Silent Intralesional Microhemorrhage as a Risk Factor for Brain AVM Rupture

Supplemental Tables

	Outcome: Index ICH									
	Univariate					Multivariate				
	OR	Lower	Upper	P Value	N	OR	Lower	Upper	P Value	N
Evidence of old hemorrhage (EOOH)	4.42	2.44	8.01	< 0.001	975	3.97	2.10	7.50	< 0.001	882
Age at diagnosis (decade)	0.89	0.82	0.95	0.001	973	0.87	0.80	0.95	0.002	882
Sex (male)	0.87	0.67	1.11	0.262	975	0.94	0.70	1.25	0.652	882
Deep only venous drainage	3.96	2.79	5.62	< 0.001	932	2.51	1.66	3.79	< 0.001	882
Maximal AVM size (cm)	0.73	0.66	0.80	< 0.001	929	0.73	0.65	0.81	< 0.001	882
Deep location	2.26	1.59	3.20	< 0.001	970	1.77	1.16	2.71	0.009	882
Associated arterial aneurysm	1.26	0.95	1.67	0.102	891	1.67	1.21	2.29	0.002	882

	Outcome: new ICH after diagnosis									
	Univariate					Multivariate				
	HR	Lower	Upper	P Value	N	HR	Lower	Upper	P Value	N
Evidence of old hemorrhage (EOOH)	2.08	0.93	4.64	0.074	699	3.53	1.35	9.23	0.010	643

Variable	OR	CI low	CI high	p	N	OR	CI low	CI high	p	N
Age at diagnosis (decade)	1.22	0.99	1.50	0.063	699	1.19	0.92	1.53	0.178	643
Sex (male)	1.00	0.50	1.97	0.992	699	0.72	0.32	1.64	0.439	643
Deep only venous drainage	0.84	0.30	2.41	0.750	683	0.81	0.24	2.72	0.740	643
Maximal AVM size (cm)	0.85	0.69	1.07	0.162	681	0.91	0.68	1.21	0.510	643
Deep location	0.70	0.27	1.83	0.472	696	1.06	0.35	3.21	0.917	643
Associated arterial aneurysm	1.00	0.48	2.09	0.990	644	1.26	0.53	2.99	0.593	643

Supplemental Table S1. Univariate and multivariable associations for association of EOOH with index ICH (top panel) and new ICH after diagnosis (bottom panel). Variables are indicator variables unless otherwise noted. Restricted to same sample as multivariable model, univariate effects similar (DNS).

|				Univariate					Multivariate	
	OR	Lower	Upper	P Value	N	OR	Lower	Upper	P Value	N
Hemosiderin positive	2.18	1.03	4.61	0.042	127	3.64	1.11	12.00	0.034	79
Age at diagnosis (decade)	0.85	0.72	0.99	0.044	148	0.58	0.42	0.79	0.001	79
Sex (male)	0.54	0.27	1.08	0.081	148	0.66	0.22	2.02	0.470	79
Deep only venous drainage	10.42	2.78	39.08	0.001	125	8.09	1.29	50.91	0.026	79
Maximal AVM size (cm)	1.14	0.87	1.49	0.355	122	0.98	0.62	1.56	0.942	79
Deep location	2.34	0.55	9.90	0.247	125	0.36	0.05	2.75	0.326	79
Associated arterial aneurysm	1.56	0.66	3.65	0.308	99	3.25	1.24	18.90	0.023	79

Supplemental Table S2. Univariate and multivariable associations for association of hemosiderin positivity with index ICH. Restricted to same sample as multivariable model, univariate effects similar (DNS).

Supplemental Figures
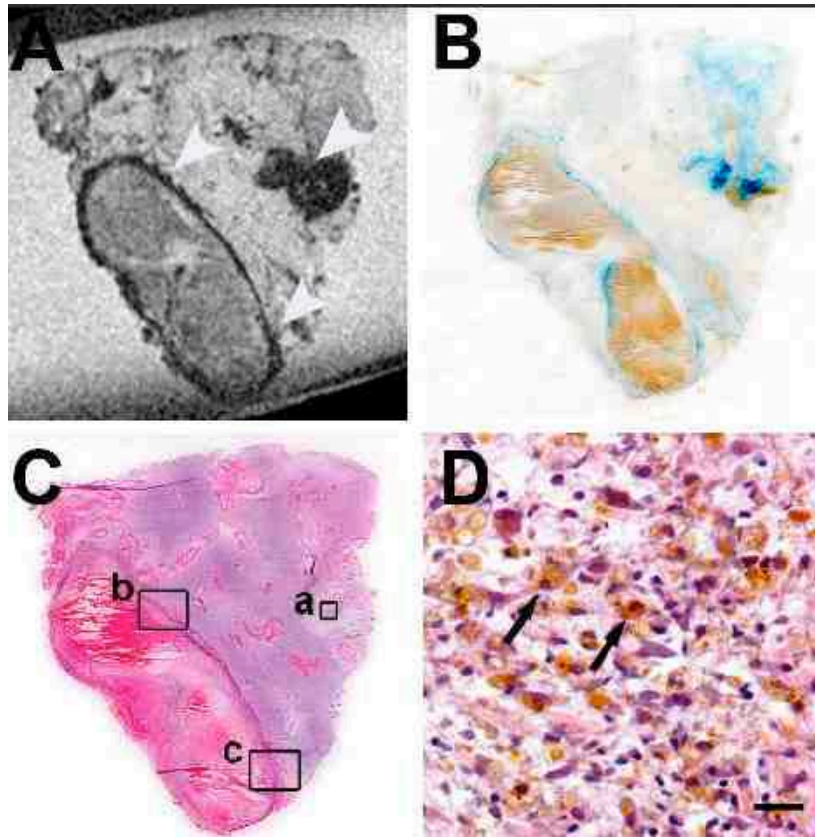
Supplemental Figure S1. Comparison of MR image with corresponding histological image in lesional tissue from an unruptured bAVM. We made a 1 mm-thick section of a resected surgical specimen that had been flash-frozen immediately after harvest in Optimal Cutting Temperature (OCT) medium. Adjacent sections were stained with H&E and Prussian Blue. The section was placed into a plastic tube suspended in saline that was doped with 1 part in 100 of Gadolinium DTPA. The tube was placed in a solenoid coil and imaged in a 1.5 T Siemens Symphony scanner (Siemens Medical Systems, Erlangen, Germany). A 3D gradient recalled echo sequence was used with the following parameters: TR/TE/flip angle = 30ms/7ms/25°; 2 averages; partition thickness = 0.43mm; FOV = 60mm x 30mm; matrix = 256 x 128 x 20; voxel size = 0.23 mm x 0.23 mm x 0.43 mm; Acquisition time = 2 min 33 sec. A single slice is shown from the 3D data reformatted to lie in a plane corresponding to that of the histological slice. Iron-rich regions cause susceptibility effects on gradient recalled images, which result in pronounced T2* effects. Regions of T2* signal loss appear as hypointense.

A. AVM **i**mage shows signal loss with associated blooming artifact (***white arrow head***). **B.** Prussian blue stain shows areas of iron deposition (***blue color***) corresponding to signal void in MR image. **C.** H&E stain shows histological structure. **D**, A high magnification image of the area (a) in D shows a large number of hemosiderin-laden macrophages (***arrows***). The corresponding area in MR image shows signal void. Scale bar for **D**: 20um.
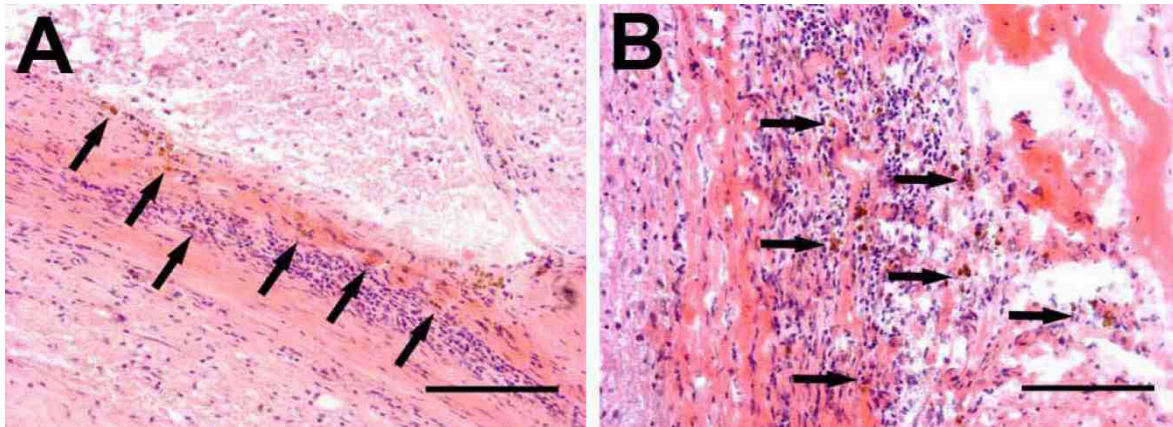
Supplemental Figure S2. Histological image of lesional tissue from the unruptured bAVM shown in Figure 2. A & B show higher magnification from selected areas (b) and (c) in Figure 2C. Hemosiderin deposition was detected in the vessel wall (arrows). Scale bars: 100 μ m.