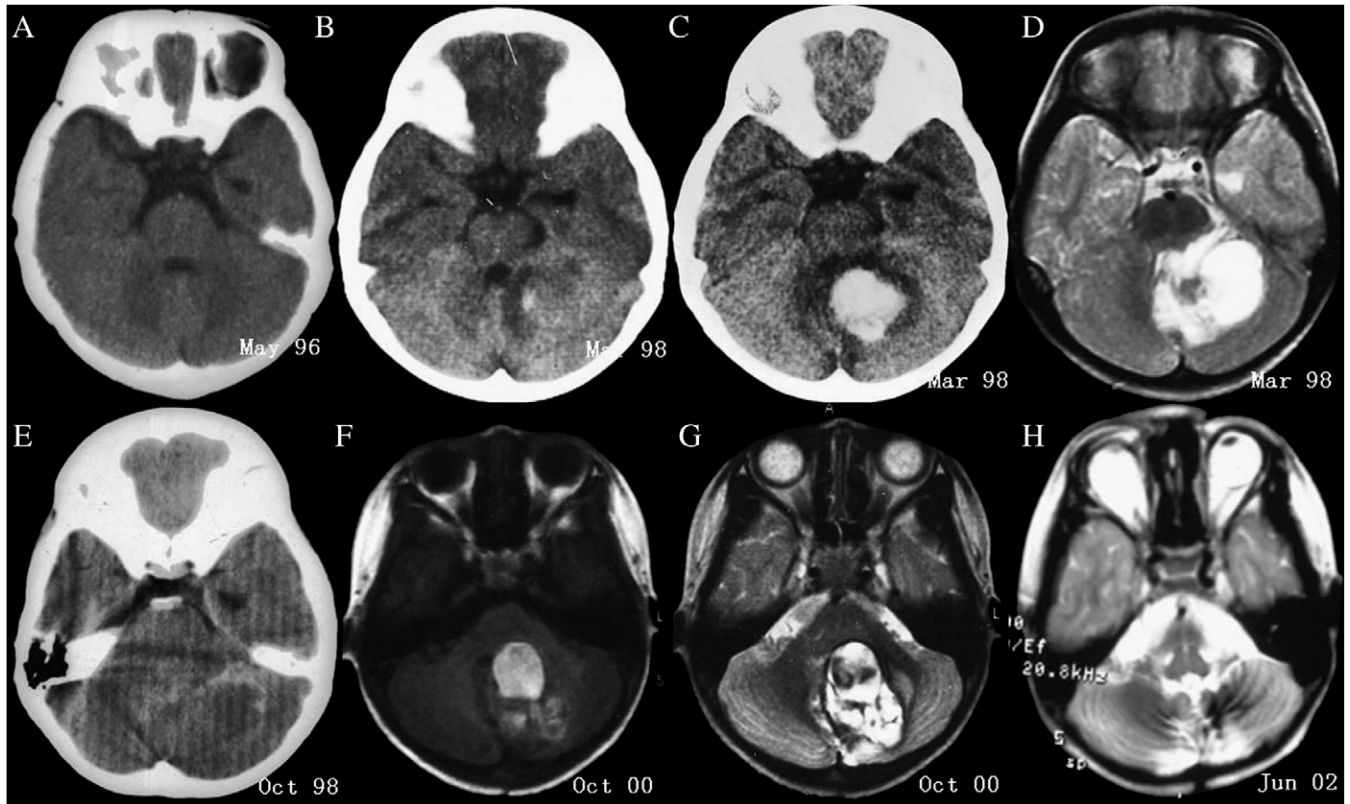


Fig. 3. CT and MR manifestations of a CM in the left cerebellum. Initial CT scan (A) was normal, but a small lesion of high density was found in the left cerebellum near the cerebellar vermis (B) 2 years after the patient's initial presentation. Two weeks later, overt hemorrhage was seen on CT and MR images (C, D). The hematoma eventually self-absorbed (E), and the preoperative (F, G) and postoperative (H) MR images are shown.

pathologic features among the CMs of this patient and the CMs of our other patients.

3. Discussion

Because the prevalence of the CMs reaches 0.3% to 0.4% of the population, and only a few patients show clinical symptoms, the biological behavior of CMs seems to be

relatively benign in most cases. However, there appears to be a subset of patients with aggressive lesions that demonstrate *de novo* formation, rapid growth, and high risk for hemorrhage [3,4].

3.1. Intracranial hemorrhage and CMs

Cavernous malformations are 1 of 4 types of cerebral vascular malformations, which include AVM, CM, VM, and

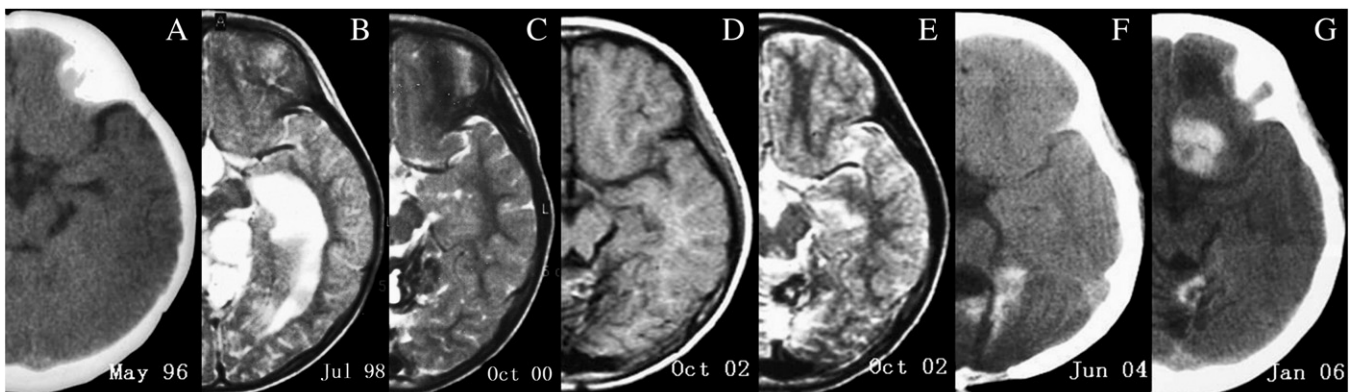


Fig. 4. Sudden hemorrhagic onset of a CM in the left frontal lobe. Previous CT (A, F) and MR (B-E) images did not reveal any abnormalities over the 8-year period. At the most recent presentation in January 2006, extralesional hemorrhage was found on CT scan (G).

Table 1
Ten-year summary of this patient's clinical presentation of multiple, hemorrhagic CMs

Location of CM	Date of CM discovery	Date of catastrophic hemorrhage	Chief complaint on presentation	Treatment and outcome	Radiologic findings
Left parietal-occipital, ×2	May 1996	Mar and May 1996; Mar and Apr 1998	Headache, vomiting, visual disturbance	Surgical resection, resolved	See Fig. 1
Right frontal	Mar 1998	N/A	N/A	Close follow-up and surveillance, lesion calcified	See Fig. 2
Left cerebellum	Mar 1998	Mar 1998	Headache, vomiting, gait ataxia	Surgical resection, resolved	See Fig. 3
Left frontal	Oct 2002	Jan 2006	Headache, vomiting	Surgical resection recommended	See Fig. 4

N/A, not applicable.

capillary telangiectasia. As CMs are low-flow, low-pressure vascular lesions, hemorrhage of a CM is more likely to be self-limited compared to an AVM. Intralesional hemorrhage of a CM suggests the hemorrhage remains confined to its capsule; this presents as mild discomfort and is often referred to as occult intracranial bleeding. Overt hemorrhage is less common than occult hemorrhage. A retrospective rate of overt hemorrhage was thought to be 0.25% to 2.3% per patient year and a prospective rate of 2.6% to 3.1% per patient year [10,11]. The expansion of intralesional hemorrhage or the extralesional hemorrhage could hardly lead to intracranial hypertension and eventually brain herniation. The only lethal hemorrhage, so far as we know, was reported by Ciurea et al [4], with the lesion in the vital brainstem.

Another interesting aspect of this case is this patient's multiple CMs, which have simultaneously hemorrhaged. To our knowledge, this uncommon phenomenon has only been reported by Chanda et al [3] in 2002, with one lesion in the occipital lobe and the other in the dorsal brainstem of his patient. The close proximity and distribution of these lesions is similar to that of our patient. We suspect that the CMs bled after simultaneous stimulation by presumably a type of hormone that could not be confirmed currently. Maiuri et al [8] studied the expression of angiogenic factors and growth factors in the walls of cavernoma vessels, perivascular tissue, and perilesional brain parenchyma. Results show that the familial occurrence and more aggressive clinical behavior of CMs are associated with higher expression of Ki-67 and bcl-2 in the cavernoma tissue, which is associated with higher expression of some growth factors in the perilesional brain parenchyma. These findings suggest neighboring vasculature and glia may be predisposed to and recruited for further growth and progression. In a previous study, we developed a modified protocol to isolate and culture cerebral CECs from surgically resected human specimens [12]. This study provided evidence that CECs had enhanced angiogenic potential and showed increased responsiveness to VEGF.

3.2. Dynamic changes of CMs

Cavernous malformations are generally regarded as congenital lesions and their de novo formation is thought to be unusual. When this occurs, it is often associated with radiation exposure, traumatic injury, or may be attributed to

genetics. Cavernous malformations with multiple foci have also been studied and a genetic basis for this disorder has been suggested. Three genes (CCM 1, 2, 3) have been identified in cases of familial CMs and sporadic cases with multiple CMs [1,2,5,7]. We have also reported on hereditary CMs in a Chinese family characterized by a novel CCM1 gene mutation [9]. In this patient's case, although no one in the family had a similar problem and MR of her parents was otherwise normal, we suspect some genetic factor may explain this patient's young age of onset, multiple sites of CMs, aggressive nature of these CMs, and their de novo formation.

3.3. Therapeutic considerations for multiple CMs in children

Although there may be simultaneous bleeding in 2 or more lesions, surgical treatment should be undertaken for lesions jeopardizing critical structures or exerting mass effects [3], especially for a young child [6]. In our patient, the lesion in the left cerebellum was the most life-threatening and was removed before the parietal-occipital ones.

In terms of timing for surgical intervention, emergency hematoma removal is not recommended unless there are suggestions of imminent brain herniation. When an extralesional hemorrhage occurs, the compression effect of the hematoma may prevent rebleeding of the CM by a tamponade-like effect, which may render the bleeding self-limiting. Symptoms usually resolve by spontaneous resorption of the hematoma. Surgery at that time will significantly lower the injury to the surrounding normal brain parenchyma, as the representative mulberry feature of the CM makes it distinguishable under the microscope and the low signal ring around the CM becomes more evident on MR.

Finally, because of the potential for de novo formation and rapid enlargement of existing lesions, children with CMs need to be followed carefully and regularly even when lesions have been quiescent for several years [6].

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