

## Are cavernous sinus hemangiomas and cavernous malformations different entities?

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✓ Cavernous hemangiomas that occur within the cavernous sinus (CS) are different from cerebral cavernous malformations (CMs) clinically, on imaging studies, and in their response to treatment. Moreover, CMs are true vascular malformations, whereas hemangiomas are benign vascular tumors. Because of these differences, the authors suggest that these two entities be analyzed and grouped separately. Unfortunately, despite these differences, much confusion exists in the literature as to the nature, behavior, and classification of these two distinct lesions. This confusion is exacerbated by subtle histological differences and the inconsistent use of nomenclature. The authors use the term “cavernous malformation” to refer to intraaxial lesions only; they prefer to use the term “cavernous sinus hemangioma” to refer to extraaxial, intradural hemangiomas of the CS.

**KEY WORDS** • cavernous hemangioma • cavernous malformation • cavernous sinus • middle fossa

**C**AVERNOUS malformations are well-characterized lesions that occur within the CNS. Despite similarities in the histological appearance of CMs and CS hemangiomas, the two lesions behave differently. Consequently, we maintain that these two entities are clinically different (Table 1). Their nomenclature should be used appropriately because the natural history and treatment paradigms of these lesions also differ. We briefly review the literature examining this issue.

### Differential Diagnosis of Cavernous Hemangiomas and CMs

Cavernous sinus hemangiomas are a rare group of extraaxial lesions that have been identified by many names, including “cavernous malformations,” “cavernous sinus hemangiomas,” and “middle fossa hemangiomas.” These terms have often been used interchangeably, causing confusion among clinicians.

Cavernous sinus hemangiomas most often occur within the CS, although they have also been reported to occur in other dural sinuses. They constitute 2 to 3% of all lesions within the CS.<sup>3,11,14</sup> Until 1992, only 53 cases of CS hem-

angiomas had been reported.<sup>11</sup> For unknown reasons CS hemangiomas are more common in women than in men,<sup>1,6</sup> and estrogen may play a role in their development.<sup>18</sup> Furthermore, CS hemangiomas usually grow during pregnancy and sometimes involute after delivery.<sup>21</sup>

There is a consensus that CS hemangiomas are extraaxial lesions and exhibit different clinical behavior than intraaxial CMs. The latter occur in both sexes and all ethnic groups. Most CMs appear to be spontaneous lesions. However, an autosomal-dominant syndrome that was first identified among Hispanics has been described, and the responsible family of gene mutations has been identified.<sup>16</sup>

In contrast, CS hemangiomas usually occur as single lesions in individuals with no familial history of the disease.<sup>26</sup> Besides their predilection for women, CS hemangiomas also predominantly occur within the Japanese population.<sup>24</sup> Although these lesions can arise within any dural sinus, they most often occur in the CS.<sup>12</sup>

Whether CS hemangiomas should be considered vascular tumors or vascular malformations (like CMs) has been a matter of controversy. Cavernous malformations are considered to be vascular malformations within the broad category of hamartomas. Thus, they are not thought to be neoplastic lesions per se. In contrast, CS hemangiomas grow over time, distorting and compressing adjacent tissues—a behavior consistent with neoplastic lesions.<sup>10</sup> As they grow, they may even expand<sup>22</sup> into the middle fossa.<sup>17</sup> Unlike intraaxial CMs, to the best of our knowledge CS hemangiomas do not manifest with acute bleeding. Rather, they

*Abbreviations used in this paper:* CM = cavernous malformation; CNS = central nervous system; CS = cavernous sinus; MR = magnetic resonance.

TABLE 1  
Distinguishing features of cavernous hemangiomas and intraaxial CMs\*

| Feature                 | Cavernous Hemangiomas   | Intraaxial CMs   |
|-------------------------|---|--|
| location                | CS, sagittal sinus, extradural, orbit   | brainstem, cerebral hemispheres, spinal cord   |
| symptoms                | cranial neuropathy, pain, diplopia  | incidental, headaches, seizures, acute bleeding  |
| cause of symptoms       | compression   | hemorrhage   |
| neuroimaging findings   |   |  |
| CT                      | occasional bone erosion, calcifications   | normal bone, no calcifications   |
| MRI                     | T <sub>1</sub> -weighted, isointense; T <sub>2</sub> -weighted, hyperintense; T <sub>1</sub> + Gd, markedly enhances; no venous anomaly | T <sub>1</sub> - & T <sub>2</sub> -weighted, heterogeneous signal; T <sub>1</sub> + Gd, minimal or no enhancement; often associated w/ DVA |
| DSA                     | 1/3 occult, 2/3 exhibit some degree of blush  | occult   |
| intraop appearance      | well-encapsulated, compact capsule  | nonencapsulated, soft, w/ blood in different stages  |
| histological appearance | channels lined w/ single layer of endothelium; no smooth-muscle or elastic fibers   | channels lined w/ single layer of endothelium; no smooth-muscle or elastic fibers  |
| thrombosis              | no evidence   | different stages of organization   |
| response to radiation   | sensitive   | nonsensitive   |

\* CT = computed tomography; DSA = digital subtraction angiography; DVA = developmental venous anomaly.

become symptomatic with the onset of acute or subacute ophthalmoparesis related to compression of the cranial nerves within the CS. Other common symptoms include facial pain, visual symptoms due to compression of the optic nerves or chiasm, and hypopituitarism. Thus, CS hemangiomas tend to be identified during surgery for lesions preoperatively diagnosed as meningiomas<sup>13</sup> or nerve sheath tumors.

In contrast, patients with CMs most often reach neurosurgical attention after they experience seizures or an acute event that leads to a focal deficit (long tract compromise) as a consequence of hemorrhage. The natural history of CMs is that these lesions tend to rupture, and by doing so cause a stepwise neurological deterioration. In retrospective studies of all CMs, based on the assumption that these lesions are present at birth, the overall annual rates of rupture have varied from 0.25 to 2.3%.<sup>7</sup>

Although they do not commonly present with hemorrhage, CS hemangiomas are high-flow vascular tumors that tend to hemorrhage profusely during resection. In a review of 53 cases, Linskey and Sekhar<sup>11</sup> reported a 36% surgery-related mortality rate, primarily associated with massive intraoperative hemorrhage. The profuse bleeding that is often encountered at surgery<sup>1,3</sup> is a common cause of incomplete resection,<sup>22</sup> and in one report was the cause of death, in eight individuals in a series of 46 patients.<sup>26</sup>

### Pathological Features

Cavernous malformations consist of a network of thin-walled, dilated vessels lined by a single layer of endothelium. The vessels are often adjacent to each other but may be separated by fibrous connective tissue and may exhibit variable hyalinization. The vascular channels lack an organized elastic lamina and tend to be devoid of smooth-muscle cells. The lumen of the vessels may be thrombosed from stagnant blood flow, and chronic lesions may be calcified. In contrast to arteriovenous malformations, intervening parenchymal tissue is scarce or absent.

Cavernous malformations and CS hemangiomas exhibit histological differences. Cavernous sinus hemangiomas often have a capsule or pseudocapsule<sup>11</sup> formed from the

dura mater;<sup>12,15</sup> the capsule may partially or completely envelop the lesion. Microscopic examination (Fig. 1) of the intervening connective tissue shows no evidence of previous hemorrhage. In contrast, CMs often demonstrate hemosiderin-laden macrophages (Fig. 3).<sup>12</sup> Typically, CMs are small and exhibit multiple vascular channels in various states of thrombosis, which likely reflects the low-flow nature of these lesions. Cavernous sinus hemangiomas, however, can be large and can contain vascular channels that lack histological evidence of thrombosis and calcification, which is consistent with their high-flow state. Orbital hemangiomas may share many of the histopathological characteristics of CS hemangiomas, including a pseudocapsule and the absence of previous hemorrhage.<sup>1</sup> However, similarly to CMs, vascular thrombosis has been reported within orbital cavernous hemangiomas.<sup>1</sup>

Based on both pathological and clinical differences, CS hemangiomas have been classified into two subtypes.<sup>21</sup> Subtype A is reported to be associated with severe intra-

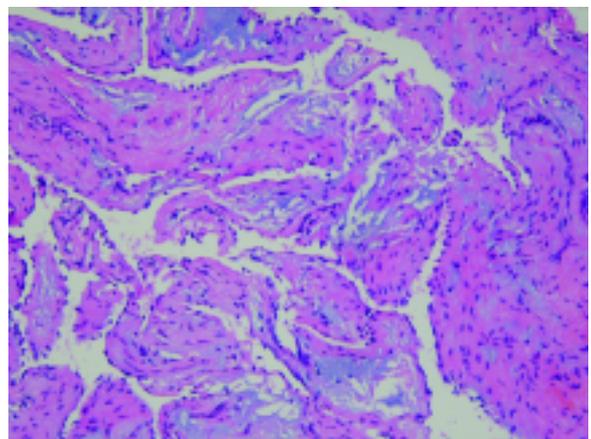


FIG. 1. Photomicrograph of tissue used for examination of a CS hemangioma shows no evidence of thrombosis, calcification, or hemosiderin-laden macrophages in this vascular lesion. H & E, original magnification  $\times 100$ . Printed with permission from Barrow Neurological Institute.

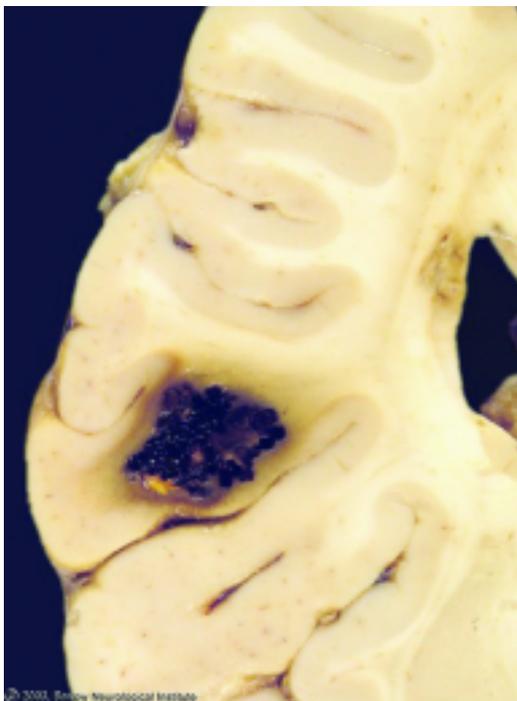


FIG. 2. Photograph of a gross specimen of an intraaxial CM showing the characteristic mulberry appearance of the lesion as well as the hemosiderin stain surrounding the parenchymal tissue. Printed with permission from Barrow Neurological Institute.

operative bleeding. Pathologically, these lesions exhibit thin-walled, sinusoidal, adjacent vessels with scant intervening connective tissue. In contrast, Subtype B CS hemangiomas are more easily removed than Subtype A and are associated with fewer surgical complications. Subtype B lesions have more intervening connective tissue than

Subtype A CS hemangiomas. The vessels of Subtype B are less sinusoidal than those of Subtype A, and their size and shape are more variable and irregular.

### Treatment Considerations

The orbitozygomatic approach with extradural drilling of the anterior clinoid process has been suggested as the approach of choice for lesions of the CS. It simultaneously offers access to the CS and to the frontal and middle fossae. Despite the massive bleeding associated with CS hemangiomas, their complete resection is possible. Nevertheless, iatrogenic injury to the sixth cranial nerve<sup>11</sup> frequently occurs. Because this cranial nerve is compromised during surgery, extraocular movements fail to improve after resection in many patients.<sup>20</sup>

To the best of our knowledge, Shibata and Mori<sup>23</sup> first reported the use of radiation to treat incompletely resected CS hemangiomas as well as its preoperative use to decrease intraoperative blood loss. A significant body of evidence confirms that benign tumors within the CS,<sup>2</sup> including CS hemangiomas, respond well to external-beam radiation.<sup>8</sup> In fact, if massive bleeding is encountered during surgery, the procedure can be interrupted until radiation therapy is delivered.<sup>17</sup> This feature constitutes another major difference from CMs, which fail to shrink in response to radiation and can even respond by swelling.<sup>27</sup>

Treatment with Gamma Knife radiation has been successful, and is associated with a mean reduction of 54% in tumor volume.<sup>25</sup> It has been hypothesized that radiation induces endothelial proliferation and hyalinization of the vessel wall.<sup>19</sup> A mean dose of 14 Gy applied to the 50% isodose line has been reported to be sufficient to decrease tumor volume. The optic pathways should receive no more than 10 Gy.<sup>14</sup> Fractionated external radiation has also been reported to be successful.<sup>9</sup> Theoretically, however, a single high dose of Gamma Knife radiation focused on a

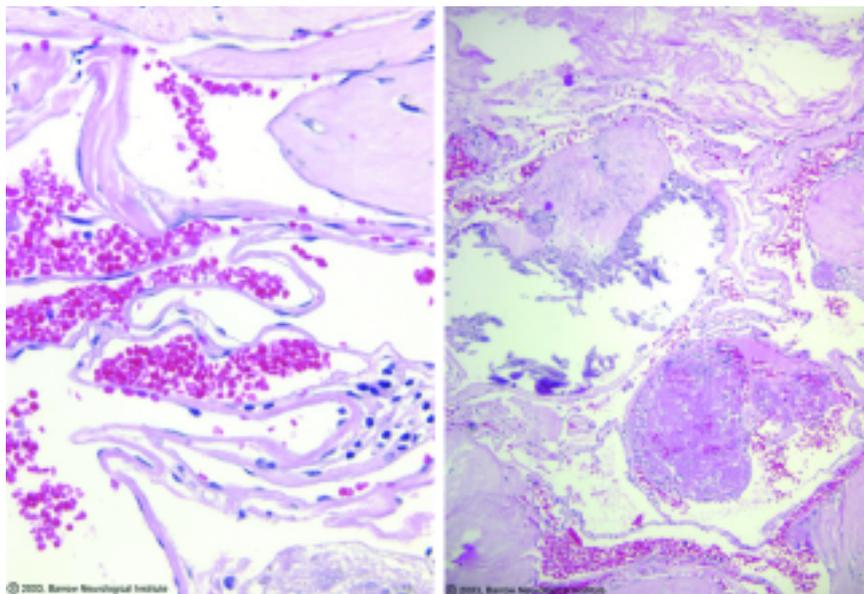


FIG. 3. Photomicrographs of histological sections of an intraaxial CM. *Left:* The characteristic adjacent sinusoidal vascular channels are shown. *Right:* The classic features of thrombosis and calcification are shown. H & E, original magnification  $\times 100$ . Printed with permission from Barrow Neurological Institute.

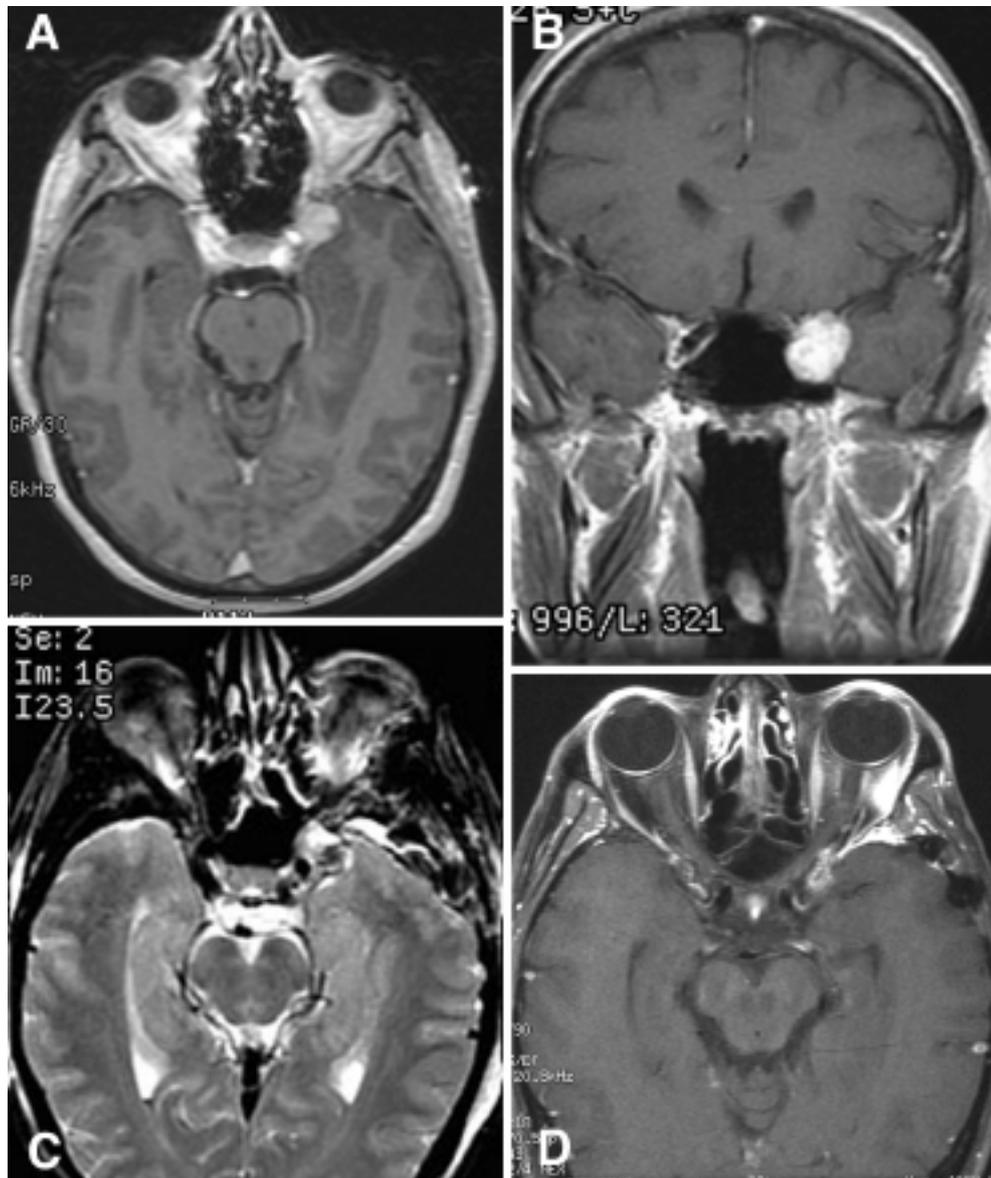


FIG. 4. Axial (A) and coronal (B) MR images obtained after addition of contrast material demonstrating enhancement of the left CS. Axial T<sub>2</sub>-weighted MR image (C) demonstrating a heterogeneous hyperintense signal from the same area. Six years after Gamma Knife radiation with 13 Gy to the 50% isodose line, an axial MR image (D) obtained after addition of contrast material demonstrates significant reduction in the size of the hemangioma.

small volume with an acute falloff at the margin may improve occlusion of vascular malformations.<sup>25</sup>

Current imaging capabilities should enable the differentiation of meningiomas and schwannomas from CS hemangiomas (Fig. 4). The distinction is critical because their treatment algorithm is different. If a CS hemangioma is suspected, an open biopsy procedure is recommended to establish a histological diagnosis. If the suspicion of a CS hemangioma is confirmed, stereotactic radiation is recommended as the definitive treatment.

#### Appearance on Diagnostic Imaging

A high index of suspicion is necessary to differentiate CS hemangiomas from other tumors such as meningiomas

and schwannomas that frequently occur in the CS. Cavernous sinus hemangiomas are usually well-defined, demarcated masses that enhance intensely after administration of contrast material (gadolinium). However, a lack of enhancement has also been reported.<sup>24</sup> A constant finding across series is the bright appearance of hemangiomas on T<sub>2</sub>-weighted MR sequences.

Angiographically, one third of the cases are occult, showing no staining.<sup>5,26</sup> The remaining two thirds exhibit some degree of “blush” characteristic of tumor feeding vessels, typically from branches of the intracavernous carotid artery, primarily the meningohypophyseal trunk. Nevertheless, branches from the external carotid artery, such as the accessory middle meningeal artery, can also be involved. Preoperative embolization has been described but

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does not appear to decrease intraoperative bleeding.<sup>15</sup>

On the arterial phase of the angiogram, some authors have reported slow flow reflected as a persistent blush.<sup>1</sup> The slow flow is considered to be responsible for the hyperintensity seen on T<sub>2</sub>-weighted MR images. Unlike meningiomas, a dural tail is seldom visible adjacent to CS hemangiomas.

Blood flow through CMs is usually slow. This stagnant flow may calcify<sup>12</sup> and is probably responsible for their occult appearance on angiography. In contrast, CS hemangiomas may exhibit the previously described blush.

Cavernous malformations are associated with blood in different stages of organization. This feature produces their typical “popcorn” appearance. Cavernous sinus hemangiomas, however, do not exhibit blood in the adjacent perivascular connective tissue.

Cavernous malformations are also often associated with a developmental venous anomaly, which does not accompany cavernous hemangiomas.<sup>4</sup> Preservation of the venous anomaly is key during the resection of CMs, whereas this issue is not a concern during the resection of CS hemangiomas.

### Conclusions

Although CS hemangiomas and CMs within the CNS share similar microscopic and gross pathological features, the two lesions exhibit clear clinical differences.<sup>3,12</sup> Poorly defined nomenclature is a major obstacle that has impeded the understanding and appropriate classification of these lesions. Based on the experience of the senior author (R.F.S.), the term “cavernous malformation” should be reserved for lesions that occur within the CNS, and “cavernous hemangioma” should be applied to lesions in extraaxial locations. Appropriate nomenclature should be used to avoid confusion and to improve understanding of these two distinct entities.

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