Case report

Familial cerebral cavernousmalformations: A Case Report

ABSTRACT

Aims: Describe the main imaging findings of familial cerebral cavernous malformations
Presentation of case: This is the clinical case of a 68-year-old woman with a history of type 2 diabetes mellitus and long-standing systemic arterial hypertension. She presents to the neurology outpatient clinic reporting dizziness, temporal-spatial disorientation, episodes of amnesia, and chronic insomnia. Based on the clinical presentation, a diagnosis of cognitive impairment, likely of vascular origin. The MRI reveals multiple supratentorial and intraxial lesions with heterogeneous components, exhibiting a hypointense ring on T1 and T2-weighted sequences with images demonstrate a "blooming" effect on the T2*/GRE sequence, characteristic of cerebral cavernomas, displaying a "popcorn" appearance.
Discussion: In the presented case, a patient with multiple cerebral cavernomas showing classic features on MRI was discussed. Clinical manifestations commonly involving seizures, hemorrhage, and focal neurological deficits. Genetic factors play a role, with familial cases following an autosomal dominant inheritance pattern. Imaging studies, particularly MRI with susceptibility-weighted imaging, aid in diagnosis, revealing characteristic "popcorn" appearance lesions. Other differential diagnoses for cerebral hemorrhages should be considered, including vascular brain malformations and conditions like cerebral amyloid angiopathy and hypertensive encephalopathy. Management involves a multidisciplinary approach, with surgical resection being the gold standard for symptomatic cases.
Conclusion: Cerebral cavernous malformations (CCM) present varied symptoms, diagnosed through MRI showcasing characteristic appearances. Accurate determination of familial or sporadic origin is crucial for tailored treatment, involving medical therapy, surgical resection, or radiosurgery. Multidisciplinary collaboration among specialties ensures personalized management for patients with CCM.

Keywords: Cavernoma, familial cerebral cavernous malformations, hemorrhage, magnetic resonance imaging, cerebral vascular anomalies.

1. INTRODUCTION

Within cerebral vascular malformations, there are fourmaintypes: cavernousmalformations (cavernoma), arteriovenousmalformations, venousdevelopmentalanomalies, and capillarytelangiectasia, eachoneof thesepresentsitsownpathologicalfeatures[1][2][3]. Amongthese, arteriovenousmalformations and cavernous cerebral malformations are themostcommon, with a prevalence of cavernomasestimated at 0.5 to 0.7% of thepopulation [1][4].

Cerebral cavernousmalformations (CCM) are intracranialflowlesionshistologicallycharacterizedbyabnormallydilatedendothelialchannels (known as caverns), with a single endotheliallayerlackingmature vascular wallcharacteristics,

leading to increasedpermeabilitypredisposing to focal hemorrhages and variousneurologicalmanifestations[5][6].

Patientswith cerebral cavernomatosis can be classifiedinto 2 groups:
1. Familialform: consideredwhenthereis more thanoneaffected individual in thefamilyor a single individual withmultiplelesions (multiple cavernomatosis).
2. Sporadicform: characterizedby a single cavernousmalformation and oftenassociatedwith a developmentalvenousanomaly[4][7].

2. PRESENTATION OF CASE

This is the clinical case of a 68-year-old female patient known to have type 2 diabetes mellitus and long-standing systemic arterial hypertension under treatment. In her family history, it is noted that she has a son with similar symptoms. With no other significant pathological or surgical history.
She presents to the neurology outpatient clinic of the General Hospital of Morelia with complaints of dizziness, temporal-spatial disorientation, episodes of amnesia, and chronic insomnia. Physical examination does not reveal significant findings.

Laboratory studies, including complete blood count and blood chemistry, are unremarkable. Given the clinical presentation, a diagnosis of cognitive impairment with amnestic features, likely of vascular origin, is made, prompting a request for a simple brain magnetic resonance imaging (MRI).

MRI images reveal multiple supratentorial and intraxial lesions with heterogeneous components withreticulatedmixed–signalintensitycoreswith a hypointenserim on T1 and T2-weighted sequences (Figure 1) with increased signal intensity on FLAIR sequence suggestive of vasogenic edema (Figure 2). Additionally, the images display a "blooming" effect on the T2*/GRE sequence (Figure 3), characteristic of cerebral cavernomas, with a "popcorn" appearance, and evidence of subarachnoid hemorrhages on the convexity.

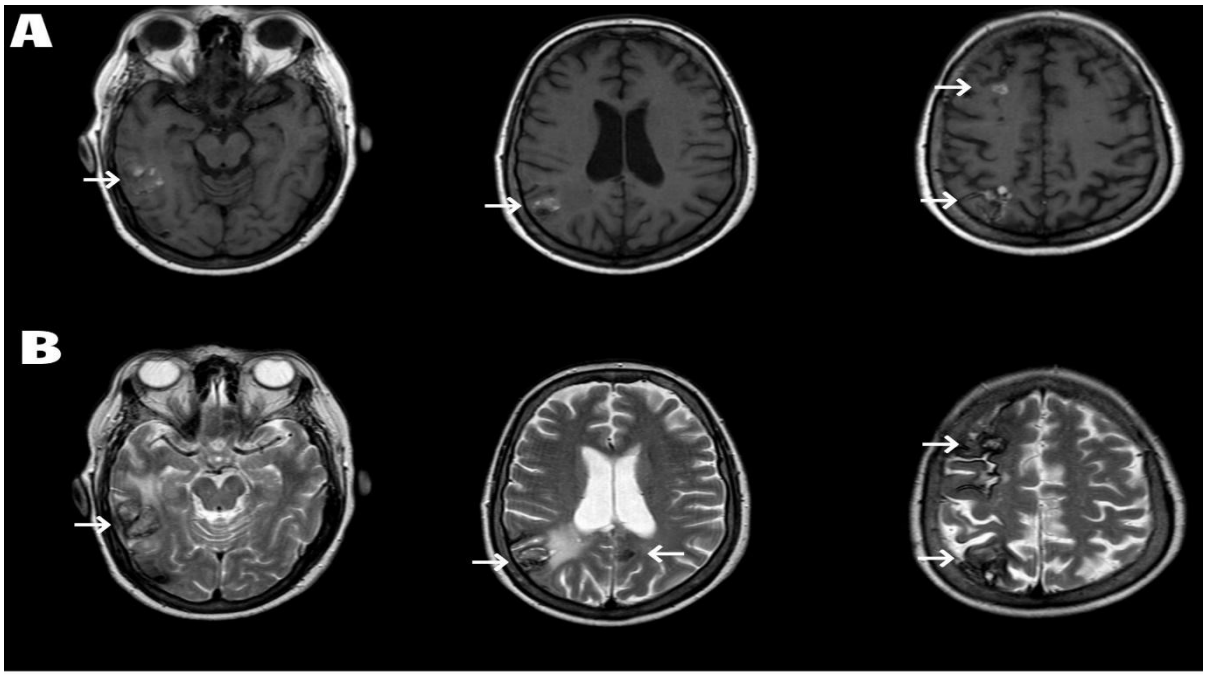

Fig. 1. MRI images axial T1 (a) and T2 (b) sequence revealing multiple heterogeneous signal intensity lesions (white arrows),with a hypointense rim.

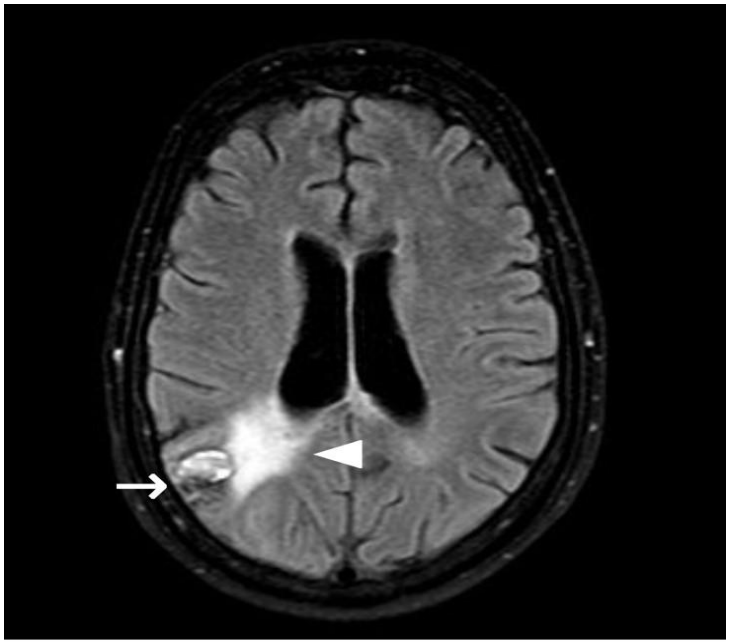

Fig. 2. MRI images in axial FLAIR sequence showing vasogenic edema (arrowhead) adjacent to the cavernoma (white arrow).

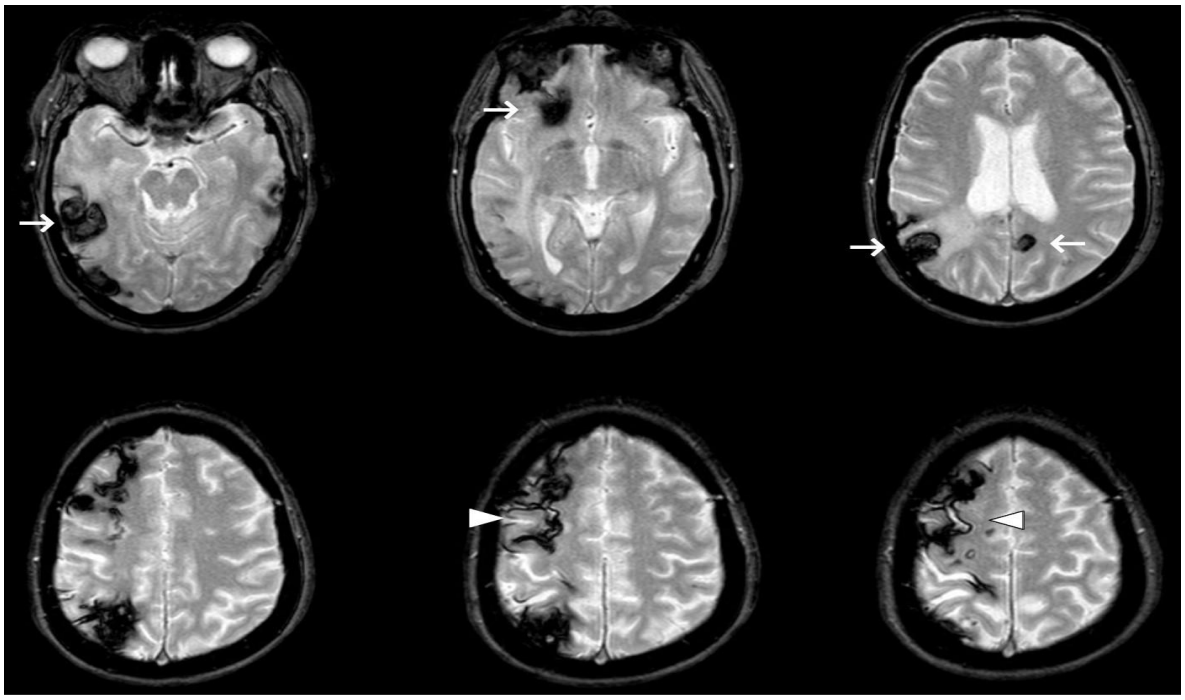

Fig. 3. MRI images in axial T2*/GRE sequence demonstrating multiple caverns (white arrows), with heterogeneous signal intensity showing "blooming" effect and, associated with subarachnoid hemorrhages of the convexity (white arrowhead) .

3. DISCUSSION

In the previous case, we presented a patient with multiple cerebral cavernomas exhibiting classic features on magnetic resonance imaging (MRI). Clinical presentation typically occurs between the 2nd and 5th decades of life, with an average age of onset around 30 years [5][8]. The most common clinical manifestations include seizures (20-40%), hemorrhage (30-40%), and focal neurological deficits (25-30%), with less frequent symptoms such as chronic headache (10-30%). Additionally, systemic vascular lesions like hepatic hemangiomas, vertebral angiomas, renal angiomas, and cutaneous capillary malformations may be present [8]. Despite this, up to 25-50% of cases remain asymptomatic, with the condition being incidentally discovered on MRI[5].

Familial multiple cerebral cavernomatosis follows an autosomal dominant inheritance pattern with incomplete clinical and neuroradiological penetrance. The three most commonly affected genes are CCM1/KRIT1, CCM2/MGC4607, and CCM3/PDCD10, which are evaluated in specific molecular genetic testing [8][9]. However, in symptomatic patients with multiple cerebral cavernomas like our case, genetic screening may not provide significant utility for clinical management [8].

Imaging studies for evaluation typically include computed tomography (CT) and MRI, with the latter being more precise for cerebrovascular pathology. The use of 3T MRI with susceptibility-weighted imaging (SWI) is recommended over gradient-echo (T2*/GRE) or T2 fast spin echo (FSE)sequences, as it can detect a higher number of lesions, especially in familial cases [5][7].

Cerebral cavernous malformations can be classified into different types based onpathological and imaging features, according to the Zabramski classification where type 2

lesions are the most characteristic of the FCCM [8]. On CT, these lesions appear as poorly defined with calcifications. MRI typically reveals the "popcorn" appearance, demonstrating caverns with heterogeneous signal due to blood in various stages, calcification, and a hemosiderin ring. T1-weighted sequences show a mixed signal core, T2-weighted sequences show a reticulated mixed signal core with a hypointense rim (hemosiderin ring), and T2*/GRE sequences demonstrate the "blooming" effect of hemosiderin, increasing sensitivity for cavernoma visualization [5]. And the use of SWI sequences demonstrate the number of lesions 1.7 higher than that seen in T2*/GRE and 8 times higher than that in T2 FSE images [10].

Despitetheimagingfeaturesof the FCCM,other causes of cerebral haemorrhages are to be considered as othertypes of vascular brainmalformationsconsist of capillarytelangiectasias, aneurysms, and arteriovenousmalformations.
Sporadic cerebral cavernousmalformations (SCCM**),**istypicallycharacterizedby a single cavernousmalformation and oftenassociatedwith a developmentalvenousanomaly (DVA); CCM can occur in thesporadicform, butthey are alwayssituatedaroundornear a DVA. Some series indicatethat up to 30% of sporadicCCMs are associatedwith a DVA. In a studyusing 7 Tesla MRI imaging, 100% of individualswithsporadicCCMswerefound to haveabnormalvenous output fromthecavernousmalformation. Of note, DVAs are rarelyseen in individualswith FCCM [7][11].
Anotherconditionslikecerebral amyloidangiopathy, numeroussmallfocimayhave a similar imagingappearance, with a predilection, however, fortheperipheral subcortical whitematter. Theremayalso be a history of prior (larger) lobar haemorrhageor superficial siderosis. (Chronic) hypertensiveencephalopathy has a predilectionfortheregion of the basal ganglia.And in diffuseaxonalinjury, there is a history of severe trauma, and thelesionshave a typicaldistribution at thebordersbetweenthe cortical grey matter and theunderlyingwhitematter[12].

Management of cerebral cavernous malformations involves a multidisciplinary approach. depending on whether the patient is asymptomatic or presenting with symptoms [7]. Medical management withtheaim of reducingtherisk of hemorrhageis based on the use of of statin, beta-blocker, and/orantithromboticmedication. In a studypatientswith FCCM present a probability of rehemorrhageduring a 5-year follow-up (FU) similar to that in patientswithsporadic CCM. Additionally, althoughtherelationshipwasnotsignificant, theynoted a tendencytoward a decreasedrisk of rebleeding in patientswithantithrombotic and statinintakeduring FU [13].
Surgical resection is considered the gold standard of interventional treatment, with common indications including first hemorrhage with accessible cavernomas, recurrent hemorrhage, intractable seizures, or mass effect with declining neurological function [7][14]. Radiosurgery is an option for surgically inaccessible lesions with a high risk of bleeding. In areas where traditional surgery or radiosurgery is challenging, minimally invasive techniques such as stereotactic laser ablation have been implemented, showing reduction in lesion size without neurological sequelae [14].

4. CONCLUSION

Cerebral cavernous malformations (CCM) present a wide range of symptoms, including seizures, focal neurological deficits, and hemorrhages, with the possibility that some patients may remain asymptomatic. The diagnosis of FCCM is based on imaging studies, with magnetic resonance imaging (MRI) being the preferred method for evaluation. The characteristic "popcorn" appearance on T2*/GRE or SWI sequences is typical of cerebral cavernomas. Determining whether the FCCM is familial or sporadic is crucial for treatment planning and may require specific genetic evaluation. In terms of management, therapeutic

options include symptomatic medical therapy, surgical resection, and radiosurgery, with the choice depending on the location and number of lesions, as well as the patient's symptoms. Multidisciplinary collaboration among neurology, neuroradiology, neurosurgery, and rehabilitation is essential for comprehensive and personalized management of patients with FCCM.

CONSENT.

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

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