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Research

Comprehensive Review of Cranial Cavernous Malformations: Results of a Single-center Study of 31 Cases

Kraniyal Kavernöz Malformasyonlar Üzerine Kapsamlı Bir İnceleme: 31 Olguluk Tek Merkezli Bir Çalışmanın Sonuçları

Buruç Erkan[1], Suat Demir[1], Ebubekir Akpınar[1], Tuba Özge Karaçoban[1], Yusuf Kılıç[2], Ozan Barut[3], Ozan Haşimoğlu[1], Musa Çırak[4], Bekir Tuğcu[1]

[1]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Neurosurgery, İstanbul, Türkiye

[2]Bulanık State Hospital, Clinic of Neurosurgery, Muş, Türkiye

[3]Bingöl State Hospital, Clinic of Neurosurgery, Bingöl, Türkiye

[4]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Neurosurgery, İstanbul, Türkiye

ABSTRACT

Objective: To evaluate the demographic, clinical, radiological features, and surgical outcomes of 31 patients who underwent surgery for cranial cavernous malformations (CCM).

Methods: A retrospective analysis was conducted on 31 patients who underwent CCM between July 2020 and January 2024. Data included demographic and clinical, radiological, intraoperative, and histopathological findings, and postoperative complications. Detailed neurological examinations were performed before and after surgery. All patients underwent preoperative computed tomography and magnetic resonance imaging (MRI), and the lesions were evaluated using the Zabramski classification. Surgeries aimed at total resection using neuronavigation, intraoperative MRI, and ultrasonography when needed. The average follow-up duration was 25.3 months.

Results: Thirty-three transcranial microsurgical excisions were performed in 31 patients (48% male, 52% female; mean age 30.8 years). Lesions were most commonly parietal (39%) and frontal (26%). Clinical findings included epilepsy (62%), headache (20%), and focal neurological deficits (6%). According to Zabramski, 42% were type I, 52% were type II, and 6% were type III. Total excision was achieved in 94% of the patients, with 6% requiring a second operation. Postoperative seizures were absent in 74% of patients with epilepsy. The average length of hospital stay was 5.7 days, with no permanent neurological deterioration or mortality.

Conclusion: Surgical resection is effective for treating symptomatic CCM. Total resection cases should be closely monitored due to the risk of recurrence. A conservative approach is recommended for asymptomatic, deep-seated, or eloquent lesions, and radiosurgery is considered for high surgical risk cases. Multidisciplinary and personalized treatment protocols can improve outcomes in patients with CCM.

Keywords: Cavernoma, cavernous angioma, cavernous hemangioma, surgery, vascular malformation

ÖZ

Amaç: Bu çalışmada, kraniyal kavernöz malformasyon (CCM) nedeniyle opere edilen 31 hastanın demografik, klinik, radyolojik özelliklerini ve cerrahi sonuçlarını değerlendirmek amaçlanmıştır.

Gereç ve Yöntem: Temmuz 2020 ve Ocak 2024 arasında CCM nedeniyle ameliyat edilen 31 hastanın yaş, cinsiyet, semptomlar, nörolojik bulgular, radyolojik veriler, intraoperatif ve histopatolojik bulgular, postoperatif komplikasyonlar ve takip sonuçları retrospektif olarak incelendi. Tüm hastalara preoperatif bilgisayarlı tomografi ve manyetik rezonans görüntüleme (MRG) yapıldı; lezyonlar Zabramski sınıflamasına göre değerlendirildi. Cerrahiler total rezeksiyon hedeflenerek yapıldı ve bazı olgularda nöronavigasyon, intraoperatif MRG ve ultrasonografi gibi yardımcı teknikler kullanıldı. Ortalama takip süresi 25,3 aydı.

Bulgular: Otuz bir hastaya 33 transkraniyal mikrocerrahi eksizyon uygulandı. Hastaların %48'i erkek, %52'si kadın olup, yaş ortalaması 30,8 idi. Lezyonlar en sık pariyetal (%39) ve frontal (%26) bölgelerdeydi. Klinik bulgular en sık epilepsi (%62), baş ağrısı (%20), fokal nörolojik defisit (%6) idi. Zabramski sınıflamasına göre %42 tip I, %52 tip II, %6 tip III olarak değerlendirildi. Yirmi dokuz hastada (%94) total eksizyon sağlandı.

Address for Correspondence: Buruç Erkan, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Neurosurgery, İstanbul, Türkiye

Phone: +90 507 992 33 34 E-mail: burucerkan@hotmail.com ORCID ID: orcid.org/0000-0001-8586-0613

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ÖZ

Epilepsi hastalarının %74'ünde postoperatif nöbet görülmedi. Hastanede yatış süresi ortalama 5,7 gündü. Kalıcı nörolojik kötüleşme veya eksitus görülmedi.

Sonuç: Semptomatik CCM tedavisinde cerrahi rezeksiyon etkilidir. Total çıkarılamayan olgular yakın takip edilmelidir. Asemptomatik, derin veya eloquent bölge lezyonları için konservatif yaklaşım önerilirken, yüksek cerrahi risk durumlarında radyocerrahi düşünülebilir. Multidisipliner yaklaşımlar ve kişiye özel tedavi protokolleri, CCM hastalarının yaşam kalitesini ve prognozunu iyileştirebilir.

Anahtar Kelimeler: Kavernoma, kavernöz anjiyoma, kavernöz hemanjiyoma, cerrahi, vasküler malformasyon

INTRODUCTION

Cavernous malformations, also known as cavernoma and cavernous hemangiomas, are well-demarcated, mulberry-like hamartomas typically located within cerebral hemispheres. These lesions lack intervening neural tissue and lack arteries and draining veins (1). The prevalence of cranial cavernous malformations (CCM) in the general population ranges from 0.4% to 0.8%, accounting for 10-25% of all vascular malformations (2).

Clinically, CCMs can present with hemorrhage, epilepsy, headache, focal neurological deficits, and, rarely, mass effects. However, 20-50% of cases remain asymptomatic and are incidentally detected during imaging studies. The symptoms and clinical findings vary according to the presence of hemorrhage, lesion size, and location. Although CCMs can occur in any part of the central nervous system, 70-80% are found supratentorially (3). These malformations can occur sporadically, be familial, or be induced by radiation. Familial forms typically present with multiple CCMs, whereas sporadic cases usually exhibit a single CCM (4). The standard treatment for CCMs is total resection via microsurgery; stereotactic radiosurgery is considered for cases unsuitable for surgery, and observation is preferred for asymptomatic cases (3).

The current study aimed to retrospectively evaluate the characteristics and surgical outcomes of 31 patients who underwent surgery for CCM.

METHODS

In this study, we conducted a retrospective analysis of 31 patients who underwent surgery for CCM at our clinic between July 2020 and January 2024, with complete medical records available. Patients were followed for an average duration of 25.3 months (range: 3-47 months).

Patients were assessed according to demographic, clinical, and radiological characteristics. Data collected included age, sex, family history, presenting symptoms, neurological examination findings, preoperative and postoperative radiological findings, intraoperative findings, histopathological features, postoperative complications, and follow-up outcomes. Detailed neurological examinations were performed during preoperative and postoperative follow-ups, incorporating the Glasgow Coma scale, cranial nerve examinations, motor and sensory examinations, and the presence and frequency of seizures. All patients underwent preoperative cranial computed tomography (CT) and magnetic resonance imaging (MRI). Functional MRI was performed for CCMs located in eloquent cortical areas, such as the motor and speech regions (Figure 1). Radiological evaluations on CT included the presence of acute hemorrhage or calcification, whereas MRI assessments were based on the Zabramski classification (4), lesion size, and location (Figure 2).

All patients underwent their initial surgery. Surgical procedures aimed at total resection, including the hemosiderin ring, were performed under general anesthesia with antibiotic prophylaxis. Depending on lesion location and size, adjunctive techniques, such as neuronavigation, intraoperative MRI, and ultrasonography, were utilized in select cases. All surgical specimens underwent histopathological examination and were confirmed to be consistent with CCM. In the postoperative period, patients were evaluated with MRI to assess for residual lesions or hemorrhage.

This study was approved by University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (decision no: 91, date: 14.02.2024), and all data were reviewed retrospectively.

Statistical Analysis

Statistical analyses were performed using SPSS software.

RESULTS

In total, 33 transcranial microsurgical excision procedures were performed in 31 patients with CCM. Fifteen patients (48%) were male, with a mean age of 30.8 years (range: 7-68 years). The most common presenting symptom was seizures (62%), with an average duration of symptom onset of 26.6 months. Lesions were most frequently located

in the parietal region (39%). In 3 patients (9.7%), cranial CT findings were normal, while 5 patients (16.1%) had acute hemorrhage, and 9 patients (29%) had calcifications (Figure 3A, B). Preoperative digital subtraction angiography was performed in 3 patients, all of which were negative. According to the Zabramski classification, the most common type was type II CCM (52%). Patient characteristics, clinical findings, lesion locations, and radiological features are summarized in Table 1.

Total excision was achieved in 29 patients (94%), while 2 patients (6%) with subtotal excision experienced hemorrhage at 4 and 6 months postoperatively, requiring reoperation. Total excision of the residual CCM was achieved in the second operation. Three patients (2 parietal, 1 temporal) developed facial paralysis in the postoperative period, which resolved during follow-up after discharge. One patient with a left parietal lesion developed a right lower extremity motor deficit (2/5 muscle strength) postoperatively, which resolved after 2 days. Another patient with a parietal lesion required evacuation of an epidural hematoma on the third postoperative day because of the development of a hematoma during craniotomy, but no permanent neurological deficit occurred. In a patient with an intraorbital lesion (Figure 3C, D), postoperative improvement in proptosis was observed. In a patient with a brainstem lesion case (Figure 3E, F), sixth cranial nerve paralysis persisted postoperatively, as did right hemiparesis in a patient with a parietal lesion. No new deficits were observed in other patients during the postoperative period. Among the 19 patients with drug-resistant epilepsy, 14 (74%) experienced no seizures postoperatively and 5 (26%) experienced a reduction in seizure frequency. The average length of hospital stay was 5.7 days. No patient experienced

Table 1. Patient characteristics, clinical findings, and radiological features

Characteristics	Number of patients (%)
Gender	
Male	15 (48%)
Female	16 (52%)
Clinical findings	
Seizure	19 (62%)
Headache	6 (20%)
FND	2 (6%)
Syncope	2 (6%)
Sixth CN palsy	1 (3%)
Proptosis	1 (3%)
Lesion localization	
Frontal	7 (23%)
Parietal	12 (39%)
Temporal	5 (16%)
Occipital	2 (6.5%)
Third ventricle	2 (6.5%)
Pons	1 (3%)
Intraorbital	1 (3%)
Multiple (frontal and parietal)	1 (3%)
Zabramski classification	
Type I	13 (42%)
Type II	16 (52%)
Type III	2 (6%)

CN: Cranial nerve, FND: Focal neurological deficit

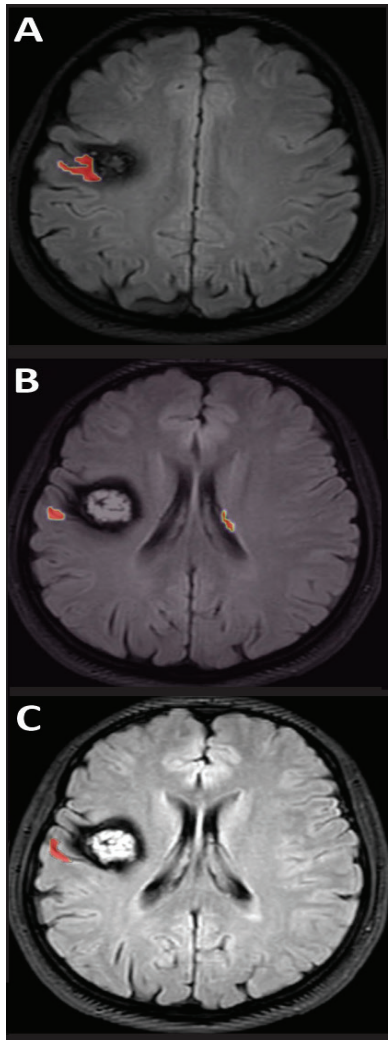

Figure 1. A-C. In case 29 from Table 2, preoperative functional magnetic resonance imaging axial sections revealed a lesion measuring 22x16x19 mm. The lesion was located less than 10 mm from the speech center and more than 10 mm from the motor centers for the left hand and left foot, respectively

permanent neurological deterioration or mortality. The demographic and clinical characteristics, radiological data, and surgical outcomes of the patients are presented in Table 2.

DISCUSSION

CCMs are one of the four principal types of vascular malformations in the central nervous system, along with developmental venous anomalies (DVA), arteriovenous malformations, and capillary telangiectasias. They are the second most common vascular malformations associated with hemorrhage (5). The exact prevalence of CCMs is not well-defined due to their often asymptomatic nature; however, they are reported to occur in 0.4-0.8% of the general population (2). While CCMs were initially classified as rare, their detection has increased with the widespread use of MRI in neuroimaging studies (6). CCMs are dynamic lesions that can develop *de novo*, change in size, or remain stable over time (7). Patients are typically diagnosed between the second and fourth decades of life. The incidence is nearly equal between men and women; however, men aged 30 years tend to be more symptomatic, whereas women are more symptomatic between the ages of 30 and 60 years (1). In our study, the male-to-female ratio was nearly equal, with a mean age of 29.5 years for men and 32 years for women.

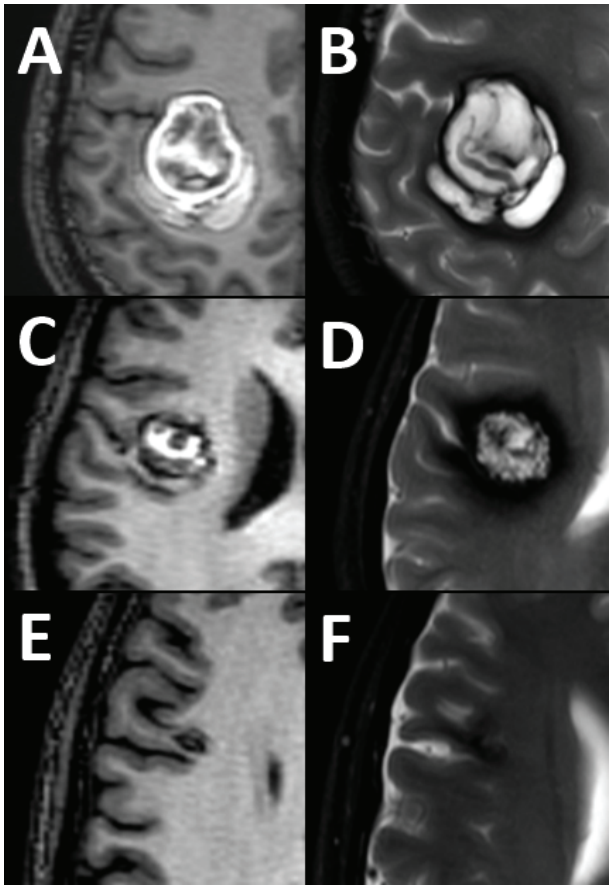

Figure 2. A, B. In case 3 from Table 2, preoperative magnetic resonance imaging axial sections, respectively in T1- and T2-weighted images, demonstrate a hyperintense type I cavernous malformation measuring 35x29x31 mm located in the right parietal region. **C, D**. In case 29 from Table 2, preoperative magnetic resonance imaging axial sections, respectively in T1- and T2-weighted images, depict a heterogeneously intense type II cavernous malformation with a "popcorn" appearance, measuring 22x16x19 mm in the right frontal region. **E, F.** In case 14, as shown in Table 2, preoperative magnetic resonance imaging axial sections, respectively, in T1- and T2-weighted images, revealed a hypointense type III cavernous malformation measuring 12x8x7 mm located in the right frontal region

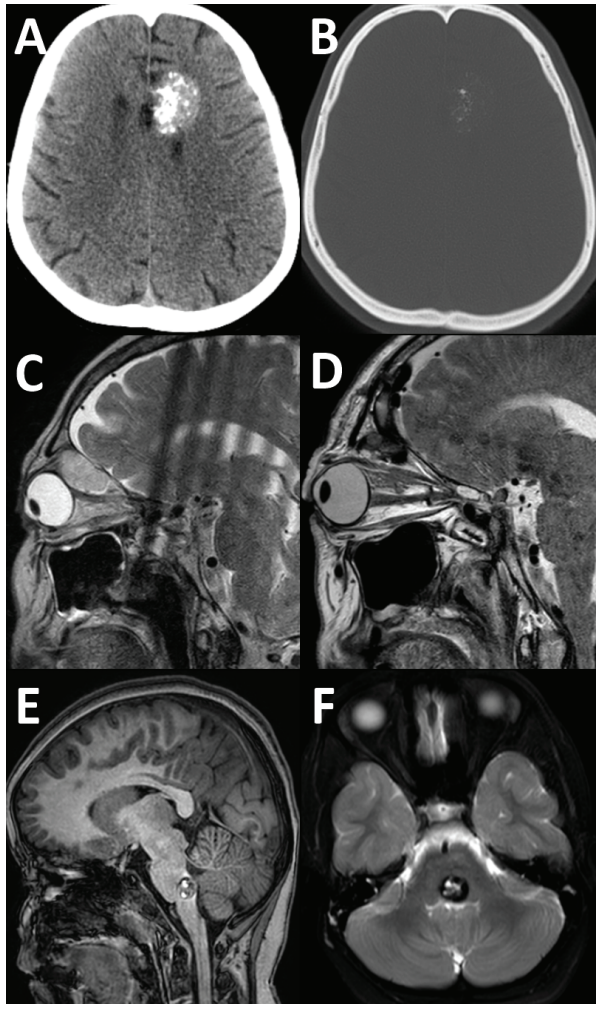

Figure 3. A, B. In case 5 from Table 2, preoperative computed tomography axial sections, respectively in parenchymal and bone window images, show a calcified lesion measuring 24x29x30 mm located subependymally in the right cerebral hemisphere's frontal lobe. **C, D.** In case 27 in Table 2, preoperative and postoperative T2-weighted magnetic resonance imaging sagittal sections, respectively, demonstrate a lesion measuring 25x18x12 mm with cerebrospinal fluid-equivalent hyperintensity that displaces the superior orbital muscle group laterally, causing exophthalmos, and show complete excision of the lesion. **E, F**. In case 25 from Table 2, preoperative T1-weighted sagittal and T2-weighted axial magnetic resonance imaging, respectively, demonstrate a lesion measuring 13x11x10 mm located posterior to the pontobulbar junction in the brainstem

Table 2. Demographics, clinical, and radiological characteristics and surgical outcomes of patients with cranial cavernous malformations

Patient	Gender /age (years)	Localization	Symptom	Lesion size (mm)	Pre/postoperative GCS	Zabramski classification	Preoperative acute hemorrhage	Calcification on CT	Resection	Follow-up (month)	Outcome
1	F/27	Occipital	Seizure	12x13x13	15/15	Type I	Yes	Yes	Total	47	Seizure control is achieved
2	F/32	Parietal	Seizure	18x13x19	15/15	Type II	No	Yes	Total	46	Seizure control is achieved
3	M/36	Parietal	Paresis	35x29x31	15/15	Type I	No	Yes	Total	43	Operated because of postoperative epidural hematoma. Paresis improved
4	M/22	Parietal	Seizure	15x12x14	15/15	Type I	No	Yes	Total	42	Seizures reduced
5	F/55	Frontal	Headache	24x29x30	15/15	Type II	No	Yes	Total	40	Stable
6	M/32	Parietal	Seizure	8x11x10	15/15	Type II	No	No	Total	37	Seizure control is achieved
7	M/39	Parietal	Seizure	25x26x22	15/15	Type I	Yes	No	Total	36	Seizure control is achieved
8	M/30	Frontal	Seizure	8x9x11	15/15	Type II	No	No	Total	35	Seizure control is achieved
9	M/17	Parietal	Seizure	10x10x8	15/15	Type II	No	Yes	Total	35	Seizures reduced
10	F/15	Temporal	Headache	14x7x9	15/15	Type II	No	No	Total	34	Stable
11	F/25	Parietal	Seizure	19x8x11	15/15	Type II	No	No	Total	33	Postoperative temporary facial paralysis resulting in seizure control
12	F/36	Temporal	Seizure	14x12x16	15/15	Type II	No	No	Total	32	Seizures reduced
13	F/35	Parietal	Headache	25x19x23	15/15	Type I	No	No	Total	30	Postoperative right lower extremity paresis (2/5) developed and resolved after 2 days
14	M/35	Frontal	Seizure	12x8x7	15/15	Type III	No	No	Total	29	Seizure control is achieved
15	M/35	Occipital	Seizure	13x12x10	15/15	Type II	No	No	Total	27	Seizure control is achieved
16	M/41	Temporal	Headache	17x13x7	15/15	Type I	No	No	Total	27	Stable
17	F/26	Parietal	Paresis, paresthesia	25x20x21	15/15	Type I	No	No	Total	26	Paresis persists
18	F/26	Frontal	Seizure	7x5x6	15/15	Type III	No	No	Total	25	Seizures reduced
19	M/13	Parietal	Seizure	43x27x27	15/15	Type I	No	No	Subtotal	24	Re-operation due to residual lesion six months later, seizure control was achieved

Table 2. Continued

Patient	Gender /age (years)	Localization	Symptom	Lesion size (mm)	Pre/postoperative GCS	Zabramski classification	Preoperative acute hemorrhage	Calcification on CT	Resection	Follow-up (month)	Outcome
20	M/34	Third ventricle	Syncope	13x16x15	14/15	Type I	Yes	No	Total	19	Stable
21	F/20	Temporal	Seizure	17x13x18	15/15	Type I	Yes	Yes	Subtotal	19	Reoperation due to residual lesion after 4 months, seizures were reduced
22	M/11	Parietal	Seizure	16x11x13	15/15	Type II	No	No	Total	18	Seizure control is achieved
23	F/41	Frontal	Seizure	16x13x15	15/15	Type I	No	No	Total	17	Seizure control is achieved
24	F/21	Frontal	Headache	15x12x13	15/15	Type II	No	No	Total	17	Stable
25	F/7	Pons	Sixth CN paralysis	13x11x10	15/15	Type II	No	No	Total	17	The sixth CN palsy persists
26	M/15	Frontal and posterior	Seizure	25x20x20	15/15	Type I	Yes	Yes	Total	11	Seizure control is achieved
27	F/68	Intraorbital	Proptosis	25x18x12	15/15	Type II	No	No	Total	6	Proptosis improved
28	M/31	Frontal	Seizure	13x15x10	15/15	Type II	No	No	Total	5	Seizure control is achieved
29	F/29	Parietal	Seizure	22x16x19	15/15	Type II	No	Yes	Total	3	Postoperative temporary facial paralysis, seizure control, improved speech
30	F/50	Temporal	Syncope	7x6x9	15/15	Type II	No	No	Total	3	Temporary facial paralysis
31	M/52	Third ventricle	Headache	14x17x12	15/15	Type I	No	No	Total	3	Stable

CN: Cranial nerve, CT: Computed tomography, F: Female, GCS: Glasgow Coma scale, M: Male

The majority of CCMs are sporadic (approximately 70-90%), but familial cases are not uncommon (10-30%) (1). Sporadic CCMs usually present as a single lesion, and 24-86% are reported to occur in association with DVAs (8). Familial CCMs exhibit autosomal dominant inheritance involving mutations in one of the following *CCM* genes: *CCM1 (KRIT1)* on chromosome 7q, *CCM2 (MGC4607)* on chromosome 7p, and *CCM3 (PDCD10)* on chromosome 3p (3). These genes encode proteins that interact at cellular junctions and in the endothelial cell cytoskeleton. The absence or dysfunction of these proteins leads to impaired endothelial cell junctions and increased vascular permeability (9). Among these, the *CCM3* gene is associated with a higher risk of hemorrhage and earlier disease onset (10).

Radiation-induced CCMs can emerge 5-20 years after radiation therapy. Advanced age and higher radiation doses during treatment are associated with a shorter latency period for CCM development. Radiation may induce CCM formation by initiating neoangiogenesis through increased levels of vascular endothelial growth factor and other vasculogenic factors or by directly causing DNA damage. Radiation-induced CCMs tend to occur at a younger age compared with non-radiation-induced CCMs, with a higher likelihood of multiple lesions, symptomatic presentation, and increased hemorrhage risk (11).

CCMs are macroscopically well-defined soft, dark red, or purple lesions. Due to very slow blood flow, thrombosis and calcification are common. Histologically, they are characterized by enlarged capillary vessels lined with a thin and weak epithelium and lacking elastic fibers and muscle layers, predisposing them to hemorrhage (6). The primary

histological feature distinguishing CCMs from capillary telangiectasias is the absence of intervening cerebral tissue between the lesions. Surrounding tissues typically exhibit gliosis and hemosiderin deposition (1).

CCMs can affect any part of the brain, and their clinical manifestations vary according to location. In symptomatic patients, the most common presentations include seizures (40-70%), focal neurological deficits without hemorrhage (25-50%), hemorrhage (25-50%), and non-specific headaches (10-30%) (12). Patients with at least one CCM and evidence of a seizure onset zone near the CCM are classified as having "definite CCM-related epilepsy" (13). Recurrent microhemorrhages around CCMs, resulting in perilesional gliosis and inflammation-both of which are epileptogenic-are believed to cause seizures in patients with CCM. These patients have a high risk of developing epilepsy after their first seizure. The risk of developing seizures after an incidental CCM diagnosis is low at 0.9% per patient-year, whereas the recurrence rate of seizures is 5.5% per patient-year in patients with seizure (14). The initiation of antiepileptic treatment should be considered for the first seizure attributed to CCM (15). Post-surgery, 75-81% of epilepsy cases achieve seizure freedom. Patients who underwent total resection had a 36.6-fold higher likelihood of achieving seizure control. Factors that increase the likelihood of successful epilepsy treatment include recent seizure onset (within the past year), CCM size 1.5 cm, and the presence of a single CCM (16). In our series, seizures were the most common symptom (62%). Postoperatively, 74% of patients experienced no further seizures, of whom 57% had lesions larger than 1.5 cm and 50% had a seizure history of more than 1 year. The remaining 26% experienced a reduction in seizure frequency and number.

The annual hemorrhage risk for patients without a history of hemorrhage is 0.7-1.1% per lesion, and it increases to 4.5% in those with a prior history (2). The hemorrhage risk depends on the location, size, presence of DVAs, and sex of the lesion. Deep-seated CCMs have a higher hemorrhage risk than superficial CCMs. The hemorrhage risk of infratentorial and supratentorial CCMs was 3.8% and 0.4%, respectively (17). Nikoubashman et al. (18) proposed a simple three-tier classification for evaluating the hemorrhage risk of CCMs in clinical practice: high risk (23.4%) if the CCM contains acute or subacute blood breakdown products; moderate risk (3.4%) if it lacks these products; and low risk (1.3%) for tiny lesions visible on T2 but barely or not at all visible on T1-weighted and T2-weighted images. Seizures and familial forms have been suggested as potential risk factors for hemorrhage, but there is insufficient evidence in the literature to support this hypothesis (19). The phenomenon of "temporal clustering," where untreated CCMs have a high initial re-hemorrhage rate that decreases 2-3 years after the previous hemorrhage, has been reported. This should be considered when determining appropriate treatment strategies for patients with CCM (12).

CCMs cannot be visualized on angiographic examination due to the lack of feeding arteries and draining veins. As a result, these lesions were historically referred to as "cryptic vascular malformations" or "angiographically occult vascular malformations" (1). Apart from detecting associated DVAs or capillary telangiectasias, angiography has limited diagnostic and therapeutic value for CCMs. In our series, digital subtraction angiography was performed preoperatively for differential diagnosis in three patients, all of whom had negative angiographic results. CT is not ideal for diagnosing CCMs, detecting only 30-50% of lesions (6). Non-calcified, non-hemorrhagic, and small CCMs may not be visible on CT. When visible, they may appear as hyperdense, calcified lesions or exhibit a mass effect (20). In our series, preoperative CT revealed calcifications in 29% of the patients, and lesions were not detected in 9.7%.

MRI is the most sensitive and specific imaging modality for diagnosing and monitoring CCMs, and it significantly outperforms CT (19). Hemoglobin breakdown products such as methemoglobin, hemosiderin, and ferritin allow CCMs to be visualized on MRI. According to the Zabramski classification, CCMs can be categorized into four types based on MRI characteristics. Type I CCMs appear hyperintense on T1 and T2 sequences because of subacute hemorrhage content characterized by a dense hemosiderin core. Type II CCMs exhibit a "popcorn" appearance with heterogeneous intensity on the T1 and T2 sequences. They are surrounded by gliotic tissue and contain loculated hemorrhage areas. Type III lesions are seen in familial forms and appear isointense on T1, T2, and gradient echo sequences due to chronic hemorrhage. Type IV lesions resembling capillary telangiectasias appear as small, punctate hypointense signals on gradient echo and susceptibility-weighted imaging sequences (4). In our series, type II CCMs were the most common (52%), followed by type I CCMs (42%). Functional MRI measures changes in cerebral blood flow related to brain activity, which aids in the resection of CCMs located in eloquent areas without increasing morbidity (19). In our study, we utilized functional MRI to aid in the complete resection of lesions located in motor or speech areas, avoiding potential complications. Gadolinium-enhanced T1-weighted sequences rarely show enhancement and are primarily useful for evaluating associated DVAs or capillary telangiectasias and for differentiating hemorrhagic or calcified neoplasms,

particularly hemorrhagic metastases, oligodendrogliomas, and pleomorphic xanthoastrocytoma (15).

The definitive treatment for CCMs is total resection via microsurgery. For single asymptomatic CCMs located in accessible, non-eloquent regions, surgical resection may be considered to prevent future hemorrhage, especially given the high cost and time commitment of follow-up, or in patients requiring anticoagulant therapy. Additionally, surgical resection is recommended for persistent seizures, progressive neurological deficits, first-time severe hemorrhage in non-eloquent regions, or second-time hemorrhage in eloquent areas (15,19). The surgical approach should minimize damage to surrounding neural tissue while ensuring complete resection of the lesion, including the epileptogenic perilesional brain tissue, as partial resection is associated with a high risk of recurrence (21). The use of intraoperative neuromonitoring, ultrasound, navigation, and MRI has improved total resection rates and reduced surgical complications and risks (16). In our study, we used these adjunctive techniques in some cases to minimize complications and increase the total resection rate. Chang et al. (22) reported a total resection rate of 96.2%, 0% mortality, and 97.4% neurological improvement in a series of 79 patients with eloquent and deep-seated supratentorial CCMs. Rapid growth (43%), mass effect (71%), and extralesional hemorrhage (29%) are common in third ventricle CCMs, which can lead to hydrocephalus, visual disturbances, and endocrine and hypothalamic symptoms, necessitating surgical resection despite the challenges and risks associated with accessing and resecting this region (23). Surgical treatment may be considered for deep-seated CCMs in the thalamus and basal ganglia in the presence of recurrent hemorrhage or progressive neurological deficit. However, these surgeries carry significant risks, with long-term surgical morbidity and mortality rates of 10% and mortality at 1.9% (24). Brainstem CCMs pose greater challenges due to their proximity to nuclei, corticospinal and spinothalamic tracts, and the reticular formation; a comprehensive meta-analysis of 1,390 cases reported a mortality rate of 1.5% and a long-term deterioration rate of 16% for these surgeries (25). Our series reported a total resection rate of 94%; two patients (6%) underwent reoperation for residual lesions, achieving total resection in the second surgery. No patient experienced permanent neurological deterioration or mortality. Many sporadic CCMs are associated with DVAs. When resecting CCMs, it is crucial to preserve the DVA to avoid serious complications, such as edema, hemorrhage, and venous infarction. For incidentally discovered asymptomatic CCMs, particularly those in eloquent, deep, or brainstem regions, a conservative approach with annual MRI follow-up is recommended (15).

If CCMs are located in eloquent areas with an unacceptable surgical risk, radiosurgery may be considered. However, the disadvantage of this approach is that it takes 1-3 years to achieve full efficacy, during which the risk of hemorrhage persists (26). In a series of symptomatic CCMs treated with radiosurgery because of the impossibility of surgery, the risk of hemorrhage decreased from 32.5% in the first 2 years to 10.8% and then to 1.06% by the end of 2 years (27). On the other hand, the risk of hemorrhage in CCMs decreases significantly by itself 2 years after the first hemorrhage, and the positive radiosurgery results may reflect the natural course of these lesions. Additionally, permanent neurological deficits have been reported in 7.3-22.2% of cases following radiosurgery (28). The benefits of radiosurgery for the treatment of CCMs remain unproven and continue to be a topic of debate (19). In our series, 2 patients had a history of radiosurgery (one 4.5 years prior and the other 10 years prior), but no improvement in symptoms or lesion size was observed.

A phase 2 study involving the beta-blocker propranolol suggested that it might be beneficial in reducing the frequency of clinical events in symptomatic familial CCMs, but the study design was not sufficiently robust (29). Laboratory studies have shown a relationship between vitamin D deficiency and aggressive CCM behavior, but there is no evidence that vitamin D supplementation prevents CCM symptoms (30). Ongoing laboratory research aims to identify potential pharmacological targets to stabilize or prevent CCM formation. These treatments require careful clinical evaluation for safety and efficacy (15).

Our relatively small sample size and retrospective study design may limit the validity of our results. Additionally, the lack of a control group and the potential biases inherent in retrospective analyses restrict the generalizability of the findings. Future studies should involve larger, prospective cohorts.

CONCLUSION

Surgical resection remains the most effective treatment for symptomatic CCMs. Cases in which total resection is not achieved require close follow-up because of the high risk of recurrence. A conservative approach is recommended for asymptomatic lesions located in deep or eloquent regions, whereas radiosurgery may be considered in cases with high surgical risk. Multidisciplinary approaches and personalized treatment protocols can significantly improve the prognosis and quality of life of patients with CCM.

ETHICS

Ethics Committee Approval: This study was approved by University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (decision no: 91, date: 14.02.2024).

Informed Consent: Since this study is retrospective, patient consent is not required.

Authorship Contributions

Surgical and Medical Practices: B.E., E.A., O.H., B.T., Concept: B.E., S.D., O.B., O.H., B.T., Design: B.E., S.D., T.Ö.K., Y.K., M.Ç., Data Collection or Processing: S.D., T.Ö.K., Y.K., O.B., M.Ç., Analysis or Interpretation: B.E., E.A., Y.K., O.H., M.Ç., B.T., Literature Search: S.D., E.A., T.Ö.K., O.B., Writing: B.E., S.D., E.A., T.Ö.K., Y.K., O.B., O.H., M.Ç., B.T.

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REFERENCES

1. Zafar A, Fiani B, Hadi H, Arshad M, Cathel A, Naeem M, et al. Cerebral vascular malformations and their imaging modalities. Neurol Sci. 2020;41:2407-21.
2. Mouchtouris N, Chalouhi N, Chitale A, Starke RM, Tjoumakaris SI, Rosenwasser RH, et al. Management of cerebral cavernous malformations: from diagnosis to treatment. ScientificWorldJournal. 2015;2015:808314.
3. Dalyai RT, Ghobrial G, Awad I, Tjoumakaris S, Gonzalez LF, Dumont AS, et al. Management of incidental cavernous malformations: a review. Neurosurg Focus. 2011;31:E5.
4. Zabramski JM, Wascher TM, Spetzler RF, Johnson B, Golfinos J, Drayer BP, et al. The natural history of familial cavernous malformations: results of an ongoing study. J Neurosurg. 1994;80:422-32.
5. McCormick WF, Hardman JM, Boulter TR. Vascular malformations ("angiomas") of the brain, with special reference to those occurring in the posterior fossa. J Neurosurg. 1968;28:241-51.
6. Cortés Vela JJ, Concepción Aramendía L, Ballenilla Marco F, Gallego León JI, González-Spínola San Gil J. Cerebral cavernous malformations: spectrum of neuroradiological findings. Radiologia. 2012;54:401-9.
7. Clatterbuck RE, Moriarity JL, Elmaci I, Lee RR, Breiter SN, Rigamonti D. Dynamic nature of cavernous malformations: a prospective magnetic resonance imaging study with volumetric analysis. J Neurosurg. 2000;93:981-6.
8. Aboian MS, Daniels DJ, Rammos SK, Pozzati E, Lanzino G. The putative role of the venous system in the genesis of vascular malformations. Neurosurg Focus. 2009;27:E9.
9. Leblanc GG, Golanov E, Awad IA, Young WL; Biology of Vascular Malformations of the Brain NINDS Workshop Collaborators. Biology of vascular malformations of the brain. Stroke. 2009;40:e694-702.
10. Yadla S, Jabbour PM, Shenkar R, Shi C, Campbell PG, Awad IA. Cerebral cavernous malformations as a disease of vascular permeability: from bench to bedside with caution. Neurosurg Focus. 2010;29:E4.
11. Cutsforth-Gregory JK, Lanzino G, Link MJ, Brown RD Jr, Flemming KD. Characterization of radiation-induced cavernous malformations and comparison with a nonradiation cavernous malformation cohort. J Neurosurg. 2015;122:1214-22.
12. Zafar A, Quadri SA, Farooqui M, Ikram A, Robinson M, Hart BL, et al. Familial Cerebral Cavernous Malformations. Stroke. 2019;50:1294-301.
13. Rosenow F, Alonso-Vanegas MA, Baumgartner C, Blümcke I, Carreño M, Gizewski ER, et al. Cavernoma-related epilepsy: review and recommendations for management--report of the Surgical Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2013;54:2025-35.
14. Washington CW, McCoy KE, Zipfel GJ. Update on the natural history of cavernous malformations and factors predicting aggressive clinical presentation. Neurosurg Focus. 2010;29:E7.
15. Akers A, Al-Shahi Salman R, A Awad I, Dahlem K, Flemming K, Hart B, et al. Synopsis of Guidelines for the Clinical Management of Cerebral Cavernous Malformations: Consensus Recommendations Based on Systematic Literature Review by the Angioma Alliance Scientific Advisory Board Clinical Experts Panel. Neurosurgery. 2017;80:665-80.
16. Sommer B, Kasper BS, Coras R, Blumcke I, Hamer HM, Buchfelder M, et al. Surgical management of epilepsy due to cerebral cavernomas using neuronavigation and intraoperative MR imaging. Neurol Res. 2013;35:1076-83.
17. Porter PJ, Willinsky RA, Harper W, Wallace MC. Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. J Neurosurg. 1997;87:190-7.
18. Nikoubashman O, Di Rocco F, Davagnanam I, Mankad K, Zerah M, Wiesmann M. Prospective Hemorrhage Rates of Cerebral Cavernous Malformations in Children and Adolescents Based on MRI Appearance. AJNR Am J Neuroradiol. 2015;36:2177-83.
19. Chalouhi N, Dumont AS, Randazzo C, Tjoumakaris S, Gonzalez LF, Rosenwasser R, et al. Management of incidentally discovered intracranial vascular abnormalities. Neurosurg Focus. 2011;31:E1.
20. Liu XW, Wang SH, Chi ZF, Su LJ, Zhao XH, Wang SJ. The value of T(2) (*)-weighted gradient echo imaging for detection of familial cerebral cavernous malformation: A study of two families. Exp Ther Med. 2013;5:448-52.
21. Kim DS, Park YG, Choi JU, Chung SS, Lee KC. An analysis of the natural history of cavernous malformations. Surg Neurol. 1997;48:9-17.
22. Chang EF, Gabriel RA, Potts MB, Berger MS, Lawton MT. Supratentorial cavernous malformations in eloquent and deep locations: surgical approaches and outcomes. Clinical article. J Neurosurg. 2011;114:814-27.
23. Katayama Y, Tsubokawa T, Maeda T, Yamamoto T. Surgical management of cavernous malformations of the third ventricle. J Neurosurg. 1994;80:64-72.
24. Gross BA, Batjer HH, Awad IA, Bendok BR. Cavernous malformations of the basal ganglia and thalamus. Neurosurgery. 2009;65:7-18.
25. Gross BA, Batjer HH, Awad IA, Bendok BR, Du R. Brainstem cavernous malformations: 1390 surgical cases from the literature. World Neurosurg. 2013;80:89-93.
26. Schneider BF, Eberhard DA, Steiner LE. Histopathology of arteriovenous malformations after gamma knife radiosurgery. J Neurosurg. 1997;87:352-7.
27. Lunsford LD, Khan AA, Niranjan A, Kano H, Flickinger JC, Kondziolka D. Stereotactic radiosurgery for symptomatic solitary cerebral cavernous malformations considered high risk for resection. J Neurosurg. 2010;113:23-9.

28. Lee SH, Choi HJ, Shin HS, Choi SK, Oh IH, Lim YJ. Gamma Knife radiosurgery for brainstem cavernous malformations: should a patient wait for the rebleed? Acta Neurochir (Wien). 2014;156:1937-46.
29. Lanfranconi S, Scola E, Meessen JMTA, Pallini R, Bertani GA, Al-Shahi Salman R, et al. Safety and efficacy of propranolol for treatment of familial cerebral cavernous malformations (Treat_CCM): a randomised, open-label, blinded-endpoint, phase 2 pilot trial. Lancet Neurol. 2023;22:35-44.
30. Girard R, Khanna O, Shenkar R, Zhang L, Wu M, Jesselson M, et al. Peripheral plasma vitamin D and non-HDL cholesterol reflect the severity of cerebral cavernous malformation disease. Biomark Med. 2016;10:255-64.