Histopathological follow-up study of 66 cerebral arteriovenous malformations after therapeutic embolization with polyvinyl alcohol

ISABELLE M. GERMANO, M.D., RICHARD L. DAVIS, M.D., CHARLES B. WILSON, M.D., AND GRANT B. HIESHIMA, M.D.

Departments of Neurological Surgery, Pathology (Neuropathology), and Radiology (Interventional Neuroradiology), School of Medicine, University of California, San Francisco, California, and Department of Neurological Surgery, Albert Einstein College of Medicine, New York, New York

Embolization with polyvinyl alcohol (PVA) is an accepted method of rendering complex arteriovenous malformations (AVM's) more amenable to surgery, but its effects on human vascular tissues have not been adequately documented. The authors reviewed the histopathology of 66 intracranial AVM's resected 1 to 76 days after embolization with PVA. The mean age of the patients was 36 years, and their AVM's were located in the cerebral hemispheres (92%), the cerebellum (6%), or the corpus callosum (2%). In 79% of cases, at least one vessel contained PVA particles; in most cases, the vessel was filled with sharp, angular PVA particles in a serpiginous pattern. Polyvinyl alcohol particles indented the endothelium in 69% of cases but were rarely found subendothelially. Clotted blood and fibroblasts were present among the particles, and abundant intraluminal mononuclear and polymorphonuclear inflammatory cells were found in all vessels containing PVA particles. Foreign-body giant cells appeared 2 to 14 days after embolization in the majority of cases. Patchy mural angioneogenesis and necrotizing vasculitis were found in 39% of the cases. Recanalized lumina were seen in 18% of PVA-embolized vessels. Foreign materials resembling cotton fibers and other particulate substances, which were probably contaminants of the contrast solution or the embolic material, were found in 65% of the cases. These findings suggest a specific chain of events in the interaction between PVA and vascular wall components and may explain some important sequelae of embolization therapy.

KEY WORDS • arteriovenous malformation • embolization • polyvinyl alcohol

Cerebral arteriovenous malformations (AVM's) may represent a serious challenge in surgical management.17 Earlier strategies for rendering large complex AVM's more amenable to resection included multistage operations and nonsselective flow-directed embolization with particulate emboli.15,26,38,43,49 As a consequence of greatly improved instrumentation and experience in interventional neuroradiology, superselective particulate embolization is now available.3,14,35 There is evidence that this technique reduces the morbidity and mortality rates after subsequent resection of AVM's.11,22

Many different materials have been used to occlude cerebral AVM's, including metallic coils, balloon catheters, liquid tissue adhesives, and particulate matter.2,5,9,12,19,45 Polyvinyl alcohol (PVA), a particulate agent, is currently favored for its biocompatibility39 and technical characteristics.8,10,21,23 Once popular as a vascular and cardiac prosthetic material15 and for intrathoracic implants after pneumonectomy,17 it was introduced as an embolic agent in 1971.31 Because it can be compressed and subsequently re-expands on contact with blood, PVA was used as an embolic plug to occlude large vessels.7,30 The refinement of embolization techniques, including microembolization by superselective catheterization, has allowed the preservation of proximal flow after distal occlusion.8,32 The use of PVA in this setting was initially limited by the difficulty of its preparation and delivery by frequent catheter obstruction.56 With further technical improvements, PVA has become more suitable for microembolization and has been successfully used for superselective embolization of vascular lesions.3,14,25,35

In experimental and clinicopathological studies, the degree of tissue reaction to PVA has been inconsistent.5,23,24,32,40,46 The sometimes conflicting results stem in part from differences in the organs studied, in the settings in which PVA has been used, and in the histo-
logical follow-up period after embolization. Moreover, the effects of PVA on normal vessels in experimental animals may have only slight relevance to its effects on cerebral AVM’s in patients. In this study, surgical specimens of 66 human cerebral AVM’s were analyzed to determine the sequence of histopathological events after embolization with PVA.

Clinical Material and Methods

Between January 1, 1986, and August 8, 1989, 88 patients underwent preoperative partial therapeutic embolization of cerebral AVM’s with PVA. In most cases, the PVA particles* ranged from 200 to 300 μm in diameter. Larger particles (300 to 1000 μm) were used if angiographic studies showed large shunts within the nidus. "Custom-cut" PVA pieces several millimeters in diameter and 4–0 silk thread were used to obliterate large fistulas; in one such case, a detachable balloon was also used. Polyvinyl alcohol was diluted with nonionic contrast material† to prevent occlusion of the catheters, and the mixture was well shaken before injection. All injections were monitored by real-time digital subtraction angiography.

Eighty-one of the 88 patients were surgically treated by one of the authors (C.B.W.); one patient had a second operation. Pathological specimens were obtained from 72 of the 89 operations. The specimens were routinely fixed in formalin, embedded in paraffin, cut into 5-μm sections, and stained with hematoxylin and eosin (H & E); a few specimens were also stained with elastica van Gieson. At least one section from each paraffin block was studied. Six specimens were unavailable for histopathological analysis. The remaining 66 specimens were carefully evaluated for the presence or absence of PVA, the morphological appearance of the embolizing material, the intraluminal reaction to PVA, vessel wall changes, the evolution of intraluminal thrombi, and the presence of other foreign material. No attempt was made to quantify the amount of foreign material or the extent and severity of the inflammatory response. In one case, a detailed pathological description was not attempted because the specimen was poorly fixed. No attempt was made to correlate the histological findings or the preoperative angiographic findings with the percent reduction of blood flow, as only part of the surgical specimen was submitted for examination.

Results

The 66 patients whose specimens were analyzed were 10 to 65 years old (mean 36 years). There were 38 males and 28 females. The AVM’s were located in the cerebral hemispheres in 60 (91%), the cerebellum in five (7.5%), and the corpus callosum in one (1.5%); their largest dimension ranged from less than 2 cm to more than 5 cm. The anatomical distribution of the lesions in each lobe is shown in Table 1. The mean interval between embolization and resection was 9 days (range 1 to 76 days), and 67% of the resections were performed within 1 week after embolization.

All specimens showed histopathological features typical of AVM’s. The vessels were of variable caliber and wall thickness, with characteristics intermediate between arteries and veins, and with abnormal laminar of the elastic and muscle fibers. Abnormal vessels within the brain parenchyma were separated by gliotic tissue; hemosiderin-laden macrophages, indicating remote bleeding, were observed in some cases. Focal mineralization of vessel walls was also seen.

Embolicizing Material

The histological findings in PVA-embolized AVM’s are summarized in Fig. 1. Changes in the histological features over time are presented in Fig. 2. In 79% of the specimens, at least one vessel contained PVA; the PVA particles appeared as sharp, flaky spicules, colored pale pink-blue in sections stained with H & E (Fig. 3) and black in those stained with elastica van Gieson. On unstained slides, the PVA particles appeared colorless and very bright through the polarizing filter; the brightness was almost absent on H & E-stained sections. In

I. M. Germano, et al.

![Graph showing histological findings in cerebral arteriovenous malformations embolized with polyvinyl alcohol (PVA). The first column represents the percentage of cases in which PVA particles were found. The other columns represent the percentage of cases with PVA-embolized vessels showing a particular histological feature. In one case, PVA was found, but inadequate fixation prevented detailed histological analysis. PMN’s/MN’s = polymorphonuclear and mononuclear inflammatory cells. N = number of cases.](image)
Histopathology of embolized AVM's

most cases, the PVA particles were clumped together to form an embolus. This observation supports the contention that PVA could occlude the arteriovenous shunt area of the AVM's. Occasionally, however, capillary channels contained single PVA particles, either adherent to the vessel wall or in a more central location. In six cases, intraluminal PVA particles with these characteristics were found along with larger, less angular, gray-green particles in a less serpiginous pattern (Fig. 4A). In four of these cases, larger PVA particles had been used; in the other two cases, the larger particles probably represent an inhomogeneity of the PVA suspension. In one case, very small PVA particles were seen together with normal-sized and larger particles. Silk suture used as an embolic material was observed in one case.

**Intraluminal Inflammatory Response**

All vessels containing PVA showed a clear inflammatory reaction, the severity and extent of which varied greatly in individual AVM's and among cases. Mononuclear and polymorphonuclear inflammatory cells were present in the majority of vessels containing PVA (Fig. 4A) and were occasionally found in lumina without PVA. Foreign-body giant cells were seen only near PVA emboli (Fig. 5). The inflammatory cell response remained fairly stable over time, whereas giant cells, although present as early as 2 days after embolization, were found more frequently when there was a longer interval between embolization and surgery (Fig. 2). Giant cells appeared to be more prominent and more numerous in lesions from younger patients. In the one case in which PVA and silk were found in the same section, the inflammatory reaction was severe in vessels embolized by PVA but was mild in vessels embolized by silk; the AVM had been resected 2 days after embolization.

**Vessel Wall Findings**

Polymorphonuclear and mononuclear inflammatory cells were present in the walls of PVA-embolized vessels in 41% of the cases. In a few cases, the inflammatory response occurred as early as 3 days after embolization. Patchy mural angioneurosis and focal necrotizing vasculitis, characterized by karyorrhexis of mural nuclei,
intense eosinophilia, and polymorphonuclear infiltration of the vessel wall, were found in 39% of the cases (Fig. 4), most commonly in AVM's resected at least 2 weeks after embolization. Vessel-wall necrosis was usually found adjacent to PVA emboli (Fig. 4) and was rarely seen in vessels without PVA. Histological evidence of extravascular hemorrhage in areas adjacent to mural angiokeratosis was seen in rare cases. The inflammation and angiokeratosis decreased with time (Fig. 2). Fibrotic changes of the vessel walls were often observed when there was a longer interval between embolization and resection.

Occasionally, the inflammatory response affected adventitial and perivascular tissue. Perivascular cuffing by mononuclear inflammatory cells around PVA-embolized vessels was rare. Thin vessel wall segments were scattered throughout the vascular malformations both near to and far from PVA emboli. In 69% of cases, sharp PVA spicules indented the endothelium (Figs. 4B and 6A) and in five cases were embedded in the vessel wall (Fig. 6B). In other cases, PVA emboli did not completely occlude the vessel lumina and had no contact with the vessel wall (Fig. 6B). No PVA emboli were found outside the vessels. Well-organized and more recent mural thrombi were more common in vessels that contained PVA than in those that did not.

In two cases, the walls of PVA-embolized vessels contained many eosinophils; also present were a remarkable subintimal polymorphonuclear and mononuclear response, signs of angiokeratosis, and necrosis.

Fig. 5. Photomicrographs of a cerebral arteriovenous malformation resected 32 days after embolization with polyvinyl alcohol (PVA). Left: Numerous foreign-body giant cells (arrows) are seen surrounding the PVA emboli. H & E, original magnification × 300. Right: Specimen showing partial recanalization of the intraluminal PVA thrombi. Newly formed small channels (arrows) inside a well-organized thrombus are lined by endothelium. Several foreign-body giant cells are also present. H & E, original magnification × 500.

Fig. 6. Photomicrographs of cerebral arteriovenous malformations embolized by polyvinyl alcohol (PVA). A: A sharp PVA particle indents the endothelium (arrow). The interval between embolization and surgery was 2 days. H & E, original magnification × 150. B: Specimen showing PVA particles incorporated into the vessel wall (curved arrows). The PVA emboli (asterisks) do not occlude the vessel lumen. The interval between embolization and surgery was 25 days. H & E, original magnification × 200.
Histopathology of embolized AVM's

of the majority of the inflammatory cells. These findings suggest an allergic reaction, which has not been reported previously.

Intimal proliferation in reaction to PVA emboli and disruption or defects in the internal elastic lamina were difficult to assess because of the intrinsic structural abnormalities in the vessel wall of AVM's. No neoplastic changes were seen.

Embolization and Revascularization

The clotted blood between the PVA particles began to organize 5 days after embolization, as indicated by the presence of fibroblasts. In the following weeks, as this process became more marked, PVA appeared as a matrix entrapping fibrous tissue in its interstices and became part of the thrombus.

Overall, thrombosis and revascularization were observed in 18% of the cases. Signs of revascularization were found mostly in specimens with a 4-week interval between embolization and surgery. In those cases, intraluminal thrombi in PVA-embolized vessels often contained newly formed capillaries with obvious endotheilum and, occasionally, intraluminal red blood cells (Fig. 5 right).

Absence of PVA Emboli

In 14 (21%) of 66 cases, no PVA emboli were found. In seven of these cases, all of the resected material had been submitted for examination; in the other seven, only samples were available. In eight cases, two embolic materials (PVA and either 4-0 silk suture or balloon) and/or larger custom-cut PVA pieces were used. In two other cases, only one of the feeding branches was superselectively embolized by PVA. In all of these 10 cases, angiographic studies revealed decreased flow in the distribution of the embolized vessels. A technical problem was documented during embolization in one case, and a very small specimen was received in another. In the remaining two cases, the feeding branches were embolized with standard PVA emboli without documented technical problems.

Other Foreign Materials

Foreign material other than PVA was found in 63% of the cases. Short fiber-like particles, which appeared intensely bright under polarized light and were usually surrounded by multinucleated giant cells, were found in 58% of cases (Fig. 7). These particles were probably cotton fibers introduced during embolization. In 19% of cases, rounder particles were found that were probably also contaminants.

Discussion

The ideal material for superselective embolization of cerebral AVM's would: 1) be readily available; 2) be easily prepared and injected; 3) have low tissue toxicity; 4) cause minimal inflammation; and 5) produce reliable and permanent occlusion. The results of this study show that PVA may allow occlusion of the arteriovenous shunt areas of the AVM, but it does not possess all the characteristics of the ideal embolic material.

Tissue Response to PVA

The inflammatory response to PVA in experimental studies has varied widely. Minimal inflammation was found after PVA embolization in the renal artery of the pig, in the mesenteric and other arteries of the dog, in the cerebral cortex of the rat, and in one human cerebral AVM. An acute inflammatory reaction to PVA emboli was found in the splenic artery of the dog and in two human AVM's. In our study of human cerebral AVM's, PVA caused mild to severe inflammation in all embolized vessels. The severity and extent of the reaction varied greatly, which may partially explain the inconsistent results from studies of small numbers of animals.

Polyvinyl alcohol also induces a rapid, strong foreign-body reaction, including giant cells. Multinucleated giant cells are a common response to foreign bodies, tumors, acquired immunodeficiency syndrome, and other infectious and autoimmune diseases. Formed
by fusion of specialized macrophages, giant cells can release hydrolytic enzymes but have minimal phagocytic activity. It has been suggested that their role is to produce a barrier-like structure around foreign material that cannot be eliminated by other mechanisms. In most experimental studies, giant cells appear 3 to 6 days after foreign bodies are implanted. In our study, giant cells were seen as early as 2 days after embolization, which suggests that PVA can induce an exceptionally fast foreign-body response. Moreover, in the one case where both silk and PVA were found on the same histological section, inflammation was present around the PVA particles but not around the silk 2 days after embolization. Thus, PVA may induce a faster acute inflammatory response than silk, a known reactive material. In the longer term, PVA caused mild intravascular scarring; long-term cases in which silk was used are not available for comparison.

Perivascular extravasation of PVA has been reported in human bronchial vessels 10 months after embolization, possibly through a sequence of events starting with focal angionecrosis. A similar mechanism was suggested to explain the presence of bucrylate in the neuroglial interstices surrounding embolized cerebral AVM's; bucrylate particles were routinely observed in the extravascular space 41 days after embolization and occasionally earlier. In contrast, PVA emboli were not found outside the vessel walls 9 months after embolization in the cerebral cortex of rats. In our study, PVA particles were occasionally embedded in the walls of PVA-embolized vessels but were never observed extravascularly. Thus, PVA seems to have a lower tendency for transvascular migration than bucrylate, at least for the first 76 days after embolization.

The absence of PVA in examined tissue after embolization has also been reported. It has been postulated that insects in these cases PVA emboli migrated distal to the studied specimens. In our study, PVA was not found in 14 (21%) of 66 cases. In eight of these cases, however, large PVA pieces or two different embolic materials were used (PVA and silk or balloon); a proximal occlusion by the larger embolic material might have obstructed the flow of PVA particles to the distal part of the nidus. Nevertheless, this proximal occlusion was clinically effective, as angiography documented decreased flow in the embolized territories. Alternatively, the absence of PVA could be ascribed to tissue sampling; in seven of the 14 cases without PVA, not all of the excised material was submitted for histological study.

Clinical Considerations

Knowledge of the fate of embolizing substances that will persist in human tissues for months or years is extremely important for a clinical understanding of complications after embolization. Necrotizing vasculitis is a well-documented response to embolic materials. When tissue adhesives are used, their breakdown may produce both heat and toxic compounds. However, the patchy mural necrosis in PVA-embolized channels in our study probably results from other mechanisms. Lytic enzymes released by polymorphonuclear and mononuclear cells near PVA emboli might have had a cytotoxic effect on the vessel wall layers. Alternatively, hypoxia resulting from PVA occlusion of the major blood supply to the AVM might have caused the mural necrosis. However, angionecrosis was usually seen adjacent to PVA emboli and probably resulted from a tissue reaction to PVA. A third mechanism, possibly observed in two cases, could be an allergic reaction to the embolic material. Hemorrhages during the first 3 weeks after therapeutic embolization with PVA may be partially explained by arterial rupture or aneurysm formation due to necrotizing vasculitis. However, the vessel wall fibrosis observed 4 weeks after embolization would likely protect against delayed hemorrhage.

It appears that occlusion with PVA is not necessarily permanent, as previously reported. Cerebral AVM's may recanalize and revascularize even after embolization with tissue adhesives, which are considered the most permanent embolic materials. Most often, the embolic material partially fills the injected vessel, and the remainder of the lumen becomes occluded by thrombus, which subsequently organizes. This type of occlusion may not remain stable for two reasons: angiogenesis and capillary regrowth due to vascular proliferation inside the thrombus, and migration of the embolic material into the vessel wall and adjacent tissue. In vitro studies suggest that lymphocytes, macrophages, and other products of cell division may induce vascular proliferation. Since PVA induces a severe inflammatory response, revascularization is a potential sequel. In one study, recanalization lumina only partially obstructed by PVA were observed in human bronchial vessels 10 to 28 months after embolization; in one case, blood flow through vessels embolized by PVA 20 months previously was documented angiographically. In another study, recanalization of canine spleen arteries had not occurred 9 months after embolization, despite strong evidence of an inflammatory reaction to PVA. Similarly, recanalization was not found up to 42 weeks after PVA embolization of canine renal arteries. The presence of small, newly formed vascular channels inside PVA-embolized vessels in 18% of our cases confirms that revascularization may occur after PVA embolization. The potential for small capillaries to re-establish the AVM nidus cannot be determined from our study.

The uniformity and purity of the PVA suspensions are also important clinical considerations. Confirming previous reports, our study showed great variability in the shape and size of PVA particles. Life-threatening sequelae may occur when "small" PVA particles escape into cervical or pulmonary arteries via large abnormal anastomotic channels of the AVM nidus. The presence of single PVA particles in small channels indicates that particles may have reached the venous portion of the AVM. We have no information about whether such
Histopathology of embolized AVM's

particles could reach the pulmonary circulation or would remain adherent to the vessel wall.

Refractile foreign particles have been reported in cerebral AVM's investigated angiographically before resection\(^4\) as well as in embolized AVM's.\(^5\) There is a consensus that these particles are cotton fibers and talc powder,\(^{4,13,18}\) which commonly contaminate most contrast-material solutions.\(^6\) It is also possible that foreign material could originate from the equipment (such as the syringes, catheters, or flushing media) used during embolization and angiography\(^4\) or from the embolic material itself. On morphological grounds, the needle-like refractile foreign particles observed in our study appear to be cotton fibers, while the rounder particles are probably talc or plastic/glass debris.\(^4,11\) Since foreign material was found in 63% of the embolized AVM's in our study, compared with 5% of nonembolized AVM's,\(^41\) the introduction of foreign matter appears to represent a risk of embolization. The source of such foreign matter should be investigated further.

The clinical and pathological significance of foreign material is difficult to determine. Autopsy studies have shown that fibers introduced angiographically may cause vascular occlusion and infarcts in surrounding brain.\(^{13,36}\) It has been speculated that some of these fibers could also pass through the AVM into normal brain and produce focal necrosis.\(^6\) Vinters, \textit{et al.},\(^4\) described four patients who had foreign fibers in cerebral AVM's but did not have clinical signs of thrombosis. In our study, the needle-like refractile foreign particles were usually surrounded by giant cells, indicating the presence of a strong foreign-body response. Further investigation is needed to determine if the presence of foreign fibers in the brain could contribute to "aseptic" fever spikes often observed after embolization.

**Surgical Considerations**

From a surgical standpoint, the presence of PVA in major feeding arteries poses no problem but, to be safe, the embolized vessels should be interrupted only after the proximal stump has been occluded with a metal clip. The presence of PVA in the nidus rarely complicates dissection of the AVM from adjacent brain, and the minor added difficulty is more than offset by the advantage of reduced flow through the malformation.

**Conclusions**

Our findings do not contraindicate the use of PVA to embolize cerebral AVM's. Nevertheless, PVA is not an ideal embolic agent, as it caused a rapid foreign-body response and inflammation in all of the embolized vessels examined. Vascular mural injury induced by PVA, which may lead to arterial rupture or aneurysm formation and revascularization, occurred for the most part when more than 2 weeks elapsed between embolization and resection. Thus, a short interval between embolization and surgery seems to be preferable. When PVA embolization is the only treatment used, angiographic follow-up studies may be indicated to identify early recanalization. Technical improvements are needed to prevent the injection of other foreign material during embolization with PVA.

**Acknowledgments**

The authors thank the University of California, San Francisco, interventional neuroradiology team, particularly Stanley L. Barnwell, M.D., Ph.D., Christopher F. Dowd, M.D., Kathy Finch, R.N., Van V. Halbach, M.D., and Randall T. Higashida, M.D., who cared for the patients presented in this study. We are grateful to Michael S. B. Edwards, M.D., Philip H. Gutin, M.D., Griffin R. Harsh IV, M.D., and Yoshio Hosobuchi, M.D., for allowing us to include seven of their patients in our study. Finally, we thank Stephen Ornday for editorial assistance.

**References**


Manuscript received November 13, 1990. Accepted in final form September 6, 1991.
Address reprint requests to: Isabelle Germaino, M.D., c/o The Editorial Office, Department of Neurological Surgery, 1360 Ninth Avenue, Suite 210, San Francisco, California 94122.

I. M. Germaino, et al.