Case Report

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Rare asymptomatic giant cerebral cavernous malformation in adults: two case reports and a literature review

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Abstract

Cavernous malformations are benign vascular malformations. Giant cavernous malformations are very rare. All reported cases have been symptomatic because of the large size and compression of the surrounding brain tissue. We report two asymptomatic cases of giant cavernous malformation that were both misdiagnosed as neoplasms because of their atypical presentations. The first case was a 54-year-old man whose computed tomography and magnetic resonance imaging scans revealed an inhomogeneous lesion of 6 cm diameter and mild enhancement in the left frontal lobe. A left lateral supraorbital and transcortical approach was applied and the lesion was completely removed. The second case was a 36-year-old man with an irregular large mass in the parasellar region. Craniopharyngioma was suspected and gross total resection was performed. Post-surgical pathological analyses confirmed the diagnoses as cavernous malformations. Both patients recovered uneventfully. The rare asymptomatic giant cavernous malformations reported here in adults had benign behavior for this specific disease entity. The different clinical characteristics of ordinary cavernous malformation and adult and pediatric giant cavernous malformation imply complex and distinct genetic backgrounds. Concerns should be raised when considering giant cavernous malformation as a differential diagnosis for atypical large lesions. Surgical resection is recommended as the primary treatment option.

Keywords

Asymptomatic, adult giant cavernous malformation, benign course, differential diagnosis, surgical intervention, gross total resection, atypical lesion

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Introduction

Cavernous malformations (CMs), also known as also cavernomas or cavernous angiomas, are vascular malformations consisting of sinusoidal spaces lined by a single layer of endothelial cells, often surrounded by gliotic neuronal tissue and hemosiderin staining.[1,2] The size of CMs can vary from a few millimeters to a few centimeters. Giant CMs (GCMs), although rare, have been reported in several case reports. Although it is a relatively arbitrary cutoff, Lawton et al. defined GCM as a CM with a diameter greater than 6 cm.[3] GCMs are more commonly seen in the pediatric population. Until now, only 19 cases of adult GCMs have been reported, with onset symptoms ranging from seizures to headaches to neurological deficits. The diagnosis of GCM is not as straightforward as that of ordinary CM, and GCMs are usually misdiagnosed as neoplasms. Here, we describe the first two reported cases of asymptomatic atypical adult GCMs, in which a diagnosis of CM was not initially considered. Surgical interventions were performed and the patients had good recoveries.

Case report

Case 1

A 54-year-old man went to his local hospital because of a runny nose and dizziness. He received a head computed tomography (CT) scan, which incidentally revealed a large mass in the left frontal lobe. He was then referred to our hospital. His medical history was unremarkable and he had not had any seizures. Vital signs were stable and his neurological examination was intact. A CT scan revealed an inhomogeneous hyperdense mass with a diameter of 6 cm. Calcification and peri-lesional edema were also noted. The mass presented as a central hypointensity with surrounding nodular hyperintensity on T1-weighted images, a central hyperintensity with mixed nodular signals on T2-weighted images, and a mild central enhancement with contrast. The left ventricle was compressed and the midline was mildly shifted (Figure 1). Melanoma, astrocytoma, and teratoma were all considered as possible diagnoses. Although the patient was symptom-free, open surgery was recommended considering the large size and mass effect of the lesion, and to determine the pathology. A left lateral supraorbital approach was applied. After cortectomy of the middle frontal gyrus, a purple/black mass with multiple cystic formations was visible, containing organized hematoma and rust-colored liquid (Figure 1). Internal debulking was conducted with a Cavitron Ultrasonic Surgical Aspirator (CUSA), followed by careful dissection and piecemeal resection of the capsule. The middle cerebral artery was compressed posteriorly by the lesion, and special attention was paid when dissecting the posterior margin. The arachnoid layer was present over the middle cerebral artery, and the dissection was performed strictly within the arachnoid planes to preserve the artery trunk and branches. Postoperative magnetic resonance imaging (MRI) demonstrated gross total resection (GTR), and pathology results confirmed the diagnosis of CM (Figure 1). The patient's recovery was uneventful and he was discharged 8 days after the operation.

Case 2

A 36-year-old man went to his local hospital because of a transient mild headache and received a head CT scan, which revealed a mass around the right anterior horn of the lateral ventricle. His medical history included well-controlled hypertension and hepatitis, without any suspected seizures. A physical examination showed unremarkable findings. MRI revealed an irregular large mass with a diameter of 6 cm in the right lateral

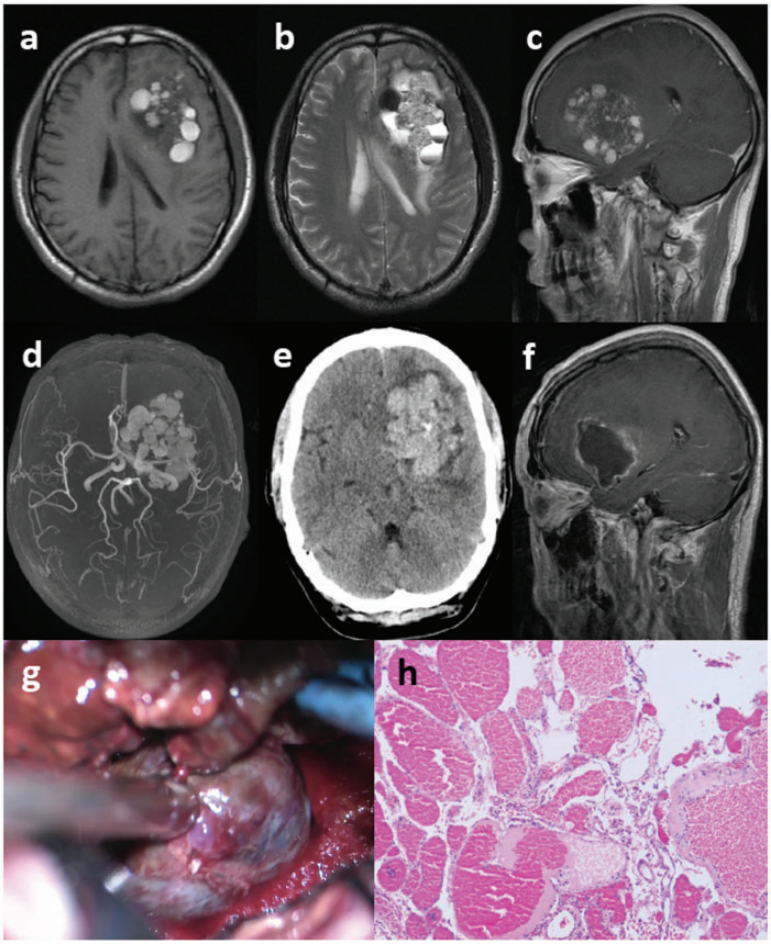

Figure 1. Radiological and pathological presentation of Case 1. MRI scans of the patient show the lesion as a central hypointensity with surrounding nodular hyperintensity on a T1-weighted image (a), central hyperintensity with mixed nodular signal on a T2-weighted image (b), and mild central enhancement with contrast (c). Magnetic resonance angiography shows that the anterior and middle cerebral arteries were displaced by the large mass (d). A CT scan shows an inhomogeneous hyperdense mass with calcification and a diameter of 6 cm (e). A post-surgical sagittal T1-weighted image with contrast demonstrates the complete resection of the lesion (f). Intraoperative visualization of a purple/black mass with multiple cystic formations (g). Hematoxylin and eosin staining confirming the GCM diagnosis (h).

suprasellar region, which displayed as an inhomogeneous signal on both T1- and T2-weighted images, with a surrounding ring of hypointense signal on T2-weighted images and insignificant enhancement after contrast (Figure 2). Surgical resection was recommended because of hydrocephalus and the mass effect on the ventricular system. Left external ventricular drainage was first conducted to release the intracranial pressure and a right pterional approach was applied. After dissection of the sylvian fissure, a vascularized dark mass was observed, which was very adhesive to the optic nerve. There was compression of the internal carotid artery, anterior cerebral artery, and middle cerebral

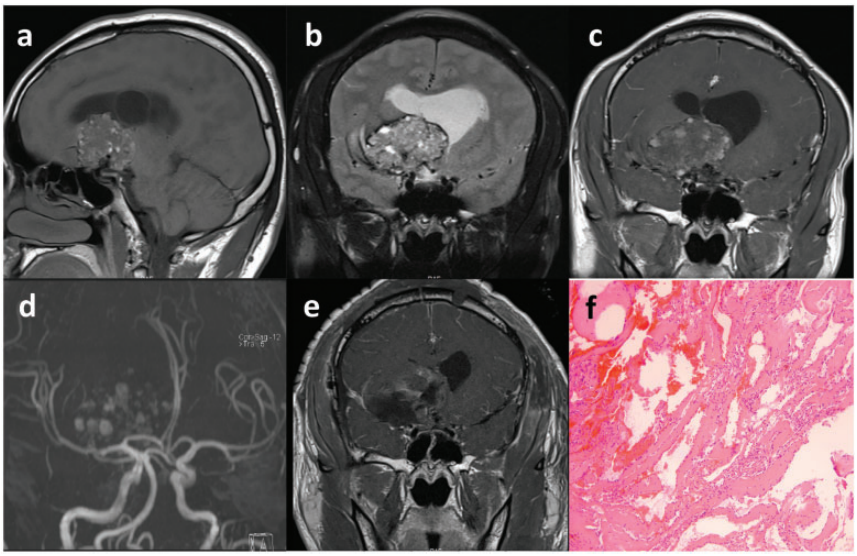

Figure 2. Radiological and pathological presentation of Case 2. MRI scans reveal an irregular large mass in the parasellar region, displaying as an inhomogeneous signal on both T1- (a) and T2- (b) weighted images, with a ring of hypointense signal around the mass on the T2-weighted image (b) and insignificant enhancement after contrast (c). Magnetic resonance angiography shows that the anterior and middle cerebral arteries were displaced (d). A post-surgical coronal T1-weighted image with contrast demonstrates the complete resection of the lesion (e). Hematoxylin and eosin staining confirming the GCM diagnosis (f).

artery inferiorly, caused by remote hemorrhage and cystic formation. After internal decompression, the mass was carefully dissected from the surrounding structures. The distal end of the middle cerebral artery was exposed and sharp dissection was performed following the main trunk toward the proximal end, with preservation of vital lenticulostriate arteries. After dissection and control of the internal carotid artery, the anterior cerebral artery was freed from the mass. GTR was achieved and pathological analysis indicated CM (Figure 2). Transient fever developed during the first 5 days after the operation. The patient finally recovered well and was discharged with no neurological sequelae.

Informed consent

Written informed consent was obtained from both patients for the publication of this case report and accompanying images.

Discussion

CMs represent 5% to 10% of all intracranial vascular malformations.[4] According to radiological studies and autopsy series, the prevalence of CMs is estimated to be between 0.4% and 0.5%.[5] CMs usually occur in patients between the ages of 20 and 40 years old, and are equally distributed between men and women.[5] The majority of CMs are located in the supratentorial region, with an average size of 1 to 2 cm.[4]

GCMs were first reported by Penfield in 1948, and are extremely rare lesions.[6] They were defined by Lawton as having a diameter >6 cm.[3] GCMs are different from CMs in many ways. They have a higher prevalence among the pediatric population, with the youngest reported case in a 3.5-month-old infant, and there seems to be a female preponderance.[5,7] Familial cases account for 20% to 50% of ordinary CMs, but no

familial association has been reported in adult GCM, and it has only been reported in two cases of infant GCM.[4,8] Multiple CMs, which is a common phenomenon, have never been reported in any GCM cases.[9] Together, these findings indicate that GCMs might be a different disease entity from ordinary CMs.

The common initial symptoms in pediatric GCM patients include seizures, focal neurological deficits, and macrocephaly.[10] A thorough literature review revealed 19 previously reported cases of adult GCMs.[4,6,7,9–18] They were all symptomatic cases with indolent lesions, and manifested mainly as seizures and mass effects. True hemorrhage occurrence was relatively rare.[9] GCMs in children, however, have an increased hemorrhage risk and are more aggressive compared with those in adults, implying distinct, age-related biological behaviors.[19] To the best of our knowledge, GCMs have never before been detected incidentally or reported as asymptomatic.[4] Sansone et al. reported a 72-year-old woman with metastatic breast carcinoma who had a dumbbell-shaped cavernous lesion in the pituitary region that was detected incidentally on post-mortem examination. However, because the diameter of the CM was less than 6 cm, it cannot be listed as a case of GCM according to Lawton's definition.[20] Here we report two male patients who had their intracranial lesions discovered incidentally, further demonstrating a benign course for adult GCMs.

The familial forms of CM are inherited in an autosomal dominant manner, with identified loci on chromosomes 7q21.2 (CCM1), 7p15-p13 (CCM2), and 3q25.2-q27 (CCM3).[21,22] In contrast, genetic analysis of GCM is rare. In the report by Lawton et al., there were no mutations in either the CCM1 or CCM2 genes in tissue from a surgical specimen.[3] Lew reported two cases of infants with familial CM who presented with hemorrhagic posterior fossa CMs, and concluded that infants with familial CM should be screened for GCM to reduce the incidence of life-threatening conditions.[8] Based on these findings and the different clinical presentations among CM and adult and pediatric GCM, a complex genetic background may underlie this seemingly simple disease. Future studies should therefore focus on the genetic analysis of GCM.

Pathologically, GCMs are characterized by sinusoidal spaces lined by a single layer of endothelium, gliotic neural tissue, surrounding hemosiderin staining, and a lack of intervening brain parenchyma.[7,23] The main driving force of lesion growth is hypothesized to be a repetitive small amount of bleeding from friable vessels, followed by blood clot organization and pseudo-capsule formation.[3,9] This benign pathological process matches well with the indolent clinical manifestations of adult GCMs, and is summarized in Table 1. Expansile growth without hemorrhagic events has also been observed in GCMs, mimicking neoplasm development.[9,10]

The radiological appearance of GCMs is variable. The reported MRI features of GCMs include non-enhancing multi-cystic lesions with mixed intensity and a surrounding hemosiderin ring, large masses with a "salt and pepper" appearance, and spherical lesions consisting of acute and subacute hematomas.[24] The presentation after contrast injection is highly inconsistent, ranging from nonexistent to intense enhancement.[9,14] GCMs can also appear as complete solid masses and be misdiagnosed as neoplasms. GCM with concurrent diffuse multiple calcifications has been reported, and needs to be differentiated from diseases such as toxoplasmosis, rubella, and cytomegalovirus as congenital infections.[14] Van Lindert et al.[7] described three cases that were not initially considered as GCMs in their differential diagnoses by radiologists, neurologists, and neurosurgeons.

Table 1. Literature review of adult GCMs fulfilling the diagnostic criteria proposed by Lawton et al.

No.	Age (years)	Sex	Location	Clinical presentation	Diameter (cm)	Treatment	Outcome	Author
1	27	M	Left temporal	Seizure, right hand numbness and tremor	7.5	GTR	Improved	Siddiqui (2001)
2	45	F	Intraventricular	Memory difficulties, personality changes, headache, balance difficulties	6.5	GTR	Improved	Anderson (2003)
3	56	F	Right temporal	Seizures, left hemiparesis	6	GTR	Improved	Gelal (2005)
4	22	F	Right frontal	Seizure	6	GTR	Improved	Kim (2006)
5	36	F	Right temporo-parieto-occipital	Headache, nausea	6.5	GTR	Improved	van Lindert (2007)
6	35	F	Left frontal	Seizures, a dilated pupil	6	GTR	Improved	van Lindert (2007)
7	20	F	Left frontal and basal ganglia	Seizure	7	GTR	Improved	Son (2008)
8	30	M	Left parietal and thalamus	Seizure, right side weakness	6	N/A	N/A	Kan (2008)
9	26	M	Left lateral ventricle	Headache	6.2	GTR	Improved	Muccio (2008)
10	24	F	Right parieto-occipital	Seizure	6	GTR	Improved	Jhawar (2010)
11	25	F	Left fronto-parietal	Seizures, right-side limb weakness	6.5	GTR	Improved	Jhawar (2010)
12	21	M	Right temporal	Seizure	6	Biopsy	Seizure	Penfield (1948)
13	77	M	Right frontal and parietal	Neurological deterioration	>10	GTR	N/A	Hyodo (2000)
14	36	F	Left frontal and basal ganglia region	Dizziness, nausea, numbness of right limbs	6	GTR	Improved	Wang (2018)
15	22	M	Right temporal	Headache, nausea, vomiting	6.1	GTR	Improved	Wang (2018)
16	50	F	Right temporal	Headache	6.6	GTR	Improved	Wang (2018)
17	26	M	Right lateral ventricle	Headache, slurred speech	6.3	GTR	Improved	Wang (2018)
18	50	F	Bifrontal	Headache, nausea, vomiting	6	GTR	Improved	Wang (2018)
19	19	M	Left fronto-parietal and basal ganglia	Right-side motor weakness	7.2	GTR	Improved	Kim (2013)
20	54	M	Parasellar	Asymptomatic	6	GTR	Uneventful	Present study
21	36	M	Right lateral suprasellar	Asymptomatic	6	GTR	Uneventful	Present study

Abbreviations: GTR, gross total resection; N/A, not available.

The two cases reported here were also not considered as CMs prior to surgical intervention. Therefore, for a large mass with an odd appearance that is inconclusive of any pathology, GCM should be considered. Gradient-echo sequences and susceptibility weighted imaging are highly sensitive for imaging hemosiderin, and may provide useful diagnostic information.[10]

For GCMs, surgical resection is the treatment of choice. The current surgical indications for GCM include recurrent bleeding, progressive neurological deterioration, medically intractable epilepsy, and significant mass effect.[9] Complete surgical removal is the goal, because good recovery is possible and morbidity is low.[7,9] As summarized in Table 1, GTR has been achieved in almost all cases, except in a 21-year old patient with seizures as the chief complaint, who had a biopsy to confirm the pathology. Preoperative symptoms are largely improved after GTR. However, any remnants can lead to recurrent symptomatic hemorrhage in 25% of surgically treated patients.[10] Despite their large size, GCMs are usually low-flow vascular malformations; therefore, strategic internal debulking and piecemeal resection can be used to reduce brain retraction and lead to GTR. Hyper-vascular intraparenchymal GCM with an arteriovenous shunt has also been reported, and embolization was applied to reduce bleeding.[25]

Conclusions

GCMs are rare and easily misdiagnosed lesions. Because of their large size, all GCMs reported in the literature have been symptomatic, with seizure and mass effect as the main complaint. Here, we report the first two asymptomatic cases to be discovered incidentally, further demonstrating a benign natural course for adult GCMs. A literature review of GCMs revealed that they are different in many respects from ordinary CMs, and even behave differently within the pediatric and adult subtypes, suggesting complex and distinct genetic driving forces. The purpose of presenting these two cases is to raise awareness among clinicians, so that they consider GCMs as a differential diagnosis for atypical large lesions. GTR is the standard treatment for GCMs, and internal debulking and piecemeal resection are the recommended surgical points for low-flow vascular types.

Authors' contributions

Wang (WZ) drafted the first manuscript and made a contribution to the acquisition and interpretation of data. Hu performed the clinical work-up and literature search. Wang (WC) revised the manuscript that led to the final approval of the current submission. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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