Analysis of Cavernous Malformations: Experience with 18 Cases

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ABSTRACT

AIM: To analyze the results of stereotactic radiosurgery (SRS) or surgical treatment of 18 cases with cavernous malformation and report 2 cases with unusual localization and size.

MATERIAL and METHODS: We present 11 and 8 patients who underwent surgery and SRS between 2010 and 2018 respectively. The operated group comprised six men and five women (mean age, 33.6 years). SRS was performed in five men and three women (mean age, 33.3 years). All patients were diagnosed and followed-up with magnetic resonance imaging. Stereotactic navigation was not used for lesion localization. The lesion, including the area with hemosiderin, was easily excised using microsurgical approach.

RESULTS: Except for recurrent headache, all symptoms of patients who underwent surgery resolved rapidly. Hemorrhage developed in two of our patients after SRS. One of them refused to undergo surgery and recovered completely with steroid therapy, whereas the other underwent surgery after detection of cavernous malformation at the posterior fossa, with a dimension of 26.8×26.2 mm and occluding the fourth ventricle.

CONCLUSION: In patients without significant preoperative morbidity risk, surgical excision is the gold standard of treatment. SRS is performed in surgically inaccessible, deeply located, multiple cavernous malformations in the brain stem and eloquent area. Of note, giant aneurysm is defined as an aneurysm with a diameter of at least 25 mm; however, there is no dimension threshold defined for giant CM, and the size of giant aneurysm can be accepted as a valid criterion for giant CM. Our 2 cases had giant CM and up to our knowledge the case with giant CM at the posterior fossa is the first giant CM at the posterior fossa in the English literature.

KEYWORDS: Cavernous malformation, Giant cavernous malformation, Stereotactic radiosurgery
Popcorn appearance is typical in magnetic resonance imaging (MRI) and is pathognomonic in diagnosis. Computer tomography visualizes fresh blood and calcification and is normal in 50% of the patients. Digital subtraction angiography is also normal. CM is an angiographically occult malformation; however, it is associated with capillary accumulation, venous angioma, and caput medusa appearance (5,13,15,19).

No medication can stabilize the lesion. Conservative treatment, surgery, and stereotactic surgery (SRS) are being used as therapeutic procedures. Natural progression is allowed with conservative therapy, and 70% patients survive without seizure and symptoms with medical therapy. Surgery is performed in patients with severe symptoms, intractable seizures, and progressive deterioration. SRS is preferred in deep-seated, surgically inaccessible CMs (2,4,8,13).

Although there is no consensus regarding the treatment of CM, microsurgical gross total resection of CM is considered the gold standard of treatment.

Here, we present and discuss 18 patients with CM who underwent surgery and/or SRS.

**MATERIAL and METHODS**

Eighteen patients were diagnosed with CM between 2010 and 2018; surgery and SRS were performed in 11 and 8 of these. The operated group comprised six men and five women (mean age, 33.6 years). SRS was performed in five men and three women (mean age, 33.3 years).

Solitary CM was detected in nine patients; seven and two of these were settled superficially and located deep, respectively. We detected a giant CM of 30.8 × 30.6 mm in the deep posterior frontal area at the outer side of the lateral ventricle frontal horn; surgery was performed due to suspicion of tumor (Figure 1A-F).

In a patient with multiple CM, papillary stasis and hydrocephalus developed 2 months after application of 12 Gy SRS in two of the CMs in the posterior fossa. A giant CM of
26.8 × 26.2 mm was detected, starting from the left cerebellar peduncle and filling the fourth ventricle; the patient underwent surgery (Figure 2A-F).

Multiple CM with superficial and deep localization in the hypothalamus and pedunculus was detected in two patients. One of these patients underwent surgery because of hemorrhage in the sylvian CM. In the other patient, the entire brain had multiple CM (Table I).

CM was multifocal in four of the patients who underwent SRS. We applied 12 Gy SRS to four CMs of three of these cases. We applied 10 Gy SRS to the CM in the vermis of the ninth case, and 12 Gy SRS was applied to the CM in the pons and left temporal lobe. Cervical spinal cavernous malformation was detected in one of these patients, and this patient had two thalamic, two pontine, and one occipital CM (Figure 3A-F).

All patients were diagnosed and followed-up with MRI. Stereotactic navigation was not used for lesion localization. The lesion, including the area with hemosiderin, was easily excised using a microsurgical approach. Localization of the CM was easy because of discoloration around the lesion. (Figure 4A,B).

### RESULTS

Surgery was performed in six men and five women (mean age: 33.6 years). Five men and three women (mean age: 33.3 years) underwent 10–14 Gy SRS. In patients who underwent surgery, headache, seizure, headache and seizure, seizure and right hemiparesis, and papillary stasis and hydrocephalus were observed in four, three, two, one, and one patient, respectively. In patients who underwent SRS, headache, seizure, and dysphagia caused by lower group involvement were observed in five, one, and one patient, respectively.

No postoperative neurologic deficit was observed. The headache of one patient resolved post-operatively. In six patients with seizure, the second medication was terminated at the first postoperative month. In four patients, antiepileptic therapy was terminated at the first postoperative year. We did not terminate antiepileptic therapy in two patients because their follow-up period was short.

Hemorrhage developed in the patient with pontine CM following SRS who refused surgery, and the symptoms resolved 2 months following steroid therapy (Figure 5A, B).
Table I: Demographic and Clinical Data of the Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age</th>
<th>Location (MRI)</th>
<th>Size (cm)</th>
<th>Main symptom</th>
<th>Surgery</th>
<th>SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>22</td>
<td>Right temporal</td>
<td>1.1 × 1.3</td>
<td>Headache</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>35</td>
<td>Multiple*</td>
<td>1.8 × 1.2</td>
<td>Headache, seizures</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>17</td>
<td>Right temporal, cortical</td>
<td>1.3 × 1.2</td>
<td>Seizures</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>48</td>
<td>Left parietal, subcortical</td>
<td>1.8 × 1.5</td>
<td>Headache</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>26</td>
<td>Left centrum semiovale</td>
<td>1.5 × 1.0</td>
<td>Headache</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>38</td>
<td>Multiple*</td>
<td>0.7 × 0.5</td>
<td>Headache</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.1 × 1.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>32</td>
<td>Pons</td>
<td>1.6 × 1.3</td>
<td>Headache</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>23</td>
<td>Left thalamic</td>
<td>0.9 × 0.7</td>
<td>Headache</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>51</td>
<td>Multiple*</td>
<td>1.5 × 1.0</td>
<td>Lower group involvement</td>
<td>+</td>
<td></td>
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<tr>
<td>10</td>
<td>F</td>
<td>18</td>
<td>Right deep posterior frontal</td>
<td>1.4 × 1.1</td>
<td>Headache</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>32</td>
<td>Right occipitotemporal</td>
<td>1.7 × 1.2</td>
<td>Seizures</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>48</td>
<td>Left frontal, subcortical</td>
<td>3.08 × 3.06</td>
<td>Seizures, hemiparesis</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>19</td>
<td>Right parietal</td>
<td>1.5 × 1.3</td>
<td>Seizures</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>20</td>
<td>Multiple*-posterior fossa</td>
<td>2.62 × 2.68</td>
<td>Papillary stasis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>44</td>
<td>Right occipital</td>
<td>1.0 × 1.2</td>
<td>Headache</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>24</td>
<td>Left thalamic</td>
<td>1.3 × 1.1</td>
<td>Headache</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>35</td>
<td>Multiple* Thoracal, Spinal</td>
<td>1.5 × 1.0</td>
<td>Seizures</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>51</td>
<td>Parietal</td>
<td>1.3 × 0.6</td>
<td>Headache, seizure</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

*SRS: Stereotactic radiosurgery. *Only the size of the biggest CM is mentioned in multifocal cases.

A giant CM was detected in two patients. Except for two giant CMs, the dimension of the cavernoma was 0.5–1.8 cm.

**DISCUSSION**

CMs constitute 5%–13% of all cerebral vascular malformations. The prevalence of CM is suggested to be 0.37%–0.5%. It can occur at any age, but it usually presents in the third and fourth decade of life. Approximately 40.60% patients have been known to be multifocal familial following autosomal dominant traits. A mutation results in functional loss at the third chromosomal lodge (KRIT/CCM1, MGC 4607/CCM2, PDCD10/CCM3) (1,9,12,13,19,20).

A solitary lesion was detected in nine patients, and two of these were located deep, and the rest were superficial. Superficial lesions were treated surgically because of high hemorrhage incidence and easy excision without deficit. In the 12th case wherein the CM was deeply located, CM was suspected as a tumor and surgery was performed (Figure 1A-F).

Surgery was performed in two patients with multifocal CM. One of them underwent surgery because of bleeding of left sylvian CM, whereas CM filling in the fourth ventricle 2 months following 12 Gy SRS was detected in the other patient. Other patients with multiple CM underwent SRS. The relatives of patients with multiple CM also underwent MRI, and left thalamic CM was discovered in one patient’s son (Figure 6A-C).

CM can be found in the brain, cortical basal ganglion, thalamus, brainstem, cerebellum, eye, dura, cranial, and spinal root and medulla spinalis (Figure 3A-F).

CMs are asymptomatic in 40% of the patients. The commonly known symptoms are seizure, headache, and focal neurologic deficit in 60%, 25%, and 15% patients, respectively.

Blood degrading products are the main reason for the development of epilepsy, and 40% of these patients are resistant to antiepileptic drugs. Ferrous deposits causing gliosis and accumulation of blood, glutamate, and lactic acid around the CM are also risk factors. In the hemorrhagic area, the level of serine, glycine, and ethanol is 5-, 10-, and 20-fold more than the normal levels, respectively; this provokes epilepsy.

Epilepsy was found in six of our patients, and seizure persisted against multiple antiepileptic drugs. Following the excision of CM and the surrounding gliotic tissue, only one drug was found to be efficient. The drug was terminated at the first postoperative year in four patients.
The reason for headache is occult, oozing microhemorrhage. In patients with CM, the incidence of hemorrhage is 0.07%–1.1% per year; however, it increases to 4.5% in patients with previous hemorrhage. CM combined with hemorrhage is found in the supratentorial and infratentorial in 0.04% and 3.8%; hence, localization of CM is important in patients with hemorrhage. The incidence of hemorrhage is higher in superficial CM, and the tendency increases in women, children, and pregnant women. The size of CM and the presence of developmental venous anomaly (DVA) are also risk factors in increasing hemorrhage.
Headache was present in 11 of our patients, and six and five of them underwent surgery and SRS, respectively. Headache resolved in only one patient post-operatively. Therefore, it can be stated that headache can be caused by several factors besides hemorrhage (2,5,7,14,15,16,19).

MRI revealed old and new hemorrhage and hydrocephalus in only one patient (Figure 2A-F).

We applied SRS to a 20-year-old man with multifocal CM and headache. Two months later, he was admitted to our hospital because of severe headache, nausea, and vomiting. We detected papillary stasis, and MRI revealed a CM sized 2.68 × 2.62 cm filling the fourth ventricle (Figure 2A-F). The patient recovered post-operatively. Gross total excision was essential because of remnants, thereby resulting in re-bleeding and re-operation (2,3,6).

We detected right hemiparesis and epilepsy resistant to antiepileptic therapy in a patient admitted to the hospital because of seizure for 1 year. We detected a 30.80 × 30.60-mm mass in the back frontal lobe, out of the frontal horn of the lateral ventricle, adjacent to the capsula interna. We reached the ellipsoid soft mass with a red–purple capsule through the left pterional craniotomy. The mass was easily dissected from the surrounding tissue. We obtained a liquid resembling former hemorrhage by puncture. We removed the mass without injuring the vascular structure, which was considered as DVA. The histopathological diagnosis was CM, and the patient recovered post-operatively (Figure 7A-D).

Giant aneurysm is defined as an aneurysm with a diameter of at least 25-mm; however, there is no dimension threshold defined for giant CM, and the size of giant aneurysm can be accepted as a valid criterion for giant CM. Lawton described giant CM to measure at least 6 cm in one dimension; however, Giant aneurysm is defined as an aneurysm with a diameter of at least 25-mm; however, there is no dimension threshold defined for giant CM, and the size of giant aneurysm can be accepted as a valid criterion for giant CM. Lawton described giant CM to measure at least 6 cm in one dimension; however,
a CM sized 6 cm does not seem probable in the posterior fossa. To the best of our knowledge, reports of 14 giant CM are found in the literature, and none of them is reported to be located in the posterior fossa. With respect to giant aneurysm, if a 2.5 cm size is accepted as a valid dimension for giant CM, our case will be the first to report this in the literature (6,11,12).

The presence of high angiogenic activity, DVA, and capillary telangiectasia in CMs indicates that it can also develop as de novo. De novo CM following radiotherapy has been reported. Because CM is a dynamic lesion enlargement, progression or de novo formation is possible. Chronic ooze, occult bleeding or microhemorrhage into the CM is surrounded with semi-permeable pseudo-capsule and fragmentation of blood products result with increase in osmotic pressure, and external fluid flow into the capsule and bleeding due to new angiogenesis results with enlargement (Figure 8A, B) (1,3,6).

Fisher recommends surgery in brain stem CMs in the presence of microsurgical corridor or volume >2 cm³. Gornette and Spetzler reported postoperative recovery in 89.2% patients (21).

Adjuvant therapy is not administered in CM; however, conservative, surgical, and SRS treatment are. Gross total excision is important; one must remember that the presence of remnants results in re-bleeding in 40% patients and necessitates re-operation within 72 hours (5,11,13,15,16,18).

Several factors should be reviewed for considering the need for surgery.

Surgery is indicated in cases with progressive neurologic deficit not associated with unacceptable high surgical risk, recurrent hemorrhage, intractable epilepsy, hemorrhage >2 cm³ in the brain stem, superficial CM, accessible CM, and CM outside the eloquent area; moreover, surgery removes the mass effect and provides histological diagnosis.

In female young patients and pregnant women, hemorrhage occurs particularly in CMs located in the posterior fossa; therefore, surgical treatment should be prioritized if the lesion is accessible. If possible, stereotactic, ultrasound, MRI, diffuse tensor image, neuronavigation, and cortical mapping can be used during surgery (2,6,11,13,15,16,18). We performed gross total excision in our patients. Particularly, in superficial lesions, the discolored area was important for the entrance; the dissection of the lesion from the surrounding area was easy (Figure 9A, B).

Mouchtouris et al., 2015 reported that SRS decreases the hemorrhage risk in 32.5% in the first year, and adverse radiation effects develop in 18.4% (13).

We also detected recurrent hemorrhage in the brain stem in two patients; however, we did not correlate this with SRS because the hemorrhage occurred within a short-term
stem, basal ganglion, or thalamus, and in cases with recurrent hemorrhage.

The goal of this treatment is to prevent intractable seizure, mass effect, and re-bleeding, without creating additional neurologic deficits.

**CONCLUSION**

Surgical excision is the gold standard treatment in patients without significant preoperative morbidity risk. In cases with surgically inaccessible, deeply located, multiple cavernous malformations at the brain stem and eloquent area, SRS should be preferred.

Giant aneurysm is defined as an aneurysm with a diameter of at least 25 mm; however, there is no dimension threshold defined for giant CM, and the size of giant aneurysm can be accepted as a valid criterion for giant CM. Our 2 cases had giant CM and to our knowledge the case with giant CM at the posterior fossa is the first giant CM at the posterior fossa in the literature.