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Case Report

Cerebral cavernous malformation in a child leading to a fatal subarachnoid hemorrhage – "silent but sinister:" A case report and literature review

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ABSTRACT

Background: Cerebral cavernous malformations (CCMs), otherwise known as cavernous hemangiomas/cavernomas, are a type of vascular malformation. It is the third most common cerebral vascular malformation, histologically characterized by ectatic, fibrous, blood filled "caverns" with thin-walled vasculature without intervening normal brain parenchyma.

Case Description: Herein, we present a case of an original, spontaneous hemorrhage from a sporadic form of CCM without associated gross developmental venous anomaly in an 11-year-old child, which is an extremely rare occurrence, with the special emphasis on the demographic data of the affected population, risk factors associated with hemorrhage, and correlation of histopathological and radiological findings with an in-depth literature review.

Conclusion: The significant majority of the CCM are clinically occult. Hence, the development of risk assessment tools and guidelines for timely neurosurgical intervention poses a greater clinical challenge for medical experts rendering the management of the affected individuals with CCM in an anecdotal situation. Presentation of life-threatening rebleeds and neurological deficits in the diagnosed population albeit uncommon is possibly preventable outcomes.

Keywords: Cavernoma, Cavernous angioma, Cerebral cavernous malformation, Cerebral, Pediatric, Vascular disorders

INTRODUCTION

Cerebral cavernous malformations (CCMs), otherwise known as cavernous hemangiomas/cavernomas, are a type of vascular malformation. It is the third most common cerebral vascular malformation, histologically characterized by ectatic, fibrous, blood filled "caverns" with thin-walled vasculature without intervening normal brain parenchyma. The significant majority of the CCM are clinically occult. Hence, the development of risk assessment tools and guidelines for timely neurosurgical intervention poses a greater clinical challenge for medical experts rendering the management of the affected individuals with CCM in an anecdotal situation.

Presentation of life-threatening rebleeds and neurological deficits in the diagnosed population albeit uncommon is possibly preventable outcomes. Herein, we present a case of an original, spontaneous subarachnoid hemorrhage from a sporadic form of CCM without associated gross developmental venous anomaly (DVA) in an 11-year-old child which is an extremely rare occurrence with the special emphasis on the demographic data of the affected population, risk factors associated with hemorrhage, and correlation of histopathological and radiological findings with an in-depth literature review.

CASE DESCRIPTION

An 11-year-old child, Asian male, brought to the ETU of our institution when he suddenly collapsed at home. At the time of presentation, he was in asystolic cardiac arrest. Following a prolonged uninterrupted resuscitation, signs of cardiocerebral revascularization were evident with spontaneous breathing and sinus rhythm in ECG. The patient was intubated and transferred to the ICU for post-resuscitation care. Corroborative history taken from the grandmother later revealed a similar past incidence of short-lived syncopal attack with spontaneous recovery about a year ago which was not investigated. She denied any recent history of trauma to head, past events of persistent headaches, seizures, visual symptoms, or behavioral changes. Except for the presumed syncopal event, neither the medical history nor the family history was significant.

On D1 of ICU care NCCT brain revealed diffuse, superficial subarachnoid hemorrhage (modified Fisher scale Grade 3) [Figure 1] with evidence of cerebral edema, persistently low GCS (4/15) and WFNS grading of 5 (GCS <7 with deficits). According to the neurosurgical opinion, the patient was not amenable for any neurosurgical intervention at that time hence opted for conservative management with neuroprotective measures. ECG showed bradycardia with prolonged QT (QTc = 0.53 s). Correctable causes of prolong QT interval were excluded, and it was later attributed to subarachnoid hemorrhage (SAH). Elevated intracerebral pressure (ICP) was confirmed by increased optic nerve sheath diameter in ultrasonography since the fundoscopy was normal. (ICP manometry was not available at our institution).

Electroencephalogram performed on D3 suggested severely reduced cerebral activity. Neuroprotective management was continued with neuroprotective ventilation, maintaining a normocapnia ($PaCO_2$ 30–35 mmHg) and normoxia. All the metabolic parameters including serum glucose, electrolytes, lactate, and liver and renal function tests were stable at that moment.

On D7 patient was found to have deteriorating lung functions, setting hypoxia, tachycardia, and elevated temperature with lung signs. Presumptive diagnosis of sepsis with ventilator associated pneumonia was made and after taking appropriate cultures, intravenous antibiotics were escalated. Cerebral diabetes insipidus was diagnosed based on elevated serum Na+ (158–162 mmol/l), polyuria, and suggestive urinary and serum osmolalities (260 mOsmol/kg and 320 mOsmol/kg, respectively).

Despite every effort, the patient gradually deteriorated with acute renal failure with metabolic acidosis, persistent hypotension which warranted the use of multiple inotropes, deranged clotting profile with liver failure, and ultimately multiorgan dysfunction. A cluster type respiratory pattern was noticed on capnography [Figure 2]. On day 10 of ICU stay, brain stem reflexes were absent on two different occasions, bilateral pupils were found to be round, dilated, and nonreactive to light. Apneic test was negative. Ultimately, the patient succumbed to death by cardiac arrest while on ventilator on day 12.

Pathological postmortem revealed extensive SAH with diffused multiple tufts of irregular, dilated vessels in the occipital region of the basilar and interpeduncular cistern

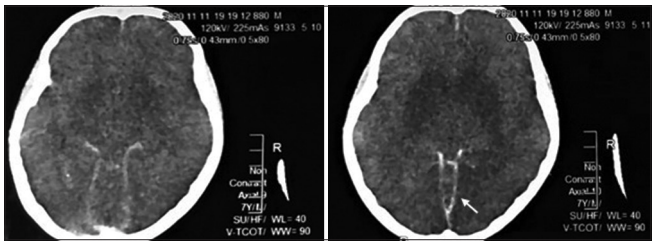

Figure 1: Extensive superficial subarachnoid hemorrhage (Fisher grade 3) with wine glass appearance (arrow).

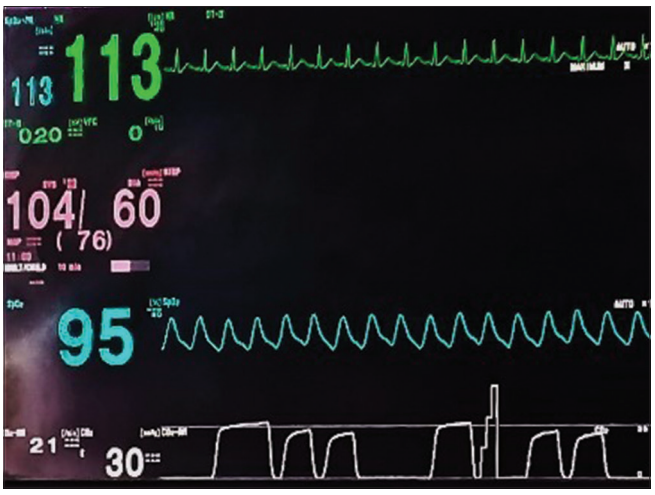

Figure 2: Cluster type respiratory pattern (bottom tracing) indicated in capnography.

area of the cerebrum. Adjacent to the blood clots evidence of pressure effect causing sulci and gyri obliteration with extensive cerebral edema was found [Figure 3]. Liquefaction of brain parenchyma was noted in several foci [Figure 4]. Histopathological specimens revealed closely packed large cavernous vascular spaces, marginated by thin fibrous tissue with the absence of intervening glial tissue which is compatible with a CCM [Figure 5a and b].

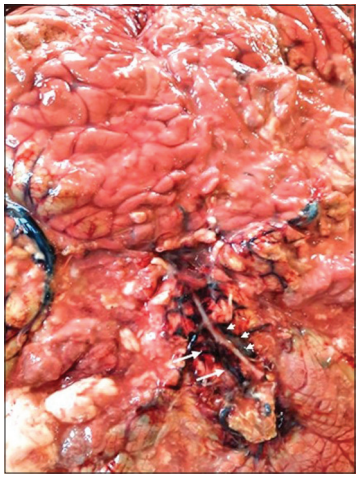

Figure 3: Supratentorial diffuse subarachnoid hemorrhage (arrows) with liquefactive necrosis of brain matter with adjacent mass of irregular, dilated vessels (arrowheads).

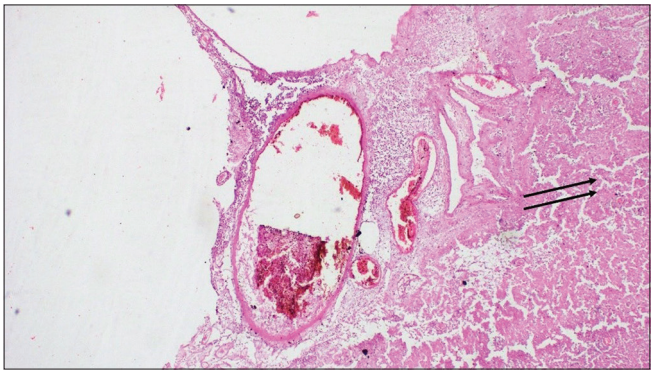

Figure 4: Adjacent brain parenchyma with liquefactive necrosis on right denoted by black arrows (H and E ×100).

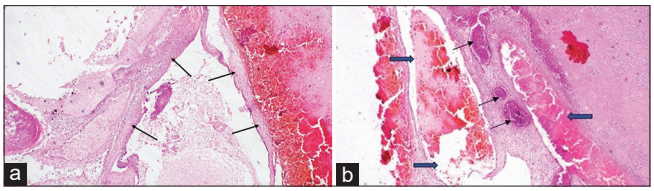

Figure 5: (a) Ectatic and fibrous vascular channels without intervening brain parenchyma – black arrows (H and E ×400), (b) malformed vascular spaces (blue arrows) with focal calcifications (black arrows) in fibrous wall (H and E ×100).

DISCUSSION

CCMs, also known as cavernous hemangiomas or cavernomas, are a type of vascular malformation found both in inherited and *de novo* forms.[6] It is the third most common cerebral vascular malformation, found throughout the body where the vascular endothelium is present, with a prevalence of 10–25% of all vascular malformations.[15] In the cerebrum, about 70–80% of the CCMs are supratentorial in location and are usually solitary.[5] About 25% of the CCMs are found in the brainstem[1] and the spinal cord, the dura, cranial nerves, skin, and rarely the retina are also known to be affected.

CCMs are ectatic, fibrous vessels characterized by "caverns" of blood filled thin-walled vasculature which lack both the elastin and the smooth muscle support in the tunica media [Figure 5a], as well the usual interendothelial junctions, thus allowing the transudation or leakage of blood. These blood filled caverns are thrombosed and calcified to varying degrees [Figure 5b]. They are usually found in the white matter without intervening normal brain parenchyma [Figure 5].

According to the International Society for the Study of Vascular Anomalies, CCMs are classified as simple nonneoplastic venous malformations.[19] CCMs are related to mutations in several different genes: Krev interaction trapped 1 (*CCM1*), malcavernin (*CCM2*), and programmed cell death 10 (*CCM3*).[8] Interestingly, the familial CCMs show the preponderance to hemorrhagic presentation, 6.5% per patient year and 1.1 per lesion year reflecting the more common tendency of CCMs to occur in multiples.[5] Although the absence of similar medical history among the kindred of our patient virtually excludes the possibility of familial CCMs, it was found that multiplicity of the lesions had a resemblance to familial form.

The diagnosis of CCM mainly resorts to radiological findings, especially the contrast axial studies. Unless large, these lesions are difficult to see on computed tomography (CT) and were the case in our patient. They do not enhance. If large, they appear as a region of hyperdensity resembling blood products and speckles of calcification. If there has been a recent bleed, then the lesion is more conspicuous and may be surrounded by a mantle of edema,[10] as opposed in our case the ground-glass appearance of brain parenchyma instead of a mantle of edema was noted in the noncontrast CT denoting severe cerebral edema resulting from SAH. In magnetic resonance imaging (MRI) studies, CCMs are identified as clusters of vessels resembling "popcorn" or a "mulberry" with a rim of signal attenuation due to hemosiderin in the periphery.[17] CCMs are angiographically occult due to low flow and hence MRI has become the investigation modality of choice for decades.[21] The typical appearance of MRI features is often recognized by the radiologists, thus avoiding further invasive

procedures such as digital subtraction angiography and biopsy.[10]

Hourihan *et al*. reviewed a series of SAH in children <20 years and concluded that etiology of SAH is similar to adults but there was a different incidence of the specific pathology producing the bleeding in this series. About 26% of cases were due to bleeding arteriovenous malformations, 52% were due to ruptured aneurysms, and in 19%, no cause was found.[11] Interestingly, among the 167 patients, 32 (19.2%) had negative four vessel angiography and no etiology was identified for SAH of which they attribute to small or largely thrombosed arteriovenous malformation, thus highlighting the fact that rarity of CCM giving rise to isolated SAH in this age group. Hemorrhage when resulting from CCM is usually intraparenchymal in nature although a few cases have been reported to be extra-axial, out of which the so-called angiographically occult SAH is rare.[18] Indeed, SAH as the presentation of CCM is extremely rare and only two such cases reported in English literature of adult patients.[18,20] Furthermore, isolated SAH as the CCM presentation in pediatric patient had not been reported to the best of our knowledge. Out of the reported cases, only one case presented an isolated SAH restricted to basal cisterns mimicking a ruptured aneurysm which is very similar to the postmortem findings of our patient.[18]

It is widely accepted that about 0.5% of the general population bear at least a single CCM by the fourth decade of life.[3] Although the prevalence slowly increases with the advancing age, CCMs are known to affect the whole age spectrum, among which the pediatric population represent one-quarter of the diagnosed individuals. Vast majority of these lesions are clinically silent but after the second decade of life, about 0.8% of the CCMs manifest with a hemorrhage rate per patient year although it is higher (3–4.5%) in patients with prior history of hemorrhage.[4,12,13] Dalyai *et al*. proposed that this rate can be as high as 7–8.9% per patient-year in a prospective cohort study.[5] In addition, a constellation of symptoms and signs including seizures, persistent headaches, and neurological deficits may be the first manifestation of CCM, respectively, in their order of prevalence.[9]

Results generated by studies vary greatly on the risk of subsequent hemorrhagic presentation of the CCMs, thus, the recommendation for surgical resection is unclear. This poses a great challenge on developing a risk assessment tool for selecting candidates for neurosurgery particularly among the familial CCM group. The size and multiplicity have not been incurred as the risk factors for hemorrhage rate[9] although the prior history of hemorrhage appear to be the most significant independent risk factor.[13] Similarly, the location of CCM, supratentorial (0.4% per patient-year)[16] versus infratentorial (3.8% per patient-year), and as reported by Kupersmith *et al*., the female gender (5.9%) as compared with men (3.3%) are thought to be risk factors for elevated risk of subsequent hemorrhage.[14]

CCMs in about 20% of cases (range 2–40%) are concurrently found with DVA in which instance they are named as mixed vascular malformations. Among the risk factors of *de novo* development of CCMs, nearly half of the sporadic lesions are associated with adjacent DVA. In contrast, the familial CCMs are found in the near absence of DVA in the vicinity.[2] However, the absence of DVA, multiplicity of the lesions aids the hypothesis that CCMs are familial in origin in our patient, which can neither be refuted nor accepted in the absence of genetic studies. Nonetheless, association between head trauma and hemorrhagic presentation of mixed vascular malformation has been reported by Fanous *et al*., especially in the pediatric age group.[7] The spontaneous nature of the massive bleed originating from presumably a sporadic form of CCM, is another unusual peculiarity of our case.

CONCLUSION

Although the significant majority of the CCMs may remain clinically silent and the studies conducted in the pediatric population show no exception, in a previously apparently well child who is presenting with a massive hemorrhagic stroke, the possibility of CCM should always be considered. Thorough family history, medical history, and neurological examination are pivotal in the fact finding process. Genetic screening of the first degree kindred of the affected patients if the family history is significant for similar events, sequential radiological follow-up and provident selection of the candidates for neurosurgery who are at risk of rebleeding are of paramount importance in the management of CCM with a prodigious outcome to minimize both the disease affected life years of the patients and health-related cost to the state.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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