Our group has identified four pediatric patients in whom an arteriovenous malformation (AVM) recurred after resection and in whom a normal postoperative angiogram had been obtained. Given what is known about the plasticity of the pediatric nervous system, we hypothesize that a trophic mechanism other than hemodynamics may be responsible for this phenomenon.

Recent work has concentrated on factors involved in the process of angiogenesis and has focused on the concept that a general mediator might be responsible for the initiation or induction of this process. Vascular endothelial growth factor (VEGF) is a possible candidate for this role, based on its specificity for vascular endothelium and its ability to serve as an endothelial cell mitogen both in vivo and in vitro. We investigated the question of whether VEGF expression might occur in association with AVMs, and whether there are any differences in expression of VEGF between the recurrent and nonrecurrent lesions. Immunocytochemical analysis was used to characterize VEGF expression in AVM tissue samples from four recurrent pediatric AVMs and 15 randomly selected adult and pediatric cases. Immunocytochemical analysis for glial fibrillary acidic protein (GFAP) was used to identify the cell type with which VEGF immunoreactivity was associated.

Clinical Material and Methods

Specimen Selection and Clinical Characteristics

Four specimens were selected from children who experienced recurrence of their AVM after a normal postoperative angiogram. Specimens from seven children (≤ 18 years of age) and eight adults were also selected at random. Table 1 provides a summary of the clinical profiles of all cases studied. The mean age of patients with a recurrent AVM was 9 years (range 8–11 years) at first presentation and 14 years at second presentation (range 12–15 years). The mean ages of the nonrecurrent pediatric and adult patients were 8 years (range 7 months–18 years) and 38 years (range 19–58 years), respectively. The specimens from patients with recurrent AVMs were only available from the first operation. Two fetal brain specimens (20 weeks) and two adult glioblastoma multiforme specimens were randomly selected from material submitted over a 10-year period to serve as positive controls. Gliotic brain autopsy specimens from a 3-month-old child with congenital heart disease and an adult with multiple infarcts were obtained from a collection in the neuropathology department. All specimens were initially fixed in 10% formalin overnight, then paraffin embedded the next day. These specimens were all stored at room temperature.
Vascular endothelial growth factor expression in AVMs

*Immunostaining With VEGF*

Pathological specimens were sectioned at 6 µ and mounted on standard lysine-coated slides. These sections were deparaffinized by treating them sequentially in xylene (15 minutes), 100% alcohol (20 minutes), and 95% alcohol (20 minutes); then rehydrating them for 5 minutes in distilled water. Endogenous peroxidase activity was quenched with 1% hydrogen peroxide for 1 hour. After treatment with 0.1% trypsin in phosphate-buffered saline (PBS: 10 mM NaHPO₄, 140 mM NaCl, pH 7.5) followed by soybean trypsin inhibitor (5875 Nα-benzoyl-L-arginine ethyl ester U/ml PBS), the slides were then placed in a moisture chamber that was used for all subsequent incubations and incubated with 10% goat serum in PBS (blocking solution) to suppress nonspecific binding of antibodies to the tissue samples. All subsequent antibody dilutions were performed using blocking solution. Rabbit anti-VEGF immunoglobulin (Ig) G polyclonal antibody (Ab2; Oncogene Science, Cambridge, MA) was added to each section at a concentration of 10 µg/ml after washing. The slides were then incubated at room temperature overnight. Negative control specimens, selected from adjacent sections of each block of tissue, were run concurrently in our immunocytochemistry protocol except that purified nonimmune rabbit IgG was replaced for the VEGF antibody or incubation with primary antibody was omitted. Specimens were processed for staining at room temperature with the peroxidase avidin-biotin complex kit and, after a 2-minute incubation in 0.1% Triton X-100 in PBS, were developed with the diaminobenzidine visualization kit (both obtained from Vector Laboratories, Burlingame, CA). Slides were then counterstained with hematoxylin and mounted on a coverslip with a nonaqueous mounting medium. Specimens from at least two separate groups of AVMs were run concurrently in each experiment to avoid bias. Fetal tissue was run concurrently with each experiment to confirm the success of VEGF immunostaining.

*Immunostaining With GFAP*

Anti-gial fibrillary acidic protein mouse monoclonal antibody (1:50 dilution; Boehringer Mannheim GmbH, Mannheim, Germany) was added to adjacent tissue sections in several runs of the above experiment. All subsequent steps were identical to those described for VEGF immunocytochemistry, using a biotinylated anti–mouse secondary antibody.

*Microscopic Analysis*

Expression of VEGF. The VEGF expression was examined in all specimens and compared with negative and positive controls. A brightfield microscope was used for this analysis. The specimens were analyzed by two investigators (A.K. and J.L.) blinded to the specimen’s origin using criteria based on initial observations. Staining characteristics, including distribution and intensity, were graded in all specimens by these two investigators. The following distributions of stain were ascertained: 1) focal cellular; 2) background; and 3) blood vessel wall. Focal cellular staining was defined as stain within the cell body. Three separate representative areas in and around the AVM nidus were examined. Each area was graded as 1+ for less than or equal to five cells per high-power field (40 ×), 2+ for greater than five cells, and 0 for no staining. Background staining was assessed in relationship to the areas of focal cellular staining. It was characterized as 1+ for patchy and 2+ for confluent. The distribution of staining on AVM vessels was also analyzed.

Cell Type Determination. Representative pediatric and adult AVM tissue sections with 2+ focal cellular staining were processed separately for VEGF and GFAP immunoreactivity on serial sections and compared, side by side, using common landmarks.

*Statistical Analysis*

Fisher’s exact test was performed to determine whether there were significant differences in 2+ focal cellular staining between groups.

*Results*

Human Fetal Brain and VEGF Immunoreactivity

Results from this experiment are illustrated in Fig. 1, which demonstrates VEGF immunoreactivity in cells migrating from the germinal matrix (Fig. 1A) to the cortical plate in the telencephalon (Fig. 1C). The inset in Fig. 1A demonstrates VEGF immunoreactivity at a higher magnification in the taillike extension of cytoplasm in young postmitotic cells. In contrast, there is no apparent staining in sections that were subjected to the immunohistochemistry protocol in the absence of the primary antibody (Fig. 1B and D). The GFAP immunoreactivity is only present in the subventricular region, but does not extend beyond this area (not shown). Fetal sections were run concurrently in the presence or absence of primary antibody, with each subsequent experiment in this study to serve as positive and negative controls.

*Immunoreactivity of VEGF in Association With Recurrent AVMs*

Table 1 offers a description of 19 AVM cases with respect to the age of the patient at the time of surgery, sex, location of the AVM, initial presentation, and VEGF staining characteristics. All four specimens obtained from recurrent pediatric cases demonstrated 2+ focal cellular staining. Only one (14%) of seven specimens from the nonrecurrent pediatric group exhibited 2+ focal cellular staining. One specimen (pediatric Case 9) showed 1+ focal cellular staining. Two (25%) of eight adult cases demonstrated 2+ focal cellular staining (adult Cases 5 and 7) without any relationship to abnormal blood vessels. Adult Case 8, with 1+ focal cellular staining, showed only faint patches of background stain. Adult Case 7 did not exhibit background stain, but we also observed that this tissue was hemorrhagic. Overall, there was an association of background staining with focal cellular staining. All recurrent AVM specimens demonstrated background staining as compared to six (40%) of 15 adult and nonrecurrent pediatric AVMs. Vessel wall staining with VEGF was seen in two of four recurrent and one of seven nonrecurrent pediatric, and in two of eight adult AVM specimens. There was no correlation between vessel wall staining and cellular staining in any of the groups.
Staining characteristics of VEGF in recurrent AVMs are presented in Fig. 2 and are summarized in Table 1. A high degree (2+) of focal cellular staining was present in all recurrent AVM specimens analyzed. Furthermore, in three of four recurrent AVMs (pediatric Cases 1, 3, and 4), stained cells were distributed over the majority of the high-power field, numbering severalfold higher than in the other specimens. In contrast, no staining of adjacent tissue sections was observed when nonimmune rabbit IgG replaced the VEGF rabbit IgG in the staining protocol (Fig. 2B and D). Instead, some brown deposits of hemosiderin were observed. The arrangement of VEGF immunoreactive cells in the recurrent AVMs varied in each tissue section examined, but the cells were mainly localized to gliotic regions either in a palisading fashion in relation to the subarachnoid spaces containing abnormal vessels (Fig. 2A) or next to abnormal vessels that were purely intraparenchymal (Fig. 2C and G). The cells themselves resembled reactive astrocytes morphologically, because these cells were stellate in appearance with extending processes (Fig. 2E). Figure 2F illustrates how some of these cells were very large and intensely stained, with immunoreactivity localized mainly in the cell body. There was a gradient of density and intensity of focal cellular staining with the highest degree starting most proximal to the abnormal blood vessel and decreasing farther out into the gliotic tissue (Fig. 2G). All of the specimens from recurrent AVMs that demonstrated focal cellular staining also contained background staining that was confluent or patchy in distribution, as illustrated in Fig. 2F. Background staining appeared to be composed of densely packed cell processes. In two of four recurrent specimens analyzed, VEGF immunoreactivity was localized to the lining of some blood vessels (Fig. 2H), within the endothelial cells that form the lumen (Fig. 2H, inset). In the other cases, the stain was shown to respect the vessel wall entirely (Fig. 2I).

Nonrecurrent pediatric and adult AVM specimens were also analyzed for the properties described in the previous section. These observations are presented in Fig. 3 and are summarized in Table 1. One nonrecurrent pediatric AVM (pediatric Case 9) had 1+ focal cellular staining, similar to that in adult Case 8 (Fig. 3A). Some nonrecurrent pediatric and adult cases exhibited focal cellular staining (pediatric Cases 8 and 9 and adult Cases 5, 7, and 8) and the cells had the morphological features described above. However, their distribution was different from the recurrent AVMs in that there did not appear to be a gradient of distribution around the blood vessels. The nonrecurrent pediatric AVMs that demonstrated focal cellular staining also contained background staining, and there was one case in which no focal cellular staining was observed but 1+ background staining was noted. Two of four recurrent and three of seven nonrecurrent pediatric AVMs and three of eight adult AVMs demonstrated vessel wall staining; and in most cases staining was apparent throughout the thickness of the wall. In two cases the stain was seen within the preserved endothelium, similar to that illustrated in Fig. 2H. For four pediatric cases and four adult cases, no VEGF immunoreactivity could be demonstrated. The lack of staining is illustrated in Fig. 3B; although the tissue section contained abnormal AVM vessels and was subjected to the VEGF immunohistochemical protocol, no staining was observed. In addition, when serial tissue sections of a
Vascular endothelial growth factor expression in AVMs

Fig. 2. Photomicrographs showing vascular endothelial growth factor (VEGF) immunoreactivity characteristics associated with recurrent arteriovenous malformations (AVMs) in children. Hematoxylin counterstaining was used in all sections. A and B: Photomicrographs showing vascular pathology in pediatric Case 1. A: Photomicrograph showing a large dilated blood vessel (arrow) in the subarachnoid space with closely associated immunoreactive cells in the gliotic and siderotic tissue surrounding the subarachnoid space. There are many cells with focal cellular immunoreactivity (arrowheads) as well as confluent background staining bordering the subarachnoid space. Magnification shown × 78. B: A section from the same region as shown in A, demonstrating the absence of staining when the VEGF antibody is replaced by nonimmune rabbit immunoglobulin G (IgG). Arrows in A and B point to the same blood vessel. Magnification shown × 78. C and D: Photomicrographs showing vascular pathology in pediatric Case 2. C: Photomicrograph depicting VEGF immunoreactivity. Magnification shown × 43. D: Adjacent areas processed with nonimmune rabbit IgG that are devoid of staining. Blood vessels are at the top and bottom of both fields. Cells are marked with arrows. Magnification shown × 43. E: A high-power view of two VEGF immunoreactive cells (arrows) near the pial border zone in a specimen from pediatric Case 1. Note that the cellular processes are stained as well as the cell body. Magnification shown × 566. F and G: Pediatric Case 3. F: Photomicrograph illustrating 2+ focal staining (arrow) with confluent background (arrowhead). Magnification shown × 113. G: Photomicrograph showing a gradient of focal cellular staining (doubleheaded arrow) in proximity to abnormal blood vessel in subarachnoid space. Magnification shown × 113. H: Pediatric Case 2. Immunoreactivity localized to abnormal blood vessel walls (arrows). Lumen is indicated by arrowheads. Magnification shown × 113. Insert shows staining localized to endothelial cells (arrow). Magnification shown × 566 with oil immersion lens. I: Pediatric Case 1 (recurrent AVM). Photomicrograph showing immunoreactivity respecting blood vessel walls (arrows). Magnification shown × 113.
Fig. 3. Photomicrographs showing vascular endothelial growth factor (VEGF) immunoreactivity characteristics associated with nonrecurrent pediatric and adult arteriovenous malformations (AVMs). Hematoxylin counterstaining was used in all sections. A: Adult Case 8. Photomicrograph showing an example of staining graded 1+: one strongly stained cell (arrow) in proximity to an abnormal blood vessel without background stain. Magnification shown × 125. B: Adult Case 2. An AVM with representative architecture and no staining present. Magnification shown × 55. C and D: Pediatric Case 10. Photomicrographs demonstrating gliosis in the absence of VEGF staining. Magnification shown × 110. No VEGF immunoreactivity is demonstrated in C, whereas D shows an adjacent section demonstrating glial fibrillary acidic protein (GFAP)–immunopositive cells (arrowheads). Arrows point to blood vessels that run through both sections. E and F: Photomicrographs of sections demonstrating the coincidence of VEGF (E) and GFAP (F) immunoreactivity (arrows) in gliotic brain tissue obtained at autopsy from a child with congenital heart disease. Magnification shown × 220. G and H: Similarly, VEGF (G) and GFAP immunoreactivity (H) can be found in the same area of gliosis in an adult brain. Magnification shown × 110. Note that there are fewer VEGF than GFAP immunoreactive cells in this area.
Vascular endothelial growth factor expression in AVMs

Nonrecurrent AVMs were stained for the presence of VEGF and GFAP (Fig. 3C and D, respectively), an astrocytic protein that predominates in gliotic tissue. It was found that although astrocytes were present, VEGF immunoreactivity was absent.

The putative localization of VEGF in reactive astrocytes of recurrent AVM tissue and the apparent absence of staining in the majority of AVMs that did not recur led us to examine other types of gliotic tissue for VEGF expression. Figure 3E and F illustrate the presence of VEGF- and GFAP-immunoreactive cells in a case of an infant with congenital heart disease. The pattern and distribution of VEGF and GFAP, respectively. Magnification shown × 118. E and F: Adult Case 7. An AVM stained for VEGF (E) and GFAP (F) immunoreactivity. Arrows point to cells of similar size and shape in each section. Magnification shown × 236.

Table 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex†</th>
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<th>Initial Presentation</th>
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<td></td>
<td></td>
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<td>1</td>
<td>8 (14), F</td>
<td>rt sylvian</td>
<td>lt hemi, SAH with clot</td>
<td>2+</td>
<td>2+</td>
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<tr>
<td>2</td>
<td>11 (14), M</td>
<td>lt medial parietal</td>
<td>ivh &amp; clot</td>
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<td>2+</td>
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<td>2+</td>
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<td>headache, ivh</td>
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<td>0</td>
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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>3, M</td>
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<td>sz, clot</td>
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<td>0</td>
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<tr>
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<tr>
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<td>sz, headache</td>
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<tr>
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<tr>
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<td>33, F</td>
<td>body rt lat ventricle</td>
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<tr>
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<tr>
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<td>rt occipital</td>
<td>headache, clot, lethargy, ivh</td>
<td>1+</td>
<td>1+</td>
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* Pediatric Cases 1 through 4 had recurrent arteriovenous malformations (AVMs). Abbreviations: hemi = hemiparesis; inter = interhemispheric; IVH = intraventricular hemorrhage; SAH = subarachnoid hemorrhage; sz = seizures; VEGF = vascular endothelial growth factor.

† Numbers in parentheses indicate patient’s age when AVM recurred.

‡ 2+ = staining > 5 cells/high-power field; 1+ = staining ≤ 5 cells/high-power field; 0 = no staining.

§ 2+ = confluent; 1+ = patchy; 0 = no staining.

Note the same blood vessel walls as landmarks (arrows). Magnification shown × 118. C and D: Pediatric Case 2, recurrent AVM. Photomicrographs illustrating adjacent regions within 30 μm with similar appearing immunoreactivity to (Fig. 4 continued →)
of stained cells in this predominantly gliotic tissue suggest that VEGF is expressed by the same cells that express GFAP. Similarly, Fig. 3G and H demonstrate that both VEGF and GFAP immunoreactive cells are present in adult gliotic brain, although there are fewer VEGF immunoreactive cells than cells expressing GFAP.

Three illustrations of the similarities in pattern and distribution of VEGF (Fig. 4A, C, and E) and GFAP staining (Fig. 4B, D, and F) in AVMs are presented in Fig. 4. The VEGF immunopositive cells (Fig. 4A and B) were observed to be distributed with the same pattern and frequency as the GFAP-immunoreactive astrocytes in proximity to the subarachnoid space containing an abnormal blood vessel that was present in each section of a recurrent AVM (pediatric Case 1). This observation was repeated for all cases and is again illustrated in Fig. 4C and D. At higher magnification, the large cells appear to be polygonal in an adult AVM (adult Case 7) with a few small stained processes extending from the cell bodies (Fig. 4E and F).

A comparison of focal cellular staining in recurrent and nonrecurrent AVM specimens revealed a significant difference in the proportion of each group that had 2+ focal cellular staining (Fisher’s exact test, p < 0.01). Thus, a significantly higher degree of VEGF staining (2+) was associated with the recurrent group. A comparison of the staining in recurrent and nonrecurrent pediatric cases alone also revealed that this was still a significant association (p < 0.015).

Correlation of VEGF Focal Immunoreactivity With Clinical Data

The clinical information for the individual cases in each group was then compared with our results for VEGF focal cellular staining. Age, sex, and location of the lesion did not correlate with focal cellular staining. The relationship between clinical presentation and staining intensity was also assessed, primarily to see if the presence of hemorrhage could be correlated with the amount of immunoreactivity. In five pediatric patients, AVM specimens showed 2+ focal staining, and the three who presented with hemorrhage and this degree of staining were all from the recurrent group. The remaining child with 2+ focal cellular staining presented with seizures. The two adult patients with 2+ focal cellular staining also presented with seizures. There were three nonrecurrent pediatric and three adult patients with AVMs who presented with hemorrhage, but had no demonstrable VEGF focal immunoreactivity. Hence, there was no correlation between previous hemorrhage and focal cellular staining.

Discussion

Our results demonstrate that VEGF, an angiogenic factor, is associated with cerebral AVMs. We have also shown VEGF immunoreactivity to be present in human fetal telencephalon during the time at which normal angiogenesis takes place.\(^1\)\(^,\)\(^13\)\(^,\)\(^15\) Furthermore, we present evidence that a high degree of focal cellular staining is preferentially associated with pathological specimens obtained from children who developed recurrent AVMs after negative postoperative angiograms, a subpopulation of patients who may be undergoing active angiogenesis.

These findings have important implications in the understanding of AVM etiology. Arteriovenous malformations are thought to result from a congenital failure of capillary development that occurs at approximately the 3rd week of gestation.\(^1\)\(^,\)\(^13\) This results in direct communication between arteries and veins without an intervening capillary bed.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\)\(^,\)\(^15\)\(^,\)\(^16\)\(^,\)\(^17\)\(^,\)\(^20\)\(^,\)\(^21\)\(^,\)\(^23\)\(^,\)\(^27\)\(^,\)\(^30\) Normal human embryonic vascular development conforms to a relatively predictable progressions.\(^1\)\(^,\)\(^15\)\(^,\)\(^19\) yet, because of the lack of availability of human fetal tissue from the entire range of gestation for study, it is not clear what factors mediate this process.\(^1\)\(^,\)\(^15\) Many animal studies have shown that the growth of blood vessels during embryogenesis and in the adult organism is tightly controlled and this growth is thought to be mediated by soluble factors.\(^3\)\(^,\)\(^6\)\(^,\)\(^9\)\(^,\)\(^10\)\(^,\)\(^17\)\(^,\)\(^20\)\(^,\)\(^21\)\(^,\)\(^23\)\(^,\)\(^31\) Because of its specificity for endothelial cells, its potent mitogenic effects on the vascular endothelium of both large and small vessels in vivo and in vitro, and its possession of a hydrophobic signal sequence, VEGF appears to be one of these factors.\(^2\)\(^,\)\(^11\)\(^,\)\(^12\)\(^,\)\(^13\)\(^,\)\(^14\) We have also found that VEGF immunoreactivity is present in many cells of the developing human telencephalon at 20 weeks of gestation (Fig. 1), a finding that supports a role for VEGF in angiogenesis. Other polypeptide factors such as basic fibroblast growth factor and platelet-derived growth factor also play a role in angiogenesis,\(^3\)\(^,\)\(^9\)\(^,\)\(^14\) their role in AVM pathology remains to be determined.

Pathological states characterized by increased vascularization, such as malignant brain tumors, are associated with increased VEGF expression and correlated with tumor grade.\(^1\)\(^,\)\(^6\)\(^,\)\(^9\)\(^,\)\(^10\)\(^,\)\(^17\)\(^,\)\(^20\)\(^,\)\(^21\)\(^,\)\(^23\)\(^,\)\(^26\)\(^,\)\(^27\)\(^,\)\(^29\)\(^,\)\(^30\) Immunoreactivity of VEGF has been found in association with the AVM nidus under certain circumstances, particularly in those patients in whom an AVM recurred (Table 1). Because we also found positive staining in some adults and nonrecurrent pediatric patients, we believe that synthesis of VEGF may be a necessary but not sufficient factor in AVM growth, formation, and maintenance.
Vascular endothelial growth factor expression in AVMs

It is possible to argue that VEGF expression in these AVMs may be a reactive phenomenon associated with gliosis, chronic ischemia, or previous hemorrhage. Examples of VEGF immunoreactivity in other gliotic non-AVM tissue in association with GFAP-positive astrocytes (Fig. 3E–H) support this hypothesis. It is possible that there may be a subset of AVMs in which the gliotic tissue selectively expresses VEGF as a result of unidentified factors inherent to the maturation state of the AVM itself. The specificity of VEGF expression in gliotic tissue to certain circumstances is supported by the observations of Strugar and colleagues, who found that no immunoreactivity was present in gliotic “control” tissue in a study of glial tumors. In addition, the three nonrecurrent patients with significant cellular staining never had a hemorrhage and many patients with previous hemorrhage did not show any VEGF staining. Furthermore, because many specimens (eight of 15) with abundant gliotic tissue in relation to nonrecurrent AVMs failed to demonstrate VEGF staining (Fig. 3B), the conclusion that VEGF expression is always linked to the reactive gliotic process is not easily drawn.

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References


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