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Resection of Intracranial Giant Cavernous Malformation: Case Report and Literature Review

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Abstract

Cerebral cavernous malformations are a rare and congenital vascular malformation that can present as a challenge in neurosurgical management. The term "giant cerebral cavernous malformations" still does not have a clear definition in the literature, with a wide variety of results. It is known, however, that there is an association between the size of the cavernoma and postoperative sequelae, especially in those with a size greater than 3 cm in its largest diameter. We present a case report of resection of a giant brain cavernoma measuring approximately 8 cm in its largest diameter, emphasizing on clinical presentation, diagnoses and postoperative evolution. Additionally, we performed a comprehensive review of the existing literature on the subject, addressing the epidemiology, pathophysiology, diagnostic methods, treatment options, and prognosis associated with this condition.

Keywords

Cavernous Malformation, Cerebral Cavernous Malformation, Giant Cavernous Malformation, Cavernous Hemangioma, Cavernous Angioma, Cavernoma, Giant Cavernoma

1. Introduction

Cerebral cavernous malformations represent a special subtype of low-flow vascular disorder. The overall prevalence of intracranial cavernous malformation (CM), cavernous hemangioma, cavernous angioma or cavernoma is 0.4% - 0.6% and the mean age of presentation is 30.6 years. The majority of cavernous malformations in the brain are small, with a mean size of 14.2 mm in diameter [1].

Although the pathophysiology of this disease is not yet fully understood, increasingly more data on clinical features are available [2]. Most of cerebral cavernomas are silent and could be discovered incidentally when imaging is done for other reasons, like vague headache, or even after car accident; other presentation is secondary to bleeding [3].

The clinical presentation is widely variable depending on the location of the lesion, and even in the presence of any bleeding, headache is still the most common presenting symptom; seizures and neurological deficits are usually after a bleeding event, which is usually limited [3].

Intracranial giant cavernous malformations (GCMs) are rarely reported because of their extremely low incidence. Knowledge of GCM is poor. The sizes of CMs are highly variable, ranging from a few millimeters to several centimeters. However, unlike giant aneurysms, which have a definite threshold (diameter > 25 mm), there exists no consensus on when to call a CM "giant" [4] [5] [6].

GCMs, although rare, have been reported in several cases reports. Although it's a relatively arbitrary cutoff, Lawton *et al.* defined GCM as a CM with a diameter greater than 6 cm. GCMs are more commonly seen in the pediatric population [7]. Until now, only 19 cases of adult GCMs have been reported, with onset symptons ranging from seizures to headaches and neurological deficits. The diagnosis of GCM is not straightforward as that of ordinary CM, and GCM are usually misdiagnosed as neoplasms [7].

Lesions that grow to extreme sizes have different clinical presentations and pathophysiological and technical considerations than average-sized lesions. For example, giant pituitary adenomas are defined as >40 mm in diameter. Giant adenomas are more invasive than smaller adenomas and often require staged or multimodal treatments. So Lawton *et al.*, hypothesized in a recent study to establish clarity and consistency in the discourse and reporting of CMs, 3 cm or more in diameter as the definition of GCM [8].

The aim of this article is discuss about GCMs, to know more about specific details: clinic manifestations, size, treatment and bringing these as important differential diagnosis of brain lesions with giant aspects at the images exams.

2. Case Report

A thirty-two-year-old female with a congenital hearing loss diagnosis presented to an outside hospital with seizures in January 2023 with normal blood tests. However, the MRI scan revealed a very large tumoral mass in the right temporo-parietal junction with a heterogeneous enhancement pattern and causing mass effect (see **Figure 1**). Several differential diagnoses were proposed based on the imaging features and location, including meningiomas, choroid plexus papilloma, and cavernous malformation.

The patient was referred to Sao Francisco Hospital, a public hospital, to further neurosurgical evaluation in March 2023, it was not noticed any other neurological deficit more than her previous hearing loss, using by reference the

modified Rankin scale (mRS) that patient was a mRS grade 0. The patient underwent neurosurgical intervention at that same month. Intraoperatively, it was observed some aspects suggesting a chronic condition, like bone-thinning associated with a point of perforation of the skull. We performed a very careful microdissection, with a maximal tumor diameter of 8 cm (Figure 2) divided into two blocks with no brain injury despite the close association with ventricle atrium.

The surgery had no intraoperative complications, and the patient was admitted to ICU alert with no other neurological deficits, being discharged from hospital after four days. An anatomopathological results shows unspecific features:

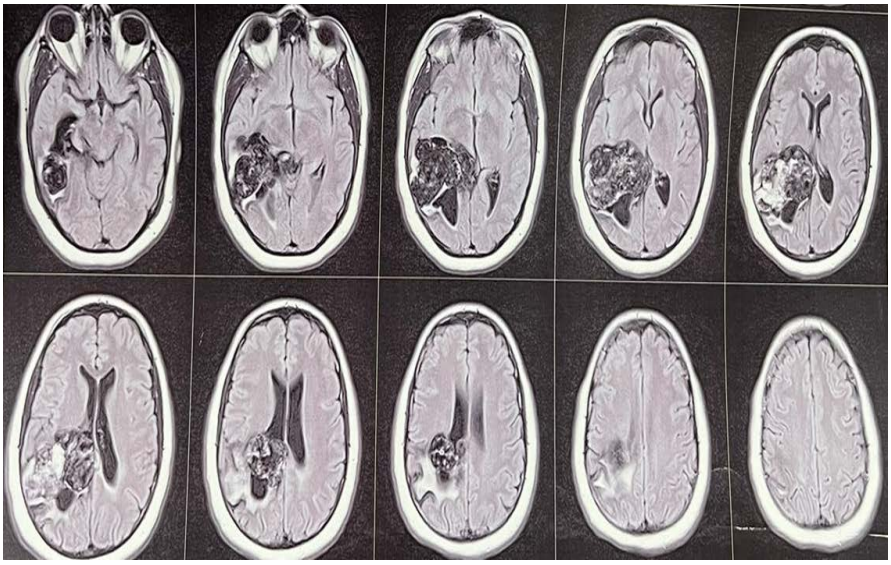

Figure 1. At up, a FLAIR-weighted image showing a heterogeneous mass with invasion of the right lateral ventricle atrium and adjacent edema.

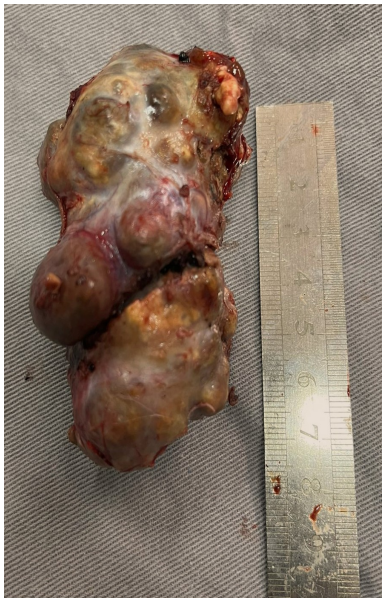

Figure 2. The specimen post-surgical resection.

vascular and fibrous changes questioning cavernous malformation or arteriovenous malformations. One week later, with immunohistochemistry analysis confirmed the diagnosis cavernous malformation (Figure 3).

During the follow up, the patient presents at the clinical with good recovery, no complications more than her previous hearing loss. There was no functional decline, keeping a mRS grade 0. Three months after the surgery, post-operative MRI shows a total resection of the GCM with preserving of the brain tissue around (Figure 4).

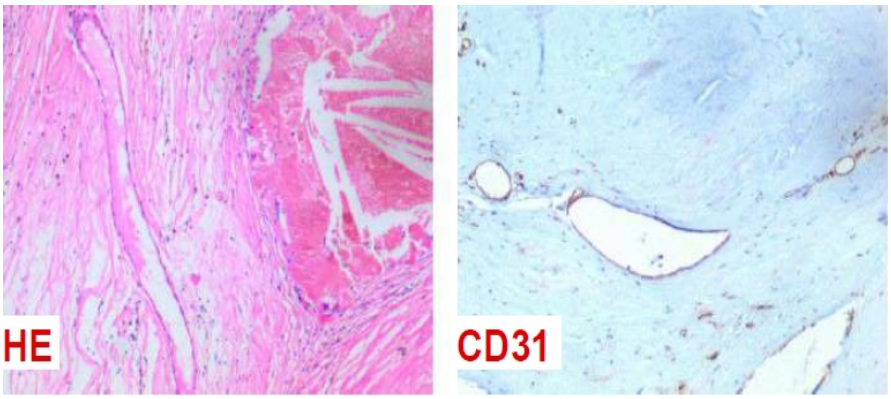

Figure 3. First, on the left image, a histopathological section stained with hematoxilyn and eosin, displaying a fiborascular aspect. On the right, a immunohistochemical preparation shows positivity for ERG and CD31.

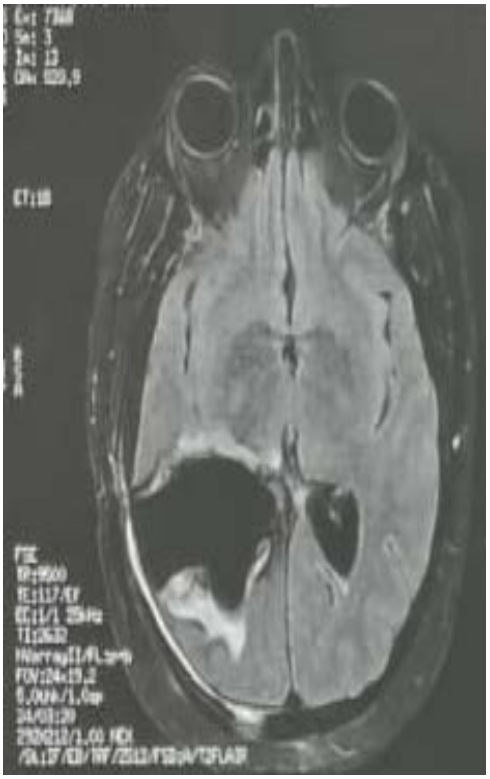

Figure 4. On the right side MRI image displaying a postoperative appearance following complete resection of the lesion, after 3 months of the surgery.

3. Discussion

The overall prevalence of intracranial CM, cavernous hemangioma, cavernous angioma or cavernoma is 0.4% - 0.6% and the mean age of presentation is 30.6 years. The majority of cavernous malformations in the brain are small, with a mean size of 14.2 mm in diameter [4] [5].

Cavernous malformations are benign collections of endothelial cells and collagenous tissue, which create cavernous space filled by blood in several types: low flow, stasis and thrombosis. The emblematic radiographic finding is a popcorn-like strawberry-like image with a hypointense portion that represents hemosiderin deposits. Expansile growth without hemorrhagic events has also been observed in GCMs, mimicking neoplasm development [1].

GCMs were first reported by Penfiel in 1948 and are extremely rare lesions [9]. The size criterion for GCM is not sharply defined; some authors use a minimum diameter of 6 cm as threshold [7], while most other authors use a diameter of 4 cm as cut-off [10]. They were defined by Lawton as having a diameter > 6 cm.

The familial forms of CM are inherited in an autosomal dominant mode, with identified loci on chromosomes 7q21.2 (CCM1), 7p15-p13 (CCM2), and 3q25.2 (CCM3). 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 [11].

Multiple CMs, which is a common phenomenon, have never been reported in any GCM cases. Together, these findings indicate that GCMs might be a different disease entity from ordinary CMs [1].

In our patient the histopathological finds sample from a lesion with an expansive, fibrous and densely collagenized appearance, with permeated hemorrhagic cysts partially covered with endothelium (ERG positive). These findings are compatible with benign fibrovascular lesion and suggest cavernoma. And the immunohistochemical were negative for cytokeratins and AE1/AE3 clone.

The subgroup of giant cavernous malformations constitutes a formidable challenge to the attending neurosurgeon, since they need to be removed by circumferential dissection. 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 [10].

The increase in size of a cavernoma can be explained by re-endothelization of the hemorrhagic cavity, formation of new blood vessels and proliferation of granulation tissue. New bleedings from this hemorrhagic cavity may further increase the size in time, in a similar fashion to what is observed in the growth of a subdural hematoma [13].

This benign pathological process matches well with the indolent clinical manifestations of adult GCMs. Expansile growth without a hemorrhagic event has also been observed in GCMs, mimicking neoplasm development [1].

Curiously, GCMs are referred in the literature without a “giant” definition. In

other pathologies, however, the term is well defined and consistently used, like in giant aneurysms for those whose diameter is more than 25 mm, and giant pituitary adenoma for those are with a diameter more than 40 mm.

GCMs with 3 cm or more of diameter are associated with a higher risk of severe neurologic worsening in the postoperative period [(2 points increase at Rankin scale modified (mRS) - OR 4.5)], as Srinivasal *et al.* observed. This study by Srinivasan and colleagues with 179 patients identified a prevalence of 18.9% of CGMs. Those patients were assessed using the mRS pre- and post-operatively and those presenting with GCM exhibited higher risk for cognitive decline [13].

A study conducted by Wang *et al.* at Beijing Tiantan Hospital and Capital Medical University found the incidence of GCMs among the entire series of central nervous system CMs to be 0.65% (9 of 1395 cases). All of them were surgically treated with gross total resection and had neurological status improved in 55.6% when assessed by mRS [6].

In a study by Lawton *et al.* published in the Journal of Neurosurgery, they compare different "variants" to analyze the risk of bleeding of a CM and the consequences about this event by means of modified Ranking scale. One of the data was the CM's size and the first cut point with a statistic significant increase in relative risk of functional decline was 3 cm in diameter, with a OR (95% CI) of 4.5 (1.2 - 16.9) ($p = 0.02$). So after this study, the conclusion was that a cut point for a CM could be consider "Giant" is 3 cm, based on the changes in functional and neurological outcomes observed as this threshold for patients with cerebral cavernomas [8].

In our case, we presented a young 32 years-old patient with 8 cm lesion in total length in the right temporo-parietal junction presenting with an intraventricular extension misdiagnosed as a neoplasm. The large dimensions made the resection challenging due to difficulty of handling the lesion without pulling out the surrounding brain structures, leading us ultimately to debulking to preserve brain functioning and achieving a good mRS grade post-operatively with no neurological disabilities.

The current surgical indications for GCM include recurrent bleeding, progressive neurological deterioration, medically intractable epilepsy, and significant mass effect. Complete surgical removal is the goal, since good recovery is possible, and morbidity is low [1].

Despite their large sizes, GCMs are usually low-flow vascular malformations; therefore, strategic internal debulking and piecemeal resection can be used to reduce brain retraction and lead to gross total resection [14].

Until now, consensus is for conservative treatment in asymptomatic CMs; however there is no guideline to the treatment of GCMs. For GCMs, surgical resection is the treatment of choice, especially when associated with recurrent bleeding, progressive neurological deterioration, medically intractable epilepsy, and significant mass effect [1].

4. Conclusion

Our case report and literature review show that GCM is a rare differential diagnosis for supratentorial neoplasm. Despite its low frequency, it is essential to keep this important disease in mind since it is a benign lesion with a good prognosis when gross total resection is achieved. Furthermore, it is necessary to standardize a threshold at which a regular CM transitions to a GCM.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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