Recurrent intraparenchymal hemorrhages from angiographically occult vascular malformations

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Thirteen patients with recurrent hemorrhages from angiographically occult vascular malformations are presented. Recurrent hemorrhages were indicated by the exacerbation of neurological deficits, the appearance of a new neurological deficit, or the onset of acute severe headache confirmed by evidence of recent hemorrhage on either computerized tomography or magnetic resonance imaging. Persistent neurological deficits correlated with an increased number of recurrent hemorrhages and their location. The median time from initial hemorrhage to the first recurrent hemorrhage was 12 months and the second rebleed generally occurred much earlier, with a median time of 2 months after the first. Eight patients underwent surgery with total excision and favorable results. One patient with a large pontine lesion underwent partial excision and has had a progressing neurological deficit from recurrent hemorrhages. Histopathological review confirmed the excised lesions to be cavernous angiomas. The authors conclude that angiographically occult vascular malformations are not the benign entity they were previously thought to be, and that they are prone to cause recurrent hemorrhages and persistent neurological deficits. Surgery can be effective and relatively safe in removing these lesions even in eloquent areas of the brain, but the necessity of occasional incomplete removal must be recognized in order to avoid creating an unacceptable neurological outcome.

KEY WORDS • occult vascular malformations • cavernous angioma • hemorrhage • rebleeding

Angiographically occult vascular malformations of the brain are increasingly being identified due to the widespread availability of sophisticated imaging techniques such as computerized tomography (CT) and magnetic resonance (MR) imaging. Recent reports have highlighted the CT and MR characteristics of these lesions and their corresponding clinical and histopathological profiles. However, the natural history of these lesions remains obscure. The incidence and impact of recurrent hemorrhage have not been analyzed in any systematic fashion.

The authors present 13 cases of documented clinically relevant recurrent hemorrhages from angiographically occult vascular malformations of the brain. These patients were evaluated between January 1, 1984, and January 1, 1989. All cases of recurrent hemorrhage were indicated by an increase in a preexisting neurological deficit, the appearance of a new neurological deficit, or the acute onset of severe headache, and confirmed by evidence of recent hemorrhage on either CT or MR imaging.

Summary of Cases

Clinical and Histological Features

The clinical and histological features of 13 patients with angiographically occult vascular malformations are presented in Table 1. There were four men and nine women, with an age range of 18 to 59 years. Eight lesions (61.5%) were located in the posterior fossa (five in the pons or pontomedullary junction) and three were in the cerebellum (one in the vermis and two in the cerebellar peduncles). Four lesions were located in the white matter or subcortical region of the cerebral hemispheres, and one was in the thalamus.

Neuroradiographic Studies

The radiographic features of the lesions in our 13 cases were typical of those described in recent publications. Cerebral angiography was negative in all patients, five of whom underwent at least two angiograms during their clinical course. No abnormal vasculature or early venous drainage was identified on
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TABLE 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Location of Lesion</th>
<th>Clinical Symptoms of Rebleeding</th>
<th>Neurological Deficit</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18, F</td>
<td>pons, floor of 4th ventricle</td>
<td>3 episodes acute HA, numbness rt side, rt hemiparesis</td>
<td>transient</td>
<td>no histology</td>
</tr>
<tr>
<td>2</td>
<td>34, F</td>
<td>vermis of cerebellum</td>
<td>3 episodes acute HA, lethargy, nausea, vomiting, ataxia</td>
<td>transient</td>
<td>cavernous angioma</td>
</tr>
<tr>
<td>3</td>
<td>59, F</td>
<td>pons, floor of 4th ventricle</td>
<td>4 episodes acute vertigo, diplopia, nausea, lt arm numbness; recurrent symptoms several months postop indicating recurrent hemmorhages</td>
<td>persistent</td>
<td>cavernous angioma</td>
</tr>
<tr>
<td>4</td>
<td>30, M</td>
<td>pons, floor of 4th ventricle</td>
<td>2 episodes acute HA, diplopia, unsteady gait; rt INO with 2nd rebleed</td>
<td>transient</td>
<td>no histology</td>
</tr>
<tr>
<td>5</td>
<td>26, M</td>
<td>rt posterior, parietal</td>
<td>3 episodes severe ictal HA, followed by grand mal seizures</td>
<td>none</td>
<td>no histology</td>
</tr>
<tr>
<td>6</td>
<td>36, F</td>
<td>lt frontal</td>
<td>3 episodes of HA, lethargy; dysphasia with 2nd rebleed</td>
<td>transient</td>
<td>no surgery</td>
</tr>
<tr>
<td>7</td>
<td>35, M</td>
<td>lt thalamus</td>
<td>4 episodes HA, rt hemiparesis, 1 seizure</td>
<td>persistent</td>
<td>cavernous angioma</td>
</tr>
<tr>
<td>8</td>
<td>39, F</td>
<td>pons, floor of 4th ventricle</td>
<td>2 episodes HA, rt facial numbness, lt UE paresthesias, numbness</td>
<td>transient</td>
<td>no surgery</td>
</tr>
<tr>
<td>9</td>
<td>27, F</td>
<td>rt brachium pontis</td>
<td>3 episodes HA, vomiting, vertigo; new ataxia with 2nd rebleed</td>
<td>transient</td>
<td>cavernous angioma</td>
</tr>
<tr>
<td>10</td>
<td>34, M</td>
<td>rt brachium pontis</td>
<td>3 episodes rt facial numbness; radiosurgery after 2nd rebleed; rebleed 3 months postop with dysphagia, blurred vision, &amp; rt-sided ataxia</td>
<td>persistent</td>
<td>cavernous angioma</td>
</tr>
<tr>
<td>11</td>
<td>34, F</td>
<td>pons, floor of 4th ventricle</td>
<td>2 episodes lower cranial nerve palsies, rt-sided cold dysesthesias, rt hemiparesis</td>
<td>transient</td>
<td>no surgery</td>
</tr>
<tr>
<td>12</td>
<td>40, F</td>
<td>rt occipital</td>
<td>2 episodes severe HA &amp; lt homonymous hemianopsia (transient after 1st rebleed)</td>
<td>persistent</td>
<td>cavernous angioma</td>
</tr>
<tr>
<td>13</td>
<td>22, F</td>
<td>lt medial</td>
<td>2 episodes severe HA, nausea, vomiting</td>
<td>none</td>
<td>cavernous angioma</td>
</tr>
</tbody>
</table>

* HA = headache; INO = internuclear ophthalmoplegia; UE = upper extremity.

The CT scans disclosed areas of mixed density with minimal contrast enhancement, indicative of hemorrhage of differing ages. In Case 3, the recurrent hemorrhage appeared as a low-density ring adjacent to an acute hemorrhage. This low-density area was confirmed to be chronic hemorrhage on subsequent MR imaging. In one case of a thalamic cavernous angioma, the lesion produced a large cyst with a hematocrit level. The major portion of the cyst was shown on MR imaging to have a low signal intensity on T1-weighted images and a high signal intensity on T2-weighted images, consistent with free methemoglobin from hemorrhage. The hematocrit level was of intermediate signal intensity consistent with intracellular methemoglobin of red blood cells (Fig. 1). All other lesions demonstrated mixed areas of increased and decreased intensity consistent with various stages of hemorrhage (Figs. 2 and 3).

Clinical Symptoms

Eleven of the 13 patients experienced exacerbation of a preexisting neurological deficit as evidence for one or more recurrent hemorrhages. Ten patients had associated headache with their recurrent hemorrhage, and two suffered a seizure. No patient in this series died of recurrent hemorrhage (Table 2).

TABLE 2

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>exacerbation of deficit</td>
<td>11</td>
</tr>
<tr>
<td>headache</td>
<td>10</td>
</tr>
<tr>
<td>seizure</td>
<td>2</td>
</tr>
<tr>
<td>death</td>
<td>0</td>
</tr>
</tbody>
</table>

Timing and Impact of Repeat Hemorrhage

The interval from the initial hemorrhage to the first recurrent hemorrhage in this series of 13 patients ranged from 1 to 60 months (median time 12 months). Generally, the second rebleed occurred much earlier, with a median time of 2 months after the first; one patient experienced recurrent hemorrhages separated by less than 1 week (Table 3).
Five patients had one clinically relevant recurrent hemorrhage. Of those five, one patient suffered a persistent new neurological deficit, three had transient exacerbations of previous neurological deficits, and one had no neurological deficit except for acute severe headache with nausea and vomiting. Six patients had two recurrent hemorrhages; of these, two experienced persistent neurological deficits, three had transient exacerbations of neurological deficits, and one had no neurological deficit as a result of the second recurrent hemorrhage. Two patients suffered a third recurrent hemorrhage; both of these developed a persistent neurological deficit. Thus, there seemed to be a relationship between the number of hemorrhages and the produc-
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### Terminology and Literature Review

The susceptibility of small vascular malformations to hemorrhage was first described in 1951 by Margolis, *et al.*,19 four of whose patients suffered fatal hemorrhage. Crawford and Russell10 subsequently introduced the term “cryptic” to describe these small (< 2 to 3 cm) vascular malformations which caused spontaneous cerebral hemorrhage. Initially, the term “cryptic” was applied to the group of vascular malformations based on their small size alone. However, more recently the terms “cryptic” and “occult” have been applied to those vascular malformations that cannot be identified by cere-

### Surgical Management

Of the nine patients who underwent surgery, eight had total excision of their lesions. The remaining patient, with a large pontine lesion, underwent partial excision and has continued to deteriorate due to radiographically documented recurrent hemorrhages. Four patients refused surgery, two of whom have subsequently suffered a recurrent hemorrhage. Microsurgical technique was used in all instances due to the relatively small size of these lesions (the majority being < 1 cm in diameter). At surgery, all lesions showed evidence of old and recent hemorrhage. The majority of lesions appeared as small tangles of delicate blood vessels under relatively low pressure, some with thrombosed or partially thrombosed lumen. One lesion had formed a large cyst which was filled with blood clot of varying ages. One lesion had a mulberry shape typical of a cavernous angioma.

Five patients improved following surgical excision, two remained unchanged, and two experienced an increased neurological deficit as the result of surgery. One patient with increased deficit had a lesion in the superior cerebellar peduncle which had hemorrhaged for a second time 9 months after stereotactic radiosurgery using the Bragg peak method. He has a mild hemisensory deficit with a slightly detectable cerebellar hemiataxia. He has returned to full activity as a chemical engineer. The second patient who experienced neurological deficit subsequent to surgery harbors a large pontine vascular malformation. Although she was ambulatory after surgery, progressive intermittent neurological deficits have persisted due to recurrent hemorrhages from the unresected part of the lesion.

None of the nine patients undergoing surgery died. In the majority of deep-seated lesions, ultrasound was utilized to identify and locate the lesion. In most circumstances, these lesions showed a mixed echogenic signal of high and low intensity similar to the signal from MR imaging. No patient underwent CT-guided stereotaxis to locate the lesion.

### Histological Findings

Detailed pathological review was available for seven of the nine surgical specimens. Originally, four of these specimens were considered arteriovenous malformations (AVM’s) but, upon further study, all cases were reclassified as cavernous angiomas.

In all seven cases with adequate tissue for histopathological examination, there was evidence of recent and old hemorrhage. Old hemorrhage was characterized by fibrosis, the presence of macrophages, and the deposition of hemosiderin pigment. In all cases, the hemorrhage and the reaction to it had obliterated normal tissues and part of the vascular malformation, and careful evaluation of the edge of the hematoma was necessary to identify the residual part of the lesion. Diagnosis of cavernous angioma was based on the identification of large endothelium-lined vascular channels separated by varying amounts of collagen (Fig. 4). Except at the edges, brain substance was not present between the vascular spaces. Fibrosis of the walls of the vascular spaces was present at least focally in all cases (Fig. 4 right) and, when extensive, resulted in a marked thickening of involved vessels. This caused a superficial resemblance to an AVM, and required elastic and trichrome stains for accurate diagnosis. The absence of elastic fibers and smooth muscle in the thickened wall (Fig. 5) rules out arterial and venous components in the vascular malformation. The demonstration that the thick walls are composed of collagen alone favors the diagnosis of cavernous angioma. The performance of special stains for elastin and smooth muscle contributed to the reclassification of four cases originally considered AVM’s as cavernous angiomas.

### Discussion

#### Terminology and Literature Review

The susceptibility of small vascular malformations to hemorrhage was first described in 1951 by Margolis, *et al.*,19 four of whose patients suffered fatal hemorrhage. Crawford and Russell10 subsequently introduced the term “cryptic” to describe these small (< 2 to 3 cm) vascular malformations which caused spontaneous cerebral hemorrhage. Initially, the term “cryptic” was applied to the group of vascular malformations based on their small size alone. However, more recently the terms “cryptic” and “occult” have been applied to those vascular malformations that cannot be identified by cere-
bral angiography. A more appropriate term would be "angiographically occult." Thus, the designation "angiographically occult vascular malformation" represents a myriad of vascular malformations with variable histology and includes cryptic AVM's, thrombosed AVM's, cavernous angiomas, and other histological vascular lesions escaping detection by cerebral angiography.

Recent reports have thoroughly reviewed the histopathology, radiographic findings, and surgical management of patients with angiographically occult vascular malformations of the brain. In these and other series, recurrent hemorrhage has been mentioned as the pathophysiological mechanism for neurological deficit. A review of the literature reveals that 80% to 90% of angiographically occult vascular malformations showed evidence of hemorrhage. Even in asymptomatic cases or those presenting with seizures, MR imaging and pathological examination have documented the presence of hemosiderin, presumably the residue of previously experienced subclinical hemorrhage. However, the clinical and temporal profiles of clinically relevant hemorrhages have not been highlighted in the past.

Location and Histopathology of Lesions

Our series of 13 patients differs in some ways from previously reported cases. In a review of the literature in 1988, Lobato, et al., found that over 75% of angiographically occult vascular malformations were located in the supratentorial region. In our series, eight of the 13 patients had lesions in either the brain stem or the cerebellum. Likewise, in Lobato's review, 31% of the lesions were cavernous angiomas. All of the lesions in this series examined pathologically were cavernous angiomas. The routine use of trichrome stain for smooth muscle and collagen and stains for elastic fibers can help differentiate among the various pathological subtypes of vascular malformations for a more accurate diagnosis and clinical correlation. In addition, the diagnosis of angiographically occult vascular malformation is not specific despite modern imaging techniques and suggestive clinical history. The diagnosis can only be made definitively by surgical pathological confirmation. It is possible, although certainly not proven here, that clinically relevant recurrent hemorrhages may be associated with either one or both of these characteristics: namely, location or histopathology.

Recurrent Hemorrhage

In our series there was good correlation between the number of recurrent hemorrhages, the location of recurrent hemorrhages, and the occurrence of persistent neurological deficit. In most cases (80%) the initial rebleed caused only a transient deficit; however, with each successive recurrent hemorrhage, the likelihood of a resultant persistent neurological deficit increased, and all of the patients with more than two rebleeds suffered persistent neurological deficits. It is difficult to determine from our small series the relative influence on outcome of location versus number of hemorrhages.

It is probable that hemorrhages, even small ones, are more likely to produce clinical symptoms or neurological deficits in those lesions involving hazardous areas of the brain, such as the brain stem, thalamus, and eloquent cortex, and to bring them to recognition earlier. Furthermore, angiographically occult vascular malformations located in eloquent areas of the brain are often initially managed conservatively, as surgery in these areas is most difficult and carries a higher risk of morbidity compared to that of angiographically occult vascular malformations located in other areas. This may partially explain the disproportionate...
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number of lesions in our series located in the posterior fossa.

Although the full spectrum of the natural history remains to be elucidated, angiographically occult vascular malformations are prone to cause recurrent hemorrhages. Histologically, all of our surgical specimens revealed evidence of chronic and recent hemorrhage. In reviewing the literature, Lobato, et al., found that 31% of patients with documented histologically verified angiographically occult vascular malformations showed evidence of both chronic and recent hemorrhage. Similarly, Wakai, et al., reported 44% of patients with chronic and recent hemorrhage. Obviously, it is difficult to determine the exact rate of rebleeding from these lesions, and long-term retrospective or prospective population studies will be necessary. However, the rate of rebleeding appears considerable and may be similar to that of high-flow angiographically apparent AVM’s.

All patients in this series presented clinical symptoms of hemorrhage or exacerbation of a previous neurological deficit. However, not all hemorrhages from angiographically occult vascular malformations may be clinically evident. Lobato, et al., reported that 24% of the patients they reviewed had a clinical course suggestive of recurrent hemorrhage; seven of their own series of 21 patients with angiographically occult vascular malformations suffered recurrent symptoms of rebleeding. Although there were no deaths as a result of a recurrent hemorrhage in the present series, it is well known that patients may suffer fatal recurrent hemorrhages from these lesions. It has, therefore, become our policy to recommend removal when they are discovered in surgically accessible noneloquent areas of the brain. Lesions found in more hazardous areas are removed only if they produce recurrent hemorrhage.

Surgical Treatment

The surgical management of angiographically occult vascular malformations is not as straightforward as some have implied. They tend to be small and are not infrequently located deep in the cerebral or cerebellar hemisphere or brain stem. Localization of the lesions at the time of surgery may prove difficult. Therefore, we have relied on intraoperative ultrasonography to assist in this endeavor; CT-guided stereotaxis may be appropriate in certain circumstances. Unlike their larger high-flow counterparts, the endpoint of surgery for angiographically occult vascular malformations may be difficult to determine. The lesions tend to be small with very fine vasculature. Frequently, the vessels are not tightly compacted, making it difficult to be certain of total removal. Even lesions with predominantly cavernous elements on histopathology may not demonstrate the classical gross appearance of the easily removed cavernous angioma. Vigorous exploration and surgical manipulation of the cavity may prove hazardous in brain-stem lesions and other eloquent areas. Total removal in certain circumstances would be associated with unacceptable complications, especially in the case of pontine lesions.

Radiation Therapy

Recent reports have shown the efficacy of radiosurgery in the treatment of AVM’s. Although of theoretical value in the treatment of angiographically occult vascular malformations, the use of radiosurgery has met with limited success in treating cavernous angiomas as opposed to high-flow AVM’s (L Steiner: personal communication, 1989). In fact, one of our patients suffered a recurrent hemorrhage with a persistent neurological deficit 9 months following stereotactic radiosurgery with Bragg peak radiation, thus emphasizing the principle that recurrent hemorrhages may occur before complete obliteration of the lesion by radiosurgery or any other technique is achieved.

In summary, this series of cases underscores the propensity of angiographically occult vascular malformations to cause recurrent hemorrhages. Each successive hemorrhage tended to occur at shorter time intervals, and each hemorrhage tended to be associated with an increased incidence of permanent neurological deficit. Surgery can be effective and relatively safe in removing these lesions even in hazardous areas of the brain.

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References


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FIG. 5. Photomicrograph of an cavernous angioma specimen, stained for elastin, showing absence of elastic fibers in the thickened vessel wall. Elastin, × 200.

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