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Idiopathic Pulmonary Arteriovenous Malformations: Clinical and Imaging  
Characteristics

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## **ABSTRACT**

**Introduction:** Pulmonary arteriovenous malformations (PAVMs) can cause stroke, brain abscess or life-threatening hemorrhage. Most PAVMs are associated with hereditary hemorrhagic telangiectasia (HHT). We aimed to describe the clinical presentation and treatment outcomes of those with idiopathic PAVMs, previously never described in the literature.

**Methods:** Patients with idiopathic PAVMs were identified at our HHT centre.

Retrospective review of charts and imaging was performed.

**Results:** Twenty patients were identified with idiopathic PAVMs. Most common symptoms reported were dyspnea and migraines (50% and 30% of patients, respectively). Previous complications of PAVMs included hemoptysis (20%), stroke (20%), and brain abscess (5%). A total of 28 focal PAVMs were identified. Most patients (80%) had a solitary PAVM. Thirteen of 28 PAVMs (46%) were located in the lower lobes. Most were simple and fistulous rather than complex and plexiform. Transcatheter embolotherapy was performed in 17 patients and was successful in improving oxygenation in all cases.

**Conclusion:** The clinical manifestations and complications of idiopathic PAVMs are similar to those associated with HHT. Idiopathic PAVMs are anatomically similar to HHT-related PAVMs except for a greater number of solitary PAVMs and a lack of lower lobe predominance. Transcatheter embolotherapy is a safe and effective method for treating idiopathic PAVMs.

## **KEYWORDS**

Lung

Hereditary Hemorrhagic Telangiectasia

Arteriovenous Malformations

Therapeutic Embolization

## **Introduction**

Pulmonary arteriovenous malformations (PAVMs) are abnormal pulmonary blood vessels in which there is a direct connection between arterial and venous vessels without intervening capillaries. As a result of this anatomical abnormality, PAVMs can be associated with a wide spectrum of clinical manifestations. These include, life-threatening hemorrhage, symptoms and complications from paradoxical embolization such as migraine, stroke, and brain abscess [1-2].

Approximately 80-95% of PAVMs are associated with hereditary hemorrhagic telangiectasia (HHT) [3-5] also known as Osler-Weber-Rendu syndrome. A number of other rare conditions are associated with acquired PAVMs such as hepatic cirrhosis [6], schistosomiasis [7], mitral stenosis [8], trauma [8], actinomycosis [8], Fanconi's syndrome [9] metastatic thyroid carcinoma [10] and other cancers. The remainder of PAVMs are presumed to be idiopathic in nature.

PAVMs are usually described according to their anatomical characteristics.

Approximately 85% of PAVMs are simple, in which the arterial supply arises from one or more branches of a single segmental pulmonary artery [11]. Most of the remainders are complex, which have multiple arterial feeder vessels from more than one pulmonary segment. A smaller percentage of PAVMs are diffuse, in which there is disseminated involvement of multiple pulmonary segments [12]. PAVMs can be further characterized according to their radiological appearance. The fistula-type PAVM has a feeding artery directly connected to a draining vein, with an intervening single aneurysmal sac. Less

commonly, PAVMs are plexiform with a multi-septated aneurysm or a cluster of multiple vascular channels.

Historically, symptomatic PAVMs were treated surgically. But since the advent of embolotherapy, percutaneous transcatheter embolization with coils has significantly decreased the rate of complications arising from PAVMs [3-5, 12]. The International HHT Guidelines recommend that PAVMs be embolized preventatively, whether or not they are symptomatic, to decrease the risk of complications [13]. The literature supports targeting PAVMs with feeding artery diameter of 3mm or greater [14-15], with consideration for embolizing PAVMs with feeding artery diameter as small as 2 mm [13].

Although there have been many recent large case series describing the clinical course and treatment outcomes of PAVMs [3-5, 16-17], these case series have been almost entirely comprised of HHT patients. Patients with idiopathic PAVMs have never been described and characterized as a separate entity in the literature. The purpose of this study was to describe the clinical presentation and treatment outcomes of patients with idiopathic PAVMs.

## **Subjects and Methods**

### ***Study Population***

The HHT clinic at St. Michael's Hospital in Toronto is a tertiary specialized HHT center. After initial patient assessment, patient data from those who had given consent were

entered into the Toronto HHT Database. Patients listed in the database and seen in clinic between May 1999 and August 2007 were recruited retrospectively. Approval from the St. Michael's Hospital Research Ethics Board was obtained. Patients with PAVMs, confirmed on unenhanced computed tomography (CT) of the chest, were included in the study. Those with "definite" HHT according to the Curacao Criteria [13, 18] or with a definite family history for HHT were excluded from this study. Any patients that had other known causes for PAVMs were also excluded.

### ***Curacao Criteria for Diagnosis of HHT***

HHT is a clinical diagnosis based on the presence of recurrent epistaxis, mucocutaneous telangiectasia, arteriovenous malformations (AVMs) involving visceral organs, and family history of HHT. HHT patients were identified using the International Clinical Diagnostic (Curaçao) Criteria [18], in which the diagnosis of HHT is definite when at least 3 out of the 4 of the above criteria are present, suspected when 2 criteria are present, and unlikely when only 1 criterion is present.

### ***Genetic Testing for HHT***

All patients were offered genetic testing for HHT. Previous studies have shown that approximately 80% of HHT families have disease-causing mutation in either the endoglin gene (*ENG*) on chromosome 9 coding for endoglin protein [19] or activin receptor-like kinase gene (*ACVRL1*) on chromosome 12 coding for activin receptor-like kinase 1 protein (ALK-1) [20]. More recently, mutations of the gene called mother against decapentaplegic homolog 4 (*MADH4*, coding for the SMAD4 protein) have been

described in 1-3% of HHT patients with a rare syndrome of combined familial juvenile polyposis (JP) and HHT [21] but can also rarely occur in HHT patients without JP [22].

Whenever possible, all three of these known gene mutations were tested.

### ***Clinical Assessments and Follow-up***

A detailed personal and family history was obtained of each patient on their initial visit to screen for potential clinical manifestations of PAVMs and HHT. If patients were found to have a history of epistaxis, they were referred to an experienced otolaryngologist to look for telangiectases. Each patient had routine bloodwork, oxygen shunt study, agitated saline transthoracic contrast echocardiography (as previously described [23-24]), and chest CT performed as routine baseline assessment for suspected PAVMs. As well, all subjects underwent further imaging studies to screen for AVMs in other visceral organs commonly affected in HHT. Each patient had brain magnetic resonance imaging to rule out cerebral AVMs and mesenteric doppler-ultrasound to screen for intrahepatic shunt. All were referred to interventional radiology for pulmonary angiography and possible embolotherapy. Patients who underwent embolotherapy were admitted to hospital for the procedure, observed overnight, and discharged the following day.

Transcatheter embolotherapy was performed from a transfemoral vein approach with the placement of embolization coils in the distal aspect of all PAVMs with feeding artery diameter greater than or equal to 3mm, based on CT measurement, according to standard technique as previously described [25].

In general, following embolotherapy, patients were reassessed in the HHT clinic at intervals of 1-2 months, 1 year, and then every 1-3 years. Oxygen shunt study and chest radiograph were performed at the 1-2 month follow-up visit. Chest CT was performed at the 1 year follow-up, then every 1-3 years after embolotherapy, depending on the presence of small untreated PAVMs. In most cases, patients were seen every other year if their PAVMs remained stable after embolotherapy.

### ***Design and Data Collection***

Data regarding patient demographics, laboratory results, oxygen shunt studies, and agitated saline transthoracic contrast echocardiography studies at presentation and during follow-up, including post-treatment studies, were obtained from our HHT Clinic Database and medical records. Data regarding genetic test results, clinical presentation, and treatment outcomes were further gathered from a retrospective clinic chart review. All available chest CTs and pulmonary angiograms (including those before and after embolotherapy) were re-reviewed with an experienced radiologist (RPC) to collect data regarding PAVM anatomical characteristics as well as imaging outcomes following embolization.

### ***Data Analysis***

Data are described as percentages or means with ranges or standard deviation (SD) as appropriate. Data are tabulated and presented in graph and chart format where appropriate.

## **Results**

### ***Patient Demographic and Clinical Presentation***

Twenty out of a total of 139 patients (14%) were identified with PAVMs on chest CT who met the study criteria. Mean age at time of presentation to our clinic was 47 years (range: 25- 86) with 13 of 20 patients (65%) being female. Nine of 20 patients (45%) were diagnosed with PAVMs as a result of symptoms or complications related to their PAVMs. Of these, 5 patients (25%) presented with serious complications related to their PAVM such as cerebral vascular accident (CVA), brain abscess, or hemoptysis. PAVMs were found incidentally in the remaining 11 patients (55%). Symptoms related to PAVMs found on initial assessment included dyspnea, hemoptysis, and migraine. Patient demographics along with patients' initial presentation are summarized in table 1.

Although all patients with “definite” HHT according to the Curacao Criteria were excluded, 7 of the remaining 20 patients (35%) had one other clinical feature in their history compatible with possible HHT (patients 2, 10, 13, 16-19). This group of patients has a mean age of 53 (range 25-85, SD 18). Patient 2 and 13 had a history of epistaxis, the former with a normal otolaryngology exam and the latter not assessed by otolaryngology. Physical findings of mucocutaneous telangiectasias were noted in patients 10, 18 and 19. Finally, evidence of hepatic shunt was noted on imaging studies in patients 16 and 17.

### ***Genetic Testing***

Sixteen of 20 patients (80%) have genetic testing results that are negative for the two most common genes predisposing patients to HHT, *ENG* and *ACVRL1*. Of these patients, all except for patients 8, 17 and 18 also underwent testing for *MADH4* mutation, and were negative. Patients 5 and 10 are no longer being followed by our clinic and patient 11 declined genetic testing. Finally, one patient (Patient 14) tested positive for an *ENG* HHT-causative gene mutation (figure 1).

### ***Imaging Characteristics***

A total of 28 focal idiopathic PAVMs were identified in 19 of 20 patients. Imaging characteristics are not reported in detail for one patient as she had bilateral diffuse PAVMs. Sixteen patients (80%) had a single PAVM, 2 patients (10%) had 2 PAVMs, and 1 patient (5%) had 8 PAVMs. Of the 28 focal idiopathic PAVMs, 13 (46%) were located in the lower lobes (figure 2). Twenty-six of 28 PAVMs (93%) were simple while the remainder were complex. Twenty-three of 28 PAVMs (82%) were fistulas while the remainder were plexiform PAVMs. The mean feeding artery diameter was 4 mm (range: 1-13mm). The imaging characteristics of all 20 patients are presented in table 2.

### ***Treatment Outcomes***

Embolization was performed for 20 of 28 PAVMs (71%) in a total of 23 sessions (including reperfusion treatments) for 17 of 20 patients (table 2). Reperfusion was determined 1 year after embolization and occurred in 5 of 17 patients, each of which requiring subsequent embolization sessions. There was immediate occlusion of flow in the feeding artery of all 20 treated PAVMs after all 23 sessions of transcatheter

embolotherapy. Of the 13 patients in which both pre- and post-embolization arterial blood gases were available, all had improvement in shunt, with 10 having complete normalization of the estimated shunt fraction (normal <8%, based on local ROC curve). The mean calculated shunt fraction decreased from 12.4% (range: 7.0-26.4%) to 6.0% (range: 2.0-10.0%). No major procedural complications such as paradoxical embolism or hemoptysis occurred as a result of embolization.

### ***Follow-up***

Patients were followed for a mean of 40 months (range: 4-90 months) as per table 1. Of all 20 patients, one declined follow-up and another was lost to follow-up. There were no deaths. No patients suffered from serious complications related to PAVMs, such as CVA, brain abscess, or hemoptysis, after embolotherapy.

### **Discussion**

PAVMs are known to cause serious complications such as stroke, cerebral abscess and life-threatening hemorrhage [3-5, 16-17]. However, all previous studies were largely comprised of HHT patients. To our knowledge, this study is the first to show that idiopathic PAVMs appear to behave similarly to HHT-related PAVMs by presenting with similar symptoms and complications at comparable frequencies (Table 3). However, there are a few notable differences between the two groups.

We observed that idiopathic PAVMs are similar to PAVMs associated with HHT in that the majority are simple (93%) and fistulous (82%) in morphology rather than complex

and plexiform (table 2). However, patients with idiopathic PAVMs differ notably from those in the HHT series in that the majority (80% in this study) present with solitary PAVMs, compared to less than 40% in HHT patients [3, 16, 21]. Also, idiopathic PAVMs appear to be more evenly distributed in all areas of the lung, differing from the 60-95% lower lobe preponderance in HHT patients suggested by numerous other studies [3-4, 14, 17].

A few possible inferences can be made from these two differences. Firstly, patients with idiopathic PAVMs might have a lower incidence of platypnea and orthodeoxia that usually results from increased ventilation-perfusion mismatching in an upright position, an observation usually seen from lower lobe preponderance. Secondly, Mager and colleagues showed in their study that patients with solitary PAVMs were more likely to have a favorable outcome after embolotherapy than those with multiple PAVMs [4]. This suggests a possible better treatment outcome for patients with idiopathic PAVMs who undergo embolotherapy. Lastly, because idiopathic PAVMs are more likely to be solitary and therefore less likely to be associated with large right-to-left shunt, this might in part explain why patients with idiopathic PAVMs might have a lower frequency of cyanosis and polycythemia (table 3). Also, previous HHT series have shown an association between number of PAVMs and cerebral abscess risk [26]. This might explain why idiopathic PAVMs are associated with a lower frequency of cerebral abscess in our series when compared with others.

Our study suggests that transcatheter embolotherapy is a safe and effective method of treating idiopathic PAVMs as per table 2. There were no major complications from the procedure, such as paradoxical embolism or hemoptysis, and no long term symptoms or sequelae. During an average 3 year follow-up period post-embolization, all patients reported improved dyspnea and none developed serious PAVM-related complications.

The prevalence of HHT in patients with PAVMs has historically ranged between 50-80% [16, 27-30], though more recent studies suggest that it may be closer to 80-95% [3-5]. This study also suggests a HHT prevalence of 86% among all patients with PAVMs in our clinic database. The reason for the trend towards higher prevalence of HHT as the underlying diagnosis is likely the result of improving recognition of the diagnosis of HHT and association between HHT and PAVMs. Furthermore, we now have better diagnostic tools, including imaging and genetic testing. However, since most of the centers reporting PAVM series are HHT tertiary referral centers, one should be cautious in interpreting these numbers since referral bias might factitiously increase the prevalence of HHT among patients with PAVMs.

The most significant limitation of our study is the small number of patients, but as this is the first series of well characterized patients with idiopathic PAVMs, we believe it contributes significantly to the literature. We do not have complete genetic data in all patients, but believe the available results are informative. Currently, HHT is still a clinical diagnosis and existing genetic testing is only approximately 80% sensitive [31]. This is because introns (non-coding regions) and promoter regions of *ENG*, *ACVRL1* and

*MADH4* are not typically sequenced given the low yield of mutations in these regions. Furthermore, there appears to be at least two other chromosomes linked to HHT, though the specific gene loci have not been identified [32-34]. Therefore, it is possible that some of our idiopathic PAVM patients might in fact have HHT, but with a mild clinical phenotype and an unrecognized causative mutation.

It remains possible that some of the patients in our series have unrecognized HHT, with this being especially plausible for the 7 patients who had epistaxis, mucocutaneous telangiectases or hepatic shunt. HHT is often unrecognized in children and young adults as the clinical expression of HHT is age-related [35]. For example, less than 50% of children with HHT have epistaxis or telangiectasia [36] but approximately 90% of adults over age 50 years having recurrent epistaxis [35, 37]. However, given that the mean age in our group of “possible” patients is over 50 years, none had a family history of HHT, and all (6/6) had negative genetic testing for *ENG* and *ACVRL1* mutation, it is unlikely that many of these patients have HHT. Interestingly, one patient with epistaxis (and normal nasal mucosa on examination by an otolaryngologist) was originally included in our study but was lost to follow up. She was later excluded from our study when she re-presented to clinic 6 years later with new telangiectases (and thus definite diagnosis of HHT). This reinforces the need for long-term follow-up of patients with idiopathic PAVMs for the presence of HHT. Though patient 14 was found to carry *ENG* mutation, this patient cannot be confirmed to have HHT, given the absence of clinical features and family history. It would not be surprising to find that *ENG* mutation could predispose to

various vascular malformations in conditions other than HHT, though this has not been explored in the literature to date.

In conclusion, the clinical manifestations and complications of idiopathic PAVMs are very similar to those associated with HHT. Idiopathic PAVMs are anatomically similar to HHT-related PAVMs with the notable differences of greater proportion of solitary PAVMs and a lack of lower lobe predominance. Finally, transcatheter embolotherapy is a safe and effective method for treating patients with idiopathic PAVMs.

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## **FIGURE LEGENDS**

Figure 1: Distribution of idiopathic PAVM cases and genotype

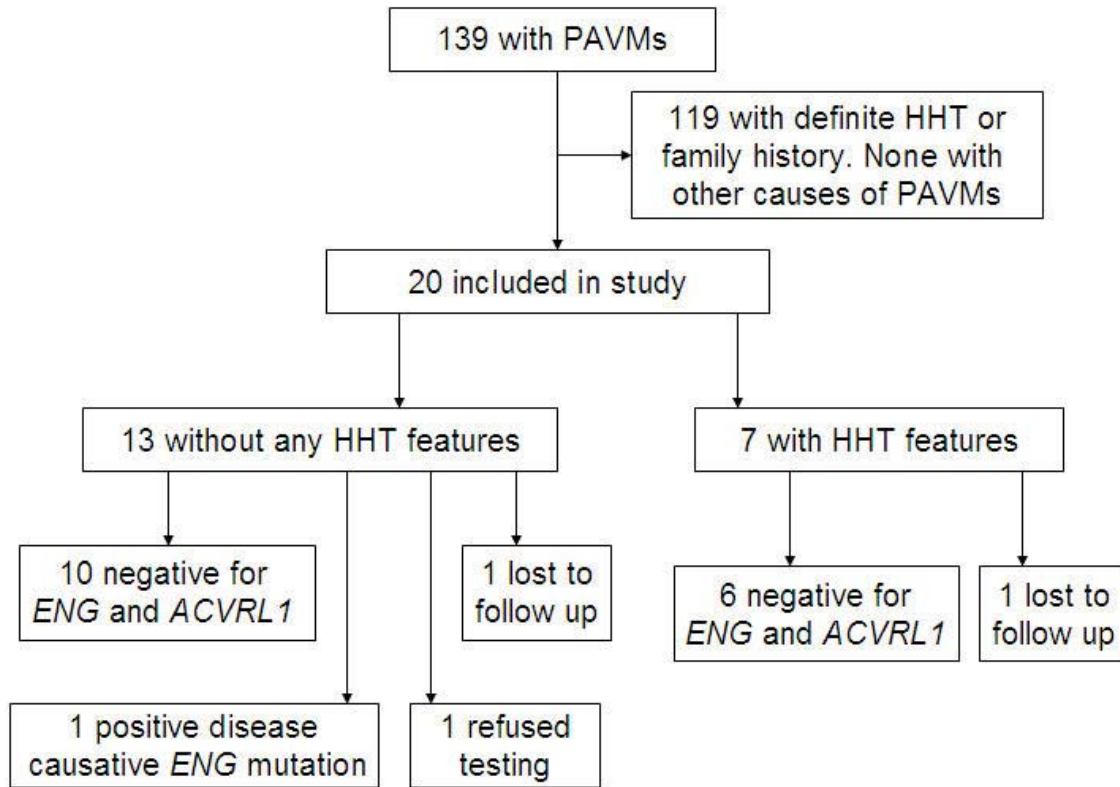
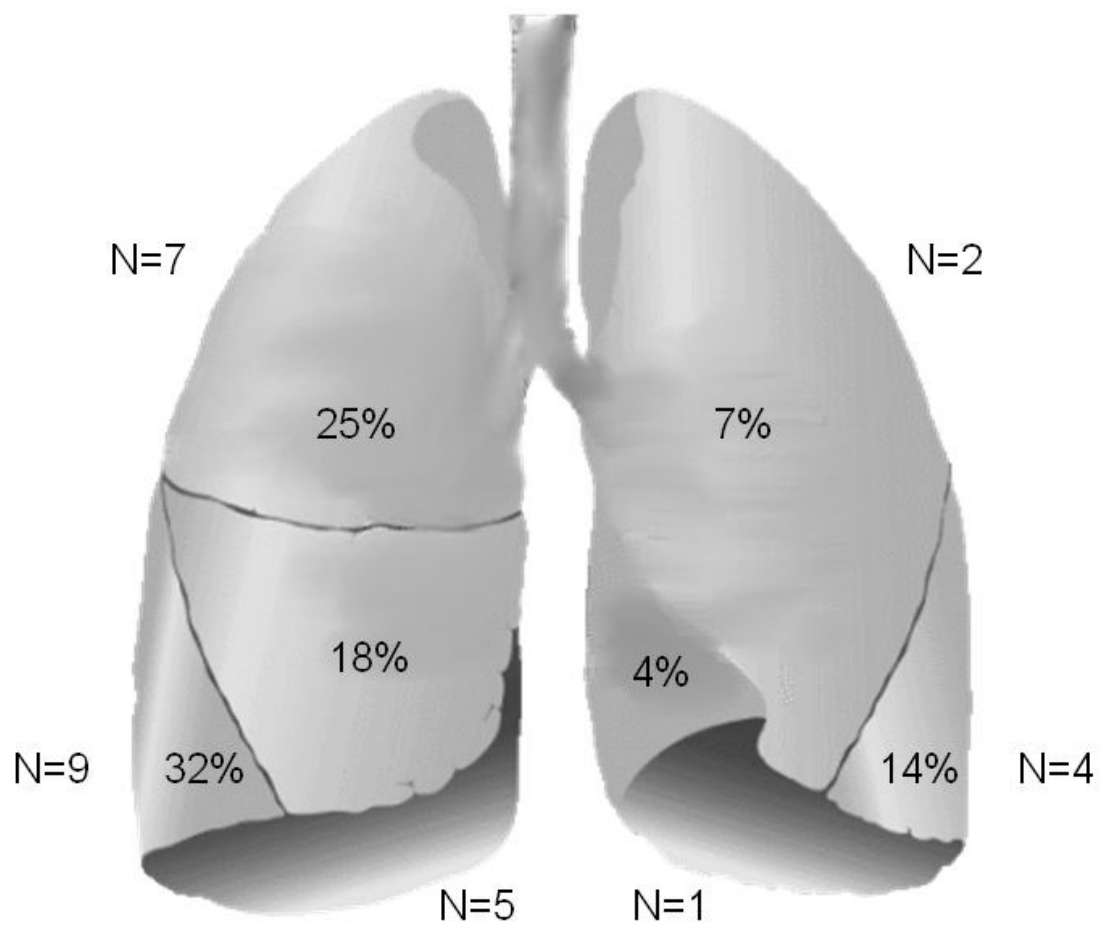


Figure 2: Location of idiopathic PAVMs



## **TABLES**

Table 1: Patient Demographics and Clinical Manifestations on Presentation

Patient	Age	Gender	Dyspnea	Hypoxemia	Migraine	Hemoptysis	Stroke	Cerebral Abscess	Initial Presentation	Follow-up (months)
1	25	F	Yes	Yes	-	-	-	-	Post-partum dyspnea* (CT)	62
2	25	F	Yes	-	Yes	Yes	Yes	-	Motor vehicle accident (CXR)	66
3	31	F	Yes	-	Yes	-	-	-	Muscular chest pain (CXR)	90
4	37	F	-	-	-	-	-	-	Post-partum dyspnea* (CT)	10
5	42	F	-	-	-	-	-	-	Pneumonia (CXR)	28 <sup>†</sup>
6	46	F	-	-	-	-	-	-	Pneumonia (CXR)	20
7	49	F	Yes	-	Yes	-	-	-	Abdominal pain (CXR)	14
8	50	F	Yes	-	Yes	Yes	-	-	Routine CXR	29
9	50	F	-	-	-	-	-	-	Recurrent cough (CXR)	15
10	54	F	Yes	-	Yes	-	-	-	Non-resolving pneumonia (CXR)	78
11	54	F	-	-	-	Yes	-	-	Minor hemoptysis* (CT)	4 <sup>‡</sup>
12	61	F	Yes	-	Yes	-	-	-	Pneumonia (CXR)	22
13	86	F	-	Yes	-	-	Yes	-	Stroke and hypoxemia* (CT)	24
14	34	M	Yes	-	-	-	-	-	Dyspnea* (CXR)	16
15	36	M	-	-	-	-	Yes	-	Recurrent embolic stroke* (CT)	74
16	42	M	-	-	-	-	-	-	Recurrent cough (CXR)	75
17	51	M	Yes	Yes	-	-	-	Yes	Cerebral abscess* (CXR)	37
18	53	M	Yes	-	-	Yes (Massive)	-	-	Dyspnea* (CT)	70
19	60	M	-	Yes	-	-	Yes	-	Stroke, seizure, and hypoxemia* (CT)	27
20	68	M	-	-	-	-	-	-	Staging for colon cancer (CT)	32
<b>Mean</b>	<b>47</b>	<b>F=13/20 (65%)</b>	<b>10/20 (50%)</b>	<b>4/20 (20%)</b>	<b>6/20 (30%)</b>	<b>4/20 (20%)</b>	<b>4/20 (20%)</b>	<b>1/20 (5%)</b>	<b>Related to PAVM = 9/20 (45%)</b>	<b>40</b>

\* Symptom considered related to their PAVM

<sup>†</sup> Lost to follow-up

<sup>‡</sup> Declined treatment and follow-up

Table 2: Imaging Characteristics and Treatment Outcomes

Patient	Number of PAVMs	Location	Number of feeding arteries	Feeding Artery Diameter	Simple versus Complex	Fistula Versus Plexiform	Number of embolization sessions	Post-treatment Infarction	Reperfusion
1	Diffuse	Diffuse	N/A	N/A	N/A	N/A	2	-	Yes <sup>‡</sup>
2	1	RLL*	1	5mm	simple	fistula	1	-	-
3	1	LLL*	2	6mm	simple	fistula	1	-	Yes
				2mm					
4	8	LUL	1	1mm	simple	fistula	1	-	-
		LUL	1	1mm	simple	fistula			
		RUL*	1	3mm	simple	fistula			
		RUL*	1	3mm	simple	fistula			
		RUL	1	1mm	simple	fistula			
		RLL	1	2mm	simple	fistula			
		RLL*	2	2mm	simple	fistula			
				10mm					
5	1	RML*	1	5mm	simple	fistula	2	-	Yes <sup>‡</sup>
6	1	RML	1	3mm	simple	fistula	0 <sup>Δ</sup>	-	-
7	1	RML*	1	3mm	simple	fistula	1	-	-
8	1	RLL*	1	4mm	simple	fistula	1	-	-
9	1	RML*	1	4mm	simple	fistula	1	-	-
10	1	RLL*	1	5mm	simple	fistula	1	-	-
11	2	RLL	1	3mm	simple	fistula	0 <sup>†</sup>	-	-
		RUL	1	4mm	simple	plexiform			
12	1	Lingula*	1	3mm	simple	fistula	1	-	-
13	2	LLL*	1	5mm	simple	plexiform	1	-	-
		LLL*	2	5mm	simple	plexiform			
				7mm					
14	1	RLL*	1	6mm	simple	fistula	1	-	-
15	1	LLL*	1	3mm	simple	fistula	1	-	-
16	1	RML*	1	6mm	simple	fistula	1	-	-
17	1	RLL*	8	3-13mm	complex	fistula	1	Yes	-
18	1	RLL*	10	2-8mm	complex	plexiform	3	Yes	Yes <sup>‡</sup>
19	1	RUL*	10	3mm each	simple	plexiform	2	-	Yes
20	1	RUL	1	2mm	simple	fistula	0 <sup>¶</sup>	-	-

\* Embolization performed

<sup>Δ</sup> Spontaneous thrombosis of feeding artery

<sup>†</sup> Declined treatment and follow-up

<sup>¶</sup> Feeding artery too small for treatment

<sup>‡</sup> Initial embolotherapy done at another center (patients entered our study when reperfusion was detected an additional embolization session was required)

Table 3: Comparison of Clinical Manifestations in Our Series to Other PAVM Series

	Our Results	Swanson <sup>16</sup> 1999	Gupta <sup>3</sup> 2002	Mager <sup>4</sup> 2004	Pollak <sup>5</sup> 2006	Cottin <sup>17</sup> 2007
N (# patients)	20	93	66	112	155	126
Mean age±SD (range)	48 ± 15 (25-86)	40 (5-83)	44 (13-77)	45 (7-85)	45 (7-77)	43 ± 17 (10-79)
Epistaxis	5%	49%	74%	-	-	90%
Telangiectasia	15%	-	-	-	-	86%
Hepatic Shunt	10%	-	-	4%	-	10%
HHT%	0%	56%	83%	96%	95%	100%
Dyspnea	50%	53%	56%	-	59%	56%
Cyanosis	0%	29%	29%	-	-	18%
Polycythemia	5%	13%	27%	-	-	-
Migraine	30%	-	38%	-	46%	16%
Hemoptysis	20%	15%	9%	1%	3%	12%
Hemothorax	0%	-	3%	3%	-	3%
CVA	20%	29%	42%	14%	33%	16%
Brain Abscess	5%	5%	17%	7%	9%	19%
Other Abscess	0%	-	3%	1%	6%	4%
Asymptomatic	30%	16%	-	34%	16%	15%