Spontaneous Regression of Cerebral Arteriovenous Malformation Following Onyx Embolization

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Abstract

Little is known about the natural history of arteriovenous malformations (AVM) and less is known about their potential for spontaneous regression. The advent of endovascular treatment for embolization or pre-surgical embolization of cerebral arteriovenous malformations (cAVM) has seen several reports of spontaneous regression of partial embolization of cAVMs in the literature.

A 66-year-old patient had an initial diagnostic cerebral angiogram revealing a left frontoparietal region Spetzler-Martin (SM) grading 4 cAVM. The patient underwent three stages of embolization over eight months leading to a 90% reduction in nidal volume, before being lost to follow up for six years. A six-vessel diagnostic cerebral angiogram was performed at that time to assess for any interval changes and surprisingly, the previously visualized left frontoparietal AVM had regressed. There was evidence of prior onyx embolization with no residual filling or recurrence.

Spontaneous regression after partial embolization may be under-reported or the natural history is simply unable to temporally unfold because the typical treatment course results in surgery following partial embolization. Given the potential to forgo the risks of an open procedure, we believe this topic deserves further attention.

Categories: Neurology, Neurosurgery
Keywords: interventional radiology guided embolization, cerebral avm, spontaneous regression, embolization, arteriovenous malformation

Introduction

Cerebral arteriovenous malformations (cAVMs) are known to be complex tangles of abnormal arteries and veins associated with high-flow arteriovenous shunting, nidus formation, and venous ectasia. Little is known about their potential for spontaneous regression, a rare phenomenon with an estimated prevalence of 1-3% of patients with cAVM [1]. The majority of spontaneous regression cases in the literature occur either without treatment of any means or after partial surgery [2]. With the advent of endovascular treatment for complete embolization or pre-surgical embolization of cAVMs, several reports of spontaneous residual regression of partial embolization cAVMs have surfaced in the literature [3-6]. We report a case of complete regression of an unruptured AVM after partial endovascular embolization with Onyx, and review the literature of cases of spontaneous regression in partially embolized cAVMs in order to compare findings associated with each case.

Case Presentation

The patient is a 66-year-old who had initially presented about eight years ago with the complaint of headache and left-sided tinnitus. The diagnostic cerebral angiogram revealed the left frontoparietal region (Spetzler-Martin [SM] grade 4 or embocure score of 5) cAVM which was fed by the left anterior cerebral artery (pericallosal and the callosomarginal) and the superior division of the left middle cerebral artery. The venous drainage was 2-5 mm deep to the superior sagittal sinus (Figure 1). The patient underwent stage I Onyx embolization with 50% reduction in the AVM nidus. About six months later, stage II Onyx embolization was performed further reducing the nidal volume by about 30% which was followed by stage III embolization after two months, during which the nidal volume was further reduced to a total of 90% (Figure 2).
FIGURE 1: Initial diagnostic cerebral angiogram.

Initial diagnostic cerebral angiogram revealing grade 4 left frontoparietal arteriovenous malformation (AVM) (black arrow) fed by the left anterior cerebral artery (orange arrow) and the superior division of the left middle cerebral artery (red arrow) and drained by superficial veins to the superior sagittal sinus (blue arrow).
FIGURE 2: Post stage 3 embolization with Onyx with 85-90% reduction in AVM volume.

AVM: Arteriovenous malformation.

The patient was lost to follow-up and presented again after about six years with the complaint of headache, dizziness, and tinnitus in the right ear. A six-vessel diagnostic cerebral angiogram was performed to assess for any interval changes and surprisingly, the previously visualized left frontoparietal AVM had regressed. There was evidence of prior Onyx embolization with no residual filling or recurrence (Figure 3).
FIGURE 3: Follow-up six-years later revealing complete regression of AVM with evidence of prior Onyx embolization.

**AVM:** Arteriovenous malformation.

Due to the patient’s living situation and poor follow-up, it is hard to judge the long-term outcomes of their partial treatment with full regression. However, on their last admission, they had no evidence of complications due to their regressed cAVM.

**Discussion**

Endovascular embolization therapy, which has been shown to be more efficacious and safer than surgery alone [7], is typically the first step of the multimodal approach to cAVM therapy with the goal of a permanent cure. Complete obliteration of cAVMs following endovascular therapy has been reported in up to 35% of cases [3], with the remaining partially embolized cases typically progressing to open or radiosurgery. In the case presented here, the patient underwent three embolization procedures with Onyx, with a final result of an 85-90% reduction of the unruptured SM grade 4 cAVM. We note that while the results of A Randomized Trial of Unruptured Brain AVMs (ARUBA) trial suggest that medical management alone is superior to interventional therapy for unruptured cAVMs, the mean follow-up of 33.3 months for this trial may not have been sufficient to capture the true risk comparison in these patients given the lifetime rupture risk of cAVMs [8]. As the patient was lost to follow-up, no additional surgeries or embolization were performed, yet the patient was found to have complete regression of the cAVM at six-year follow-up; thus, spontaneous regression of the remaining cAVM was suspected.

A number of factors have been proposed for the spontaneous regression of cAVMs. The most suspected mechanism involves alterations in hemodynamics due to mass effects from intracerebral or subarachnoid hemorrhage brain edema and vasospasm leading to reduced blood flow and thrombosis [5]. AVM morphology is also suspected, with small size, single arterial feeding vessels, single ecstatic draining veins, and superficial locations appearing to play a causative role in spontaneous thrombosis [1,5]. In children and women taking oral contraceptives, it is believed a hypercoagulable state can predispose to the spontaneous thrombosis and regression of AVMs [9].

Spontaneous regression of whole untreated cAVMs is a rare phenomenon. While estimated to occur in as
many as 20% of patients with cAVMs, most reports of spontaneous regression estimate a more conservative 1-3% [1,2,10]. Our own literature review of regression of partially treated cAVMs yielded only six other case reports (Table 1). The average age of these patients was 38 years old (ranging from 21 to 58). The cAVMs in five of the seven cases involved the parietal lobe, while the remaining two of seven involved the occipital lobe. A hematoma and vasogenic edema causing a slight mass effect was only found in one of the seven cases, while two of the seven cases presented with vasogenic edema without mass effect. A single feeding vessel was in zero of the seven cases, though a single venous draining vessel was found in four of the seven. Histoacryl ultrafluid Lipiodol ultrafluid mixture was used in four cases, Onyx in two, and N-butyl cyanoacrylate (NBCA) in one. Thrombosis or embolus was noted in the draining vein in three of the seven cases following embolization. Vasospasm, which is a previously noted potential factor in the spontaneous regression of cAVMs, due to catheter manipulation was noted in two of the seven cases. Time at the recognition of spontaneous regression in cases with regular follow-up was an average of 318 days, with a range of one day to 1186 days (six years in the current case, but the patient did not follow-up regularly).
<table>
<thead>
<tr>
<th>Case</th>
<th>Reference</th>
<th>Age</th>
<th>Presentation</th>
<th>Location</th>
<th>S-M G</th>
<th>Feeding Vessels</th>
<th>Draining Vessels</th>
<th>Embolization</th>
<th>Angiographic Findings</th>
<th>Time to Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Celleri M et al. (2003)[5]</td>
<td>45</td>
<td>Refractory seizures</td>
<td>Left parietal</td>
<td>3; 2 x 2 x 2 cm; 2 x 2 x 2 cm; 2 x 2 x 2 cm</td>
<td>Hypertrophic parietal branches of the left pericallosal and middle cerebral arteries</td>
<td>Three superficial veins courting to the superior sagittal sinus and one deep vein running to the vein of Galen</td>
<td>20% occlusion via S 0.4 and S 0.2 cc of a 20% mixture of Histoacryl and Ultrafluid (UF) Lipiodol</td>
<td>Thrombosis of the most posterior superficial draining vein</td>
<td>6 months</td>
</tr>
<tr>
<td>2</td>
<td>Celleri M et al. (2003)[5]</td>
<td>26</td>
<td>Headache, tinnitus</td>
<td>Left parietal</td>
<td>1; 2 x 2 x 1 cm central subcortical herniations in the right hemisphere</td>
<td>Superior and inferior branches off of Rolandic branch of right middle cerebral artery</td>
<td>Single distal vein of the head of the caudate nucleus courting to the thalamostriate and internal cerebral veins</td>
<td>20% mixture of Histoacryl and Ultrafluid Lipiodol UF; 2 via superior vessel, 1 via inferior to residual filling of nidus with sluggish flow of draining vein</td>
<td>Small embolus of glue passed into the draining vein, causing stagnant flow; vasospasm during coiling</td>
<td>1 day</td>
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<tr>
<td>3</td>
<td>Celleri M et al. (2003)[5]</td>
<td>54</td>
<td>Transient right hemianopsia</td>
<td>Left parietal lobe</td>
<td>2; 2 x 2 x 2 cm; 2 x 2 x 2 cm; without mass effect</td>
<td>Middle temporal branches and parietal occipital branches of the left middle and posterior cerebral arteries</td>
<td>Single cortical vein with stenosis at junction with the superior sagittal sinus</td>
<td>3 intranidal injections of a 20-50% mixture of Histoacryl and Ultrafluid into different feeding arteries</td>
<td>Spares of PCA; Decreased egress and flow velocity of the vein to superior sagittal sinus; 87% reduction in nidal size</td>
<td>3 months</td>
</tr>
<tr>
<td>4</td>
<td>Celleri M et al. (2003)[5]</td>
<td>36</td>
<td>Acute headache and vomiting</td>
<td>Left parietal lobe</td>
<td>1; 2 x 2 x 1 cm; 1; no acute bleeding</td>
<td>Single distal lenticulostriate artery and multiple small irregular perforating branches of the right middle cerebral artery</td>
<td>Two deep veins, one of which was ectatic, courting to the internal cerebral vein and straight sinus</td>
<td>2 attempts at inferior perfusing branch of the right middle cerebral artery were unsuccessful. A single injection of an 18% mixture of Histoacryl and Ultrafluid Lipiodol into the Lenticulostriate artery originating from the frontal M1 segment to the right middle cerebral artery</td>
<td>Graft reached the medial portion of the right hemisphere</td>
<td>1 year</td>
</tr>
<tr>
<td>5</td>
<td>Cao C et al. (2015)[4]</td>
<td>31</td>
<td>Right hemiparesis</td>
<td>Right occipital, left frontal, parietal, subcortical region</td>
<td>2; no acute bleeding</td>
<td>Two main arterial feeders from the left pericallosal artery (superior and anterior parietal arteries) and tiny feeding branches from the left middle cerebral artery</td>
<td>Small cortical vein draining the AVM directly into the superior sagittal sinus; thrombosis of the AVM main draining vein</td>
<td>N-butyl cyano-acrylate (NBCA) with a 21% dilution into two feeding branches from the left pericallosal artery</td>
<td>Occlusion of the nidal veins with small peripheral capillary network; shrinking; decrease in the size of the thrombosed vein at three months via MRA</td>
<td>30 months</td>
</tr>
<tr>
<td>6</td>
<td>Nas Off et al. (2017)[8]</td>
<td>21</td>
<td>Blurred vision, dizziness, nausea, headache</td>
<td>Left frontal-parietal</td>
<td>2; 2 cm</td>
<td>Right sigmoid sinus through a single venous structure</td>
<td>Branches of the right PCA were selectively coiled and Onyx injected</td>
<td>Reabsorption of AVM lesion could not be reached because feeding arteries were too thin</td>
<td>Residual AVM lesion</td>
<td>3 months</td>
</tr>
<tr>
<td>7</td>
<td>Current Case</td>
<td>59</td>
<td>Headache, encephalopathy</td>
<td>Left frontoparietal</td>
<td>4; no hemorrhage</td>
<td>Left anterior cerebral artery (pericallosal and the callosomarginal and the superior division of the left middle cerebral artery</td>
<td>2-3 superficial veins to the superior sagittal sinus</td>
<td>Three stage embolization with Onyx: 6 and 8 months</td>
<td>85-90% reduction of volume size on final embolization</td>
<td>&lt;6 years</td>
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</table>

**TABLE 1:** Case series of seven spontaneously regressing cAVMs found in the literature.


**Conclusions**

We were unable to find a single factor common to all cases of spontaneous regression following endovascular embolization; however, we note that all cases contain at least two of the factors hypothesized to contribute to spontaneous regression. We hypothesize that embolization agents result in progressive thrombosis due to...
reduced intranidal flow from both the embolization agent and catheter-induced vasospasm. Additionally, the continued thrombogenicity of the glue and the persistence of the inflammatory process following exposure of the vessels of the nidus to the embolic agent likely contribute to the spontaneous regression of partially embolized cAVMs as well. We hypothesize that spontaneous regression after partial embolization is either under-reported or the natural history is simply unable to temporally unfold because the typical treatment course results in surgery following partial embolization. However, given the risk of bleeding in partially embolized cAVMs and the inability to predict which cAVMs will spontaneously regress, it should not be considered as a treatment option. At this point, we cannot predict spontaneous regression after partial embolization and, given the potential to forgo the risks of an open procedure, we believe this topic deserves further attention.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References