

# Histopathological Features of Brain Arteriovenous Malformations in Japanese Patients

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## Abstract

Clinical features of high risk brain arteriovenous malformations (BAVMs) are well characterized. However, pathological evidences about the differences that are possessed by high risk patients are still lacking. We reviewed archived routine hematoxylin-eosin specimens from a total of 54 surgical treated BAVMs. The histopathological features in nidus were semi-quantitatively analyzed. We obtained the pathological differences of BAVMs nidus between several clinical features. Among the analyzed pathological features, the significant differences were observed in degree of venous enlargement and intimal hyperplasia. Juvenile, female, diffuse nidus, high Spetzler-Martin grade, and low flow patients had a lesser degree of those parameters compared to adult, male, compact nidus, low Spetzler-Martin grade and high flow patients. High risk profiles of BAVMs patients were well-reflected in the nidus pathology. Therefore, juvenile, female, diffuse nidus, and low flow in Japanese BAVMs patients might have different vascular remodeling process that predispose to higher tendency of hemorrhage.

Key words: arteriovenous malformations, histopathological study, clinical features, nidus

## Introduction

Brain arteriovenous malformations (BAVMs) comprise tangles of abnormally developed arteries and veins without intervening capillaries.<sup>1)</sup> As a consequence, an abnormal shunting of arteries and veins occurs and results in high-pressure vascular channels that are at a risk of rupturing, often with catastrophic results.<sup>2)</sup> Therefore, appropriate management is necessary to reduce lifetime risk of morbidity and mortality of BAVMs.

The BAVMs always provide challenge for neurosurgeons, as the risk of procedure may outweigh the benefits.<sup>3)</sup> Spetzler-Martin grading has been widely used for determining surgical-related morbidity,<sup>4)</sup> subsequently Lawton et al.<sup>5)</sup> proposed supplementary grading for determining surgical morbidity of BAVMs. However, high risk patients such as history of hemorrhage,<sup>6–8)</sup> young age,<sup>9,10)</sup> deep venous drainage,<sup>6,11,12)</sup> and female<sup>10)</sup> might need more aggressive modalities due to lifetime risk of hemorrhage. Despite high risk patients are well-identified, direct pathological evidences about the differences that are possessed by high risk patients are still lacking.

The aim of this study is to investigate the histopathological evidences of BAVMs features in association with identified risk factors for subsequent hemorrhage in Japanese patients.

## Materials and Methods

### I. Patient population

A total of 54 specimens were obtained from the surgical treatment of BAVMs of Japanese patients at Kyoto University Hospital with standard indications. Clinical data of the patients are summarized in Table 1.

### II. Sample preparation

All specimens were fixed in 10% formalin overnight and embedded in paraffin the next day. The specimens were stored at room temperature. Specimens were sliced into multiple and sequential 6- $\mu$ m thick sections, deparaffinized in xylene, rehydrated, and then used for histological studies. All specimens were stained with hematoxylin-eosin and observed with a BX51 microscope (Olympus Optical Co., Ltd., Tokyo).

### III. Assessment of infiltrating cells

We searched the focus of inflammation in the nidus by using low power magnification. Then, the

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**Table 1 Summary of clinical data**

Characteristics	Frequency
Age	
≥ 20 years	39 (72.2%)
< 20 years	15 (28.8%)
Hemorrhage presentation	27 (50.0%)
Location	
Frontal lobe	21 (38.9%)
Parietal lobe	14 (25.9%)
Temporal lobe	6 (11.1%)
Occipital lobe	10 (18.5%)
Cerebellum	3 (5.6%)
Nidal diffuseness	
Yes	41 (75.9%)
No	13 (24.1%)
Preoperative embolization	10 (18.5%)
Seizure presentation	14 (25.9%)
Sex	
Male	29 (53.7%)
Female	26 (46.3%)
Size of nidus	
< 3 cm	27 (50.0%)
≥ 3 cm	27 (50.0%)
Spetzler-Martin grade	
Grade I	14 (25.9%)
Grade II	26 (48.1%)
Grade III	12 (22.2%)
Grade IV	1 (1.9%)
Grade V	1 (1.9%)
Velocity	
High flow	36 (66.7%)
Low flow	18 (33.3%)

number of infiltrating cells was observed by using high power magnification on three adjacent fields. The average numbers of infiltrating cells were classified semi-quantitatively as follows: less than 20 (mild), 20–40 (moderate), and more than 40 (severe).

#### IV. Assessment of intimal hyperplasia

The thickest tunica intima of the vein in hematoxylin-eosin stained samples was recorded. The findings were classified semi-quantitatively as follows: less than 100  $\mu\text{m}$  (mild), 100–200  $\mu\text{m}$  (moderate), and more than 200  $\mu\text{m}$  (severe).

#### V. Assessment of microvessel accumulation

Initially, we identified the highest vascular density region in the nidus of the hematoxylin-eosin stained

samples by using low power magnification, then measured the number of microvessels (< 100  $\mu\text{m}$ ) by using high power magnification (10 $\times$  objective). The findings were classified semi-quantitatively as follows: less than 10 (mild), 10–20 (moderate), and more than 20 (severe).

#### VI. Assessment of venous enlargement

We carefully determined the largest venous diameter in hematoxylin-eosin stained samples. The findings were classified semi-quantitatively as follows: less than 1 mm (mild), 1–2 mm (moderate), and more than 2 mm (severe).

#### VII. Statistical analysis

The results of all histopathological studies were expressed as the mean  $\pm$  standard deviation. Statistical analysis was performed with SofaStats 1.4.3 (Paton-Simpson & Associates, Auckland, New Zealand). Clinical data including age, sex, occurrence of hemorrhage, seizure, velocity, size of nidus, and pre-operative embolization were analyzed along with histological data. *P* values less than 0.05 were considered statistically significant.

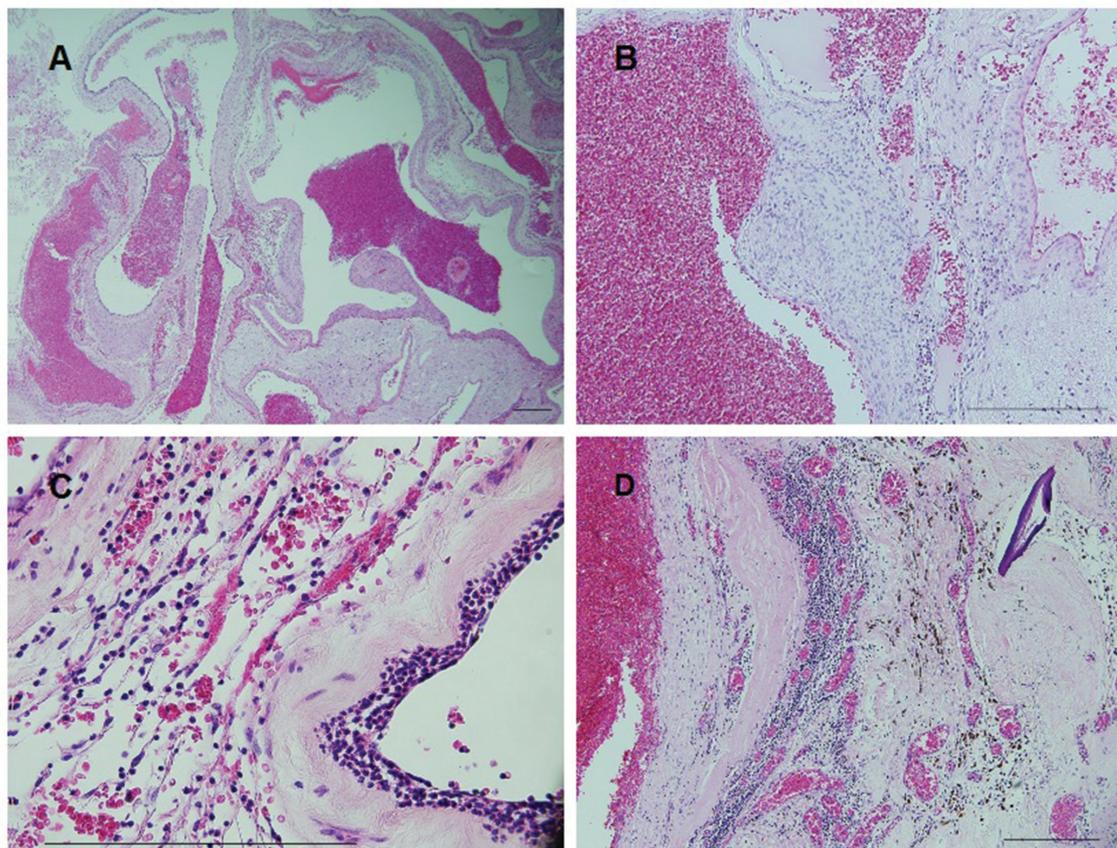
### Results

In the present study, we assessed the pathological features in the BAVMs nidus particularly focusing on infiltrating cells, intimal hyperplasia, microvessels accumulation, and venous enlargement (Fig. 1). Among the assessed parameters, only intimal hyperplasia and venous enlargement were predominantly affected by the clinical variables.

We identified several significant clinical variables highly influential for nidal pathology: ages, nidus diffuseness, sex, Spetzler-Martin grade, and nidal velocity (Table 2).

### Discussion

The present study revealed that intimal hyperplasia and venous enlargement in BAVMs nidus pathologically were the differentiating factors of clinical profiles of BAVMs patients. Our result might indirectly the vascular remodeling process was regulated differently between certain patients profiles. Younger age of onset and female patients tended to have the thinner intima and smaller drainer, although hemorrhage presentation was not increased in the aforementioned group, the condition might predispose for further hemorrhage if untreated. In line with this study, our previous report indicated that children and female patients had higher risk for subsequent hemorrhage after initial hemorrhage.<sup>10)</sup>



**Fig. 1** Hematoxylin-eosin staining of human brain arteriovenous malformations tissues. **A:** profound venous enlargement is well identified. **B:** Intimal hyperplasia is found in the venous wall. **C:** Infiltrating cells can be observed in the vascular walls and perivascular tissues. **D:** Microvessels accumulation with profound infiltrating cells at the enlarged and hyperplastic vein can be observed. Scale bars: 300  $\mu$ m.

Apparently, there is inconsistency in patients age and sex as predictors for hemorrhage in BAVMs.<sup>12,13</sup> It is noteworthy, racial background in the clinical series might contribute to those differences. At least, two reports from Scandinavian region also indicated that younger age<sup>7,14</sup> and female<sup>14</sup> are more prone to future hemorrhage. Furthermore, the fertile female might get into the pregnancy thus important consideration is needed in this management of this group.<sup>15</sup>

In this study, angiographically obtained clinical profiles such as nidus diffuseness, velocity, and Spetzler-Martin grade were influential for the intimal hyperplasia and venous enlargement. Diffuse nidus, low flow, and higher Spetzler-Martin grade were observed to have thinner intimal hyperplasia and smaller drainer. We defined low flow BAVMs as slower transition from arterial to venous phase in angiography, this indirectly reflects the venous hypertension (Y.T. and S.M.). Those aforementioned conditions were highly consistent as hemorrhagic predictors in BAVMs.<sup>6,7,10–14,16</sup> Furthermore, in our series, higher proportion of hemorrhage presentation

was obtained in low flow patients (83.3% in low flow patients, 33.3% in high flow patients). Therefore, we assumed that hemodynamic properties of BAVMs have a highly prominent role in vascular remodeling process in nidus.

To our surprise, infiltrating cells were not influenced by clinical profiles. The presence of inflammation in BAVMs nidus is well noticed,<sup>17</sup> we had reported the activation of NF-kappa B and STAT3 in the BAVMs.<sup>18,19</sup> It is noteworthy, the precised contribution of inflammation in BAVMs pathobiology remains elusive. Moreover, our semi-quantitative scoring might also contribute to the result.

The highly angiogenic environment of BAVMs nidus is well documented, abnormality in VEGF,<sup>20,21</sup> Tie-2,<sup>20,21</sup> and HIF-1 $\alpha$ <sup>22</sup> might contribute to BAVMs pathobiology. In the present study, the highly angiogenic environment was well reflected through microvessels accumulation in the nidus; however the difference was not detectable between clinical variables. We assumed the abnormal angiogenesis is a common feature of BAVMs, thus insensitive to differentiate

**Table 2 Summary of statistical analysis for histopathological features**

Clinical manifestations	Histological characteristics			
	Infiltrating cells	Intimal hyperplasia	Microvessels accumulation	Venous enlargement
Age				
≥ 20 years	1.95 ± 0.79	2.56 ± 0.72*	2.10 ± 0.82	2.90 ± 0.38*
< 20 years	1.93 ± 0.96	1.60 ± 0.74	2.27 ± 0.80	2.27 ± 0.70
Hemorrhage presentation				
Yes	2.04 ± 0.90	2.11 ± 0.89	2.33 ± 0.73	2.63 ± 0.56
No	1.85 ± 0.77	2.48 ± 0.75	1.96 ± 0.85	2.81 ± 0.56
Nidal diffuseness				
Compact	1.93 ± 0.82	2.44 ± 0.78*	2.15 ± 0.79	2.80 ± 0.51
Diffuse	2.00 ± 0.91	1.85 ± 0.90	2.15 ± 0.90	2.46 ± 0.66
Pre-operative embolization				
Yes	1.90 ± 0.88	2.00 ± 0.82	2.00 ± 0.82	2.70 ± 0.48
No	1.95 ± 0.83	2.36 ± 0.84	2.18 ± 0.81	2.73 ± 0.59
Seizure presentation				
Yes	1.86 ± 0.86	2.29 ± 0.83	2.00 ± 0.88	2.64 ± 0.74
No	1.98 ± 0.83	2.30 ± 0.85	2.20 ± 0.79	2.75 ± 0.49
Sex				
Male	1.79 ± 0.77	2.59 ± 0.78*	2.10 ± 0.82	2.86 ± 0.44
Female	2.12 ± 0.88	1.96 ± 0.79	2.20 ± 0.82	2.56 ± 0.65
Spetzler-Martin Grade				
< 3	2.03 ± 0.84	2.46 ± 0.76*	2.23 ± 0.81	2.79 ± 0.52
≥ 3	1.77 ± 0.83	1.77 ± 0.93	2.00 ± 0.82	2.46 ± 0.66
Velocity				
High	2.06 ± 0.83	2.61 ± 0.60*	2.11 ± 0.85	2.86 ± 0.49*
Low	1.72 ± 0.83	1.67 ± 0.91	2.22 ± 0.73	2.44 ± 0.62

\* indicates  $p < 0.05$ , statistical test performed with Mann-Whitney U test.

the high risk patients. Of note, our semi-quantitative scoring might also contribute to the result.

## Conclusion

In this study, the intimal hyperplasia and venous enlargement were distinctly influenced by clinical features. Younger age and female patients, as well as angiographical features of diffuse nidus, low flow, and high Spetzler-Martin grade possessed thinner intimal hyperplasia and smaller drainer. Those conditions might predispose high risk patients to higher tendency of hemorrhage in Japanese patients. Future investigation is necessary to elucidate the underlying mechanism.

## Conflicts of Interest Disclosure

The authors declare that there is no conflict of interest.

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