Growth and regression of arteriovenous malformations in a patient with hereditary hemorrhagic telangiectasia

Case report

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Data on the growth, regression, and de novo formation of arteriovenous malformations (AVMs) suggest that some of these lesions are not formed and developed only during embryogenesis. Patients with hereditary hemorrhagic telangiectasia (HHT) have a genetic propensity to form AVMs. The authors report on the growth and regression of AVMs in a single patient with HHT. This 26-day-old boy with a family history of HHT1 and a mutation in ENG on chromosome 9 presented with a generalized seizure. Results of computed tomography revealed a left frontoparietal intraparenchymal hemorrhage. Cerebral angiography revealed multiple AVMs. Follow-up angiograms obtained 5 months later showed both growth and regression of the AVMs. A craniotomy was performed for complete resection of the left parietal AVM. Histopathological features of the surgical specimen were examined. Active angiogenesis, as indicated by increased endothelial proliferation, might be a part of the underlying pathophysiology of the growth and regression of AVMs.

KEY WORDS • arteriovenous malformation • hereditary hemorrhagic telangiectasia • Rendu-Osler-Weber syndrome

HEREDITARY hemorrhagic telangiectasia or Rendu-Osler-Weber syndrome is a group of autosomal-dominant disorders characterized by systemic vascular dysplasias including vascular abnormalities of the nose, skin, lung, brain, and gastrointestinal tract. In HHT, 48% of patients suffer neurological symptoms from pulmonary AVFs that cause paradoxical thrombotic, air, or septic emboli or thrombosis due to polycythemia. In 28% of patients, the neurological symptoms are caused by cerebral vascular malformations, 22 to 23% of which are cerebral AVMs. Data in several case reports show growth or regression of a single sporadic AVM or recurrence of an AVM after angiographically confirmed complete resection. We report on a case of multiple AVMs in a single patient with HHT that grew and regressed over a short period of time, and we present the results of a histopathological study of an AVM in this patient.

Case Report

History and Examination. This 26-day-old boy with a paternal family history of HHT presented with a generalized seizure. Results of head ultrasonography studies performed in utero at 37 weeks’ gestation and at birth were normal. On admission, the patient did not open his eyes to pain but symmetrically moved all four extremities in response to light touch. A head CT revealed a 3.5 × 2.5–cm left frontoparietal intraparenchymal hemorrhage (Fig. 1). Results of MR imaging of the brain showed a left parietal hematoma with subarachnoid and intraventricular extension. There were multiple foci of T, signal abnormality in the left frontal lobe, bilateral medial occipital lobes, left caudate nucleus, and left thalamus, which could represent small hemorrhages from telangiectases or AVMs. The presence of AVMs was confirmed with cerebral angiography. A cerebral angiogram revealed a 3.6 × 2.5 × 1.9–cm Spetzler–Martin Grade III AVM in the left parietal lobe with superficial drainage into...
the superior sagittal sinus (Fig. 2). There was also a smaller 1.5-cm left parasagittal frontal AVM with superficial venous drainage. Two areas of hypervascularity were seen in the left frontal lobe and left temporal lobe without obvious shunting. Comparisons of all projections of the MR images and angiograms clearly showed that the hemorrhage originated from the left medial parietal AVM. The patient was neurologically intact on discharge, with plans for resection of the AVM when he reached the age of 6 months. Chest and abdominal CTs showed no vascular abnormalities.

An MR image obtained 5 months later showed no significant changes. An angiogram obtained 5 months after the initial hemorrhage (Fig. 2) revealed an unchanged AVM in the left parietal lobe, although the smaller left parasagittal frontal AVM was less evident compared with its appearance on the previous angiogram. Two new AVMs with early venous shunting had been previously seen as areas of abnormal hypervascularity: 1) a 1.5-cm left frontal lobe AVM supplied by the middle cerebral artery; and 2) a 2-cm diffuse region of hypervascularity with some shunting in the anterior left temporal lobe that drained into the sphenoparietal sinus.

Operation. Given the history of hemorrhage from, and the lack of any signs of regression of, the left medial parietal AVM, the patient was taken to the operating room 5 months after the intraparenchymal hemorrhage for a bifrontoparietal craniotomy for complete removal of the AVM. No preoperative embolization was done. A Stealth navigation system (Medtronic) was used for preoperative planning. All feeding arteries including those on the interhemispheric fissure were coagulated and divided. The main draining vein darkened in color and was divided. The draining vein going to the superior sagittal sinus was preserved because it also served as the draining vein for the smaller frontal AVM.

Postoperative Course. A postoperative angiogram showed complete resection of the left parietal AVM (Fig. 3). The patient had right hemiparesis postoperatively, which improved rapidly over the course of 2 weeks. At the 2-week follow-up evaluation, the patient demonstrated a mild right hemiparesis with Medical Research Council Grade 4+/5 strength, with more strength in the leg than in the arm. At the 4-month follow up, the hemiparesis had completely resolved. The patient has had no seizure episodes since the surgery.

Family History and Genetics. The patient’s extended family had participated in a previously published study on HHT and undergone extensive genetic analysis. In a linkage analysis, the patient’s father, father’s sister, father’s sister’s son, paternal grandmother, and paternal grandmother’s mother were genetically confirmed to have mutations in ENG on chromosome 9 (Fig. 4). There was no evidence of linkage to ACVRL1 (also known as ALK-1) on chromosome 12. The patient’s father, father’s sister, and paternal grandmother had frequent epistaxis. The father’s sister also had telangiectasias. The father’s sister had a child who died on Day 1 of life due to an intracerebral hemorrhage, which on autopsy was confirmed to have been caused by an AVM. This woman has another child who is asymptomatic. The paternal grandmother also had AVMs.

Histopathological and Immunohistochemical Studies. Staining with H & E, and van Gieson and elastin showed abundant abnormal vessels with and without internal elas-
tica as well as multiple infarcts and foci of hemorrhage with mineralization in the cortex, which are consistent with an AVM (Fig. 5A and B). Immunohistochemical stainings were performed on formalin-fixed paraffin-embedded tissues by using antigen retrieval and the avidin-biotin method. Nuclear Ki 67 protein expression was detected using the mAb MIB-1 (1:500 dilution, DakoCytomation). The mAb to CD34 (1:500 dilution, DakoCytomation) was used to identify endothelial cells. The Ki 67–positive endothelial cells can be seen indicating the presence of proliferating cells (Fig. 5C–F). The mAbs to CD45 (1:100 dilution, DakoCytomation) and CD68 (1:1500 dilution, DakoCytomation) were used for the detection of lymphocytes and macrophages, respectively. Staining for CD45 and CD68 showed inflammatory cells in the vessel wall and perivascular region as well as in the intervening brain parenchyma (Fig. 6A and B). Staining for CD45 and CD68 in a patient with a sporadic AVM that hemorrhaged 2 days before resection demonstrated a similar distribution of inflammatory cells, whereas the stainings in a patient with an unruptured sporadic AVM revealed many fewer inflammatory cells (Fig. 6C–F).

**Discussion**

Whereas other types of vascular malformations such as dural AVFs and cavernous malformations can be acquired after trauma, infection, inflammation, radiation, or compression, brain AVMs are often presumed to be congenital lesions that result from maldevelopment during the 4th to 8th week of embryonic development. However, there have been multiple reports of AVMs that grow or re-
Arteriovenous malformations in HHT

4–6,20,25,26,28,30,31,36–38,41–44,56–58,61,63,66 or that recur after angiographically confirmed complete resections,10,11,16,19,22,24,46,53,66 thus indicating that a subset of AVMs may not be static lesions. There have also been some reported cases of de novo AVM formation. These de novo AVMs were all associated with some abnormal vascularity or other vascular malformations, hemorrhage (intraparenchymal, subdural, or subarachnoid), infarct, or tumor in or near the same region (Table 1). Proposed explanations for de novo AVMs include growth of an occult AVM that appeared as an abnormal vascular blush; an undiagnosed AVM hidden by compression due to hemorrhage, edematous brain, thrombosis, or vaso- spasms of feeding arteries;22,39 venous hypertension caused by a preexisting dural AVF;3 hyperangiogenic environment of moyamoya disease and the local angiogenic stimulation of the cerebral infarction;55 or the enhanced angiogenic environment of a neoplasm15 or prior hemorrhage39 predisposing to the formation of AVMs. Mechanisms that have been proposed to account for the increase in size of AVMs include dilation of existing vessels due to hemodynamic stress,57 decrease in supporting brain tissue from multiple silent hemorrhages,60 a nidus that becomes visible after a change in hemodynamics,1 or ongoing active angiogenesis.17 True recurrences and true de novo AVMs, as opposed to undiagnosed residual or occult AVMs, would imply that these lesions are not necessarily formed during embryogenesis and remain static. In the present case, we have a unique example of multiple AVMs that were documented to grow and regress over a period of 5 months in a single patient, which further emphasizes the dynamic nature of AVMs.

Although there are some differences between AVMs in HHT and sporadic AVMs in terms of size and multiplicity,35 the general features are similar. Thus, one might expect spe-
In other studies authors have directly examined endoglin and ACVRL1 in sporadic AVMs. There are limited data on endoglin expression in sporadic AVMs, but endoglin is the most abundant TGFβ binding protein on endothelial cells and binds to TGFβ1 and -β3, whereas ACVRL1 is a receptor for TGFβ1 and -β3. In this case, we have the advantage of having a patient whose family has been extensively tested genetically and confirmed to have a mutation on ENG on chromosome 9 but not on ACVRL1 on chromosome 12.

Endoglin expression by activated monocytes is 50% less in patients with HHT1 compared with that in healthy patients. There are limited data on endoglin expression in AVMs, however. All blood vessels in patients with HHT1 express reduced endoglin, suggesting that a focal loss of TGFβ function is not an explanation for AVMs in patients with HHT. Furthermore, endoglin density in sporadic AVMs is not very different from control vasculature, but there is a conspicuous difference in its distribution in the perivascular space.

A number of investigations aimed at elucidating the pathogenesis of AVM formation have been conducted using transgenic mouse models of HHT. Homozygous mouse embryos deficient in ACVRL1 die in utero of severe AVMs due to fusion of the major arteries and veins. Similarly, homozygous mouse embryos deficient in endoglin die in utero of defective angiogenesis with poor vascular smooth muscle development and endothelial remodeling. Satomi and colleagues evaluated the cerebral vasculature of endoglin heterozygous mice and found that AVMs developed in three of 10 murine brains, whereas Xu et al. found that hyperstimulation of endoglin heterozygous mice with vascular endothelial growth factor increases vascular dysplasia.

Despite these advances, the pathogenesis of AVMs, HHT-related or sporadic, remains poorly understood. There have been a number of studies in which authors have examined surgically obtained sporadic AVM specimens that showed increased expression of angiogenic factors such as vascular endothelial growth factor, basic fibroblast growth factor, and TGFβ compared with those in the normal adult brain. In other studies authors have directly examined the proliferation of endothelial cells via Ki 67 staining. In the present case, we found actively proliferating cells via Ki 67 staining, which is consistent with our previous observations of a relative increase in Ki 67-positive endothelial cells in sporadic AVMs compared with controls. This increased endothelial proliferation suggests a more active angiogenic process as seen by the dynamic nature of the growth and regression of the AVMs in this patient over a short period of only 5 months. Whereas increased endothelial proliferation can be caused by a number of factors including hemorrhage and shear stress from flow, factors such as changes in hemodynamics due to embolization or inflammation from radiation are excluded in the patient in the present case who had not undergone prior embolization or radiation treatment. There are two possible explanations for the increased endothelial proliferation in this patient. On one hand, patients with HHT may have more active angiogenesis. There are no data, however, to suggest that AVMs in patients with HHT are more prone to growth and regression. On the other hand, AVMs undergoing growth and regression or in the presence of hemorrhage, independent of HHT, have more active angiogenesis.

In addition to increased endothelial proliferation, we have found inflammatory cells in and around vessel walls as well as in surrounding brain parenchyma, which is broadly consistent with sporadic AVMs. Similar patterns of inflammatory cells can be found in sporadic AVMS with more infiltrates after a hemorrhage. The increased inflammatory cells in the featured patient with HHT could also be part of an ongoing inflammation from the hemorrhage 5 months before resection. Studies of the inflammatory response in the brain to blood have shown a persistent macrophage/microglia infiltrate up to 4 weeks posthemorrhage. Otherwise, the presence of inflammatory cells may be part of the pathogenesis of actively growing or regressing AVMs. Future investigations of the roles of endoglin, ACVRL1, and the inflammatory response in AVMs should provide insight into their pathogenesis.

Fig. 6. Photomicrographs obtained during immunohistochemical analysis, demonstrating inflammatory cells in the vessel wall, perivascular region, and intervening brain parenchyma (A and B); increased numbers of inflammatory cells in a patient whose AVM hemorrhaged 2 days prior to resection (C and D); and fewer inflammatory cells in a patient with an unruptured AVM (E and F). Antibodies to CD45 (A, C, and E) and CD68 (B, D, and F); original magnification × 100.

Acknowledgment

Figure 5C to F appears courtesy of Yongmei Chen, Ph.D.
### References


### TABLE 1

*Literature review of cases of de novo brain AVMs*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age at 1st Angio (yrs), Sex</th>
<th>Reason for 1st Angio</th>
<th>Reason for 2nd Angio</th>
<th>Interval Btw Angios (yrs)</th>
<th>Location of Other Disease at 1st Angio</th>
<th>Location of AVM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porter &amp; Bull, 1969</td>
<td>22, M</td>
<td>SAH</td>
<td>SAH</td>
<td>2</td>
<td>nondoniagnostic angio</td>
<td>supplied by rt pst cerebrar artery</td>
</tr>
<tr>
<td>Krayenbuhl, 1977</td>
<td>3, M</td>
<td>SAH</td>
<td>SAH</td>
<td>9</td>
<td>nondoniagnostic angio</td>
<td>rt frontal region</td>
</tr>
<tr>
<td>Watanebe et al., 1977</td>
<td>7, M</td>
<td>chronic lt subdural hematoma</td>
<td>motor vehicle accident seizures, head CT showed AVM</td>
<td>13</td>
<td>lt hemisphere</td>
<td>rt frontal region</td>
</tr>
<tr>
<td>Peeters, 1982</td>
<td>3, M</td>
<td>SAH</td>
<td>SAH</td>
<td>23</td>
<td>rt frontal vascular abnormality</td>
<td>rt frontal region</td>
</tr>
<tr>
<td>Mendelow et al., 1987</td>
<td>NA, F</td>
<td>SAH</td>
<td>SAH</td>
<td>14</td>
<td>rt occipital vascular abnormality suspicious for AVM</td>
<td>rt occipital region</td>
</tr>
<tr>
<td>Morioka et al., 1988</td>
<td>15, M</td>
<td>comatose, rt hemiparesis, SAH by lumbar puncture, no CT</td>
<td>seizures, rt hemiparesis 5 yrs later</td>
<td>8</td>
<td>none</td>
<td>lt frontal region</td>
</tr>
<tr>
<td>Iwayama et al., 1991</td>
<td>18, M</td>
<td>ICH</td>
<td>ICH seizure, rt leg monoparesis</td>
<td>2</td>
<td>lt temporal</td>
<td>lt temporal region</td>
</tr>
<tr>
<td>Wakabayashi et al., 1991</td>
<td>8, F</td>
<td>rt hemiplegia &amp; headache; angio done 2 mos later</td>
<td>FU</td>
<td>16</td>
<td>lt frontal vascular abnormality suspicious for AVM</td>
<td>lt frontal vascular region</td>
</tr>
<tr>
<td>Schmit et al., 1996</td>
<td>2, M</td>
<td>seizures, moyamoya disease, lt parietal infarct</td>
<td>recurrent symptoms</td>
<td>9</td>
<td>lt parietal infarct</td>
<td>lt parietal region</td>
</tr>
<tr>
<td>Nussbaum et al., 1998</td>
<td>24, M</td>
<td>headache, vertigo, visual changes</td>
<td>FU</td>
<td>10</td>
<td>rt cerebellar development venous anomaly</td>
<td>rt cerebellar region</td>
</tr>
<tr>
<td>Friedman et al., 2000</td>
<td>61, M</td>
<td>vertigo, rt tentorial dural AVF treated w/ transarterial embolization</td>
<td>FU</td>
<td>2 &amp; 4</td>
<td>rt frontal vascular abnormality</td>
<td>cerebellar vermis</td>
</tr>
<tr>
<td>Harris et al., 2000</td>
<td>57, M</td>
<td>lt hemiparesis, CA stenosis</td>
<td>FU</td>
<td>6</td>
<td>none</td>
<td>rt thalamic &amp; occipital lobe AVM &amp; astrocitoma</td>
</tr>
<tr>
<td>Rodriguez-Arias et al., 2000</td>
<td>9, F</td>
<td>seizures, AVM treated w/ GKS</td>
<td>FU</td>
<td>2</td>
<td>rt parietal AVM</td>
<td>rt parietal region but medial to 1st AVM</td>
</tr>
<tr>
<td>Bulsara et al., 2002</td>
<td>26, F</td>
<td>cranial nerve deficits, vasculitis; some abnormal vascular but no shunting</td>
<td>headache</td>
<td>6</td>
<td>rt pst temporal abnormal vascularity</td>
<td>rt pst temporal region</td>
</tr>
<tr>
<td>Akimoto et al., 2003</td>
<td>17, F</td>
<td>lt IVH, 2 AVMs; angio done 4 mos post-IVH</td>
<td>headache, rt hemianestheshia, ICH</td>
<td>10</td>
<td>splenium, lt occipital AVM</td>
<td>corpus callosum &amp; cingulate gyri (adjacent to splenial AVM)</td>
</tr>
<tr>
<td>Miyasaka et al., 2003</td>
<td>50, F</td>
<td>headache, ICH; angio done 5 mos later; VA angio not done</td>
<td>headache, SAH</td>
<td>8</td>
<td>rt parietal ICH</td>
<td>rt parietal, rt frontal, lt occipital region</td>
</tr>
</tbody>
</table>

* Angio = angiogram; CA = carotid artery; FU = follow up; GKS = Gamma Knife surgery; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; NA = not available; pst = posterior; SAH = subarachnoid hemorrhage; VA = vertebral artery.

† Value expressed in weeks.


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Arteriovenous malformations in HHT


