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Idiopathic pulmonary arteriovenous malformations: clinical and imaging characteristics

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ABSTRACT: Pulmonary arteriovenous malformations (PAVMs) can cause stroke, brain abscess or life-threatening haemorrhage. Most PAVMs are associated with hereditary haemorrhagic telangiectasia (HHT). The aim of the present study was to describe the clinical presentation and treatment outcomes of those with idiopathic PAVMs, which has not previously been described in the literature.

Patients with idiopathic PAVMs were identified at our HHT centre. Retrospective review of charts and imaging were performed.

20 patients were identified with idiopathic PAVMs. The most common symptoms reported were dyspnoea and migraines (50 and 30% of patients, respectively). Previous complications of PAVMs included haemoptysis (20%), stroke (20%) and brain abscess (5%). A total of 28 focal PAVMs were identified. Most patients (80%) had a solitary PAVM. 13 out 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.

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: Arteriovenous malformations, embolisation, hereditary haemorrhagic telangiectasia, lung, therapeutic

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 haemorrhage, and symptoms and complications from paradoxical embolisation, such as stroke and brain abscess [1, 2].

Approximately 80–95% of PAVMs are associated with hereditary haemorrhagic telangiectasia (HHT) [3–5], also known as Osler–Weber–Rendu syndrome. A number of other conditions are more rarely associated with acquired PAVMs, such as hepatic cirrhosis [6], schistosomiasis [7], mitral stenosis [8], trauma [8], actinomycosis [8], Fanconi's syndrome [9], and 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 remainder are complex PAVMs, 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 characterised 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 multiseptated aneurysm or a cluster of vascular channels.

Historically, symptomatic PAVMs were treated surgically. But since the advent of embolotherapy, percutaneous transcatheter embolisation with coils has significantly decreased the rate of complications arising from PAVMs [3–5, 12]. The International HHT Guidelines recommend that PAVMs be embolised preventatively, whether or

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not they are symptomatic, in order to decrease the risk of complications [13]. The literature supports targeting PAVMs with a feeding artery diameter of $\geqslant$3 mm [14, 15], with consideration for embolising PAVMs with a 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 characterised 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 (Canada) is a tertiary specialised HHT centre. 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 by unenhanced computed tomography (CT) of the chest, were included in the study. Those with ''definite'' HHT according to the Curaçao criteria [13, 18] or with a definite family history for HHT were excluded from this study. Any patients that had other known causes of PAVMs were also excluded.

Curaçao 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 three out of the four of the criteria are present, suspected when two criteria are present and unlikely when only one criterion is present.

Genetic testing for HHT

All patients were offered genetic testing for HHT. Previous studies have shown that ~80% of HHT families have a 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 the activin receptor-like kinase 1 protein [20]. More recently, mutations of the gene called mother against decapentaplegic homologue 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 from 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, an oxygen shunt study, agitated saline transthoracic contrast echocardiography (as previously described [23, 24]) and chest CT performed as routine baseline assessment for suspected PAVMs. Also, 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 an interventional radiology dept 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 embolisation coils in the distal aspect of all PAVMs with a feeding artery diameter $\geqslant$3 mm, 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 yr and then every 1–3 yrs. Oxygen shunt study and chest radiograph were performed at the 1–2-month follow-up visit. Chest CT was performed at the 1-yr follow-up, then every 1–3 yrs 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 (R.P. Chan) to collect data regarding PAVM anatomical characteristics as well as imaging outcomes following embolisation.

Data analysis

Data are presented as percentages, or means with ranges or standard deviations as appropriate. Data are tabulated and presented in graph and chart format where appropriate.

RESULTS

Patient demographic and clinical presentation

20 (14%) out of a total of 139 patients met the study criteria, with PAVMs. The mean age at time of presentation to our clinic was 47 (range 25–86) yrs with 13 (65%) out of 20 patients being female. Nine (45%) of 20 patients were diagnosed with PAVMs as a result of symptoms or complications related to their PAVMs. Of these, five (25%) patients presented with serious complications related to their PAVM, such as cerebral vascular accident (CVA), brain abscess or haemoptysis. PAVMs were found incidentally in the remaining 11 (55%) patients. Symptoms related to PAVMs found on initial assessment included dyspnoea, haemoptysis and migraine.

TABLE 1 Patient demographics and clinical manifestations on presentation

Patient	Age yrs	Sex	Dyspnoea	Hypoxaemia	Migraine	Haemoptysis	Stroke	Cerebral abscess	Initial presentation	Follow-up months
1	25	F	+	+	-	-	-	-	*Post partum* dyspnoea[f] (CT)	62
2	25	F	+	-	+	+	+	-	Motor vehicle accident (CXR)	66
3	31	F	+	-	+	-	-	-	Muscular chest pain (CXR)	90
4	37	F	-	-	-	-	-	-	*Post partum* dyspnoea[f] (CT)	10
5	42	F	-	-	-	-	-	-	Pneumonia (CXR)	28[¶¶]
6	46	F	-	-	-	-	-	-	Pneumonia (CXR)	20
7	49	F	+	-	+	-	-	-	Abdominal pain (CXR)	14
8	50	F	+	-	+	+	-	-	Routine CXR	29
9	50	F	-	-	-	-	-	-	Recurrent cough (CXR)	15
10	54	F	+	-	+	-	-	-	Nonresolving pneumonia (CXR)	78
11	54	F	-	-	-	+	-	-	Minor haemoptysis[f] (CT)	4[§§]
12	61	F	+	-	+	-	-	-	Pneumonia (CXR)	22
13	86	F	-	-	-	-	+	-	Stroke and hypoxaemia[f] (CT)	24
14	34	M	+	-	-	-	-	-	Dyspnoea[f] (CXR)	16
15	36	M	-	-	-	-	+	-	Recurrent embolic stroke[f] (CT)	74
16	42	M	-	-	-	-	-	-	Recurrent cough (CXR)	75
17	51	M	+	+	-	-	-	+	Cerebral abscess[f] (CXR)	37
18	53	M	+	-	-	++	-	-	Dyspnoea[f] (CT)	70
19	60	M	-	+	-	-	+	-	Stroke, seizure and hypoxaemia[f] (CT)	27
20	68	M	-	-	-	-	-	-	Staging for colon cancer (CT)	32
Patients n/N (%)[#]	47[¶]	13[§]/20 (65)	10/20 (50)	4/20 (20)	6/20 (30)	4/20 (20)	4/20 (20)	1/20 (5)	9[##]/20 (45)	40

F: female; M: male; CT: computed tomography; CXR: chest radiography. -: absent; +: present; ++: present (massive). [#]: unless otherwise stated; [¶]: mean; [§]: females; [f]: symptom considered related to their pulmonary arteriovenous malformation (PAVM); [##]: related to PAVM; [¶¶]: lost to follow-up; [§§]: declined treatment and follow-up.

Patient demographics along with patients' initial presentation are summarised in table 1.

Although all patients with ''definite'' HHT according to the Curaçao criteria were excluded, seven (35%) out of the remaining 20 patients had one other clinical feature in their history compatible with possible HHT (patients 2, 10, 13 and 16–19). This group of patients has a mean±SD age of 53±18 (range 25–85) yrs. Patients 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

16 (80%) out of 20 patients had genetic testing results that were 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 HHT-causative *ENG* gene mutation (fig. 1).

Imaging characteristics

A total of 28 focal idiopathic PAVMs were identified in 19 out of 20 patients. Imaging characteristics are not reported in detail for one patient as they had bilateral diffuse PAVMs. 16 (80%) patients had a single PAVM, two (10%) patients had two PAVMs and one (5%) patient had eight PAVMs. Of the 28 focal idiopathic PAVMs, 13 (46%) were located in the lower lobes (fig. 2). 26 (93%) out of 28 PAVMs were simple while the remainder were complex. 23 (82%) out of 28 PAVMs were fistulas while the remainder were plexiform PAVMs. The mean feeding artery diameter was 4 (range 1–13) mm. The imaging characteristics of all 20 patients are presented in table 2.

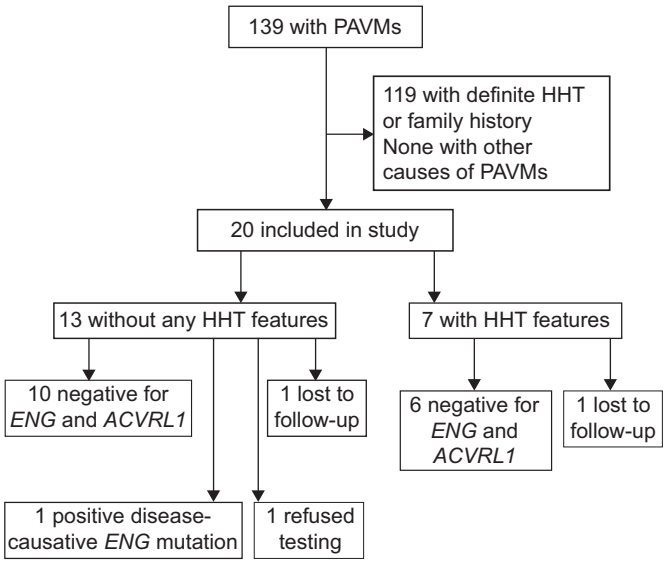

FIGURE 1. Distribution of idiopathic pulmonary arteriovenous malformation (PAVM) cases and genotypes. HHT: hereditary haemorrhagic telangiectasia.

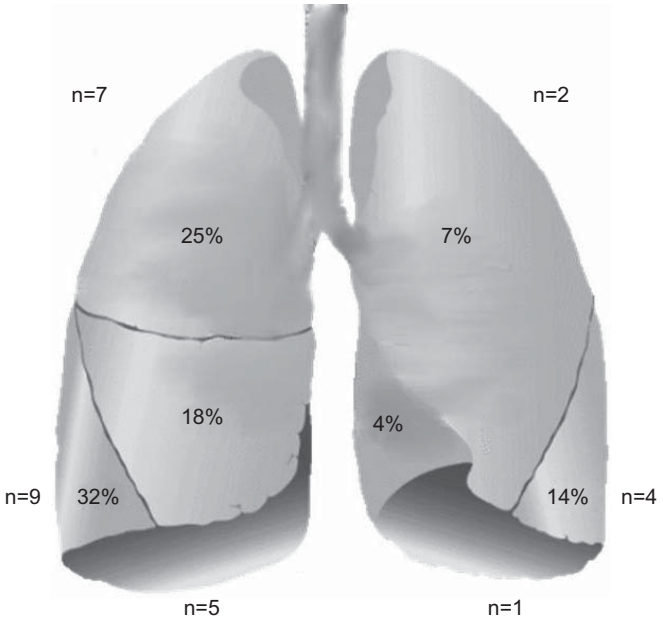

FIGURE 2. Location of idiopathic pulmonary arteriovenous malformations.

Treatment outcomes

Embolisation was performed for 20 (71%) out of 28 PAVMs in a total of 23 sessions (including reperfusion treatments) for 17 out of 20 patients (table 2). Reperfusion was assessed 1 yr after embolisation and occurred in five out of 17 patients, each of whom required subsequent embolisation 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 whom both pre- and post-embolisation arterial blood gas data were available, all had improvement in shunt, with 10 having complete normalisation of the estimated shunt fraction (normal <8%, based on local receiver operating characteristic 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 haemoptysis, occurred as a result of embolisation.

Follow-up

Patients were followed for a mean of 40 (range 4–90) months, as shown in 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 haemoptysis, after embolotherapy.

DISCUSSION

PAVMs are known to cause serious complications, such as stroke, cerebral abscess and life-threatening haemorrhage [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.

TABLE 2 Imaging characteristics and treatment outcomes

Patient	PAVMs n	Location	Feeding arteries n	Feeding artery diameter mm	Simple *versus* complex	Fistula *versus* plexiform	Embolisation sessions n	Post-treatment infarction	Reperfusion
1	Diffuse	Diffuse	NA	NA	NA	NA	2	-	+##
2	1	RLL#	1	5	Simple	Fistula	1	-	-
3	1	LLL#	2	6 2	Simple	Fistula	1	-	+
4	8	LUL LUL RUL# RUL# RUL# RUL RLL RLL#	1 1 1 1 1 1 1 2	1 1 3 3 3 1 2 2 10	Simple Simple Simple Simple Simple Simple Simple Simple	Fistula Fistula Fistula Fistula Fistula Fistula Fistula Fistula	1	-	-
5	1	RML#	1	5	Simple	Fistula	2	-	+##
6	1	RML	1	3	Simple	Fistula	0¶	-	-
7	1	RML#	1	3	Simple	Fistula	1	-	-
8	1	RLL#	1	4	Simple	Fistula	1	-	-
9	1	RML#	1	4	Simple	Fistula	1	-	-
10	1	RLL#	1	5	Simple	Fistula	1	-	-
11	2	RLL RUL	1 1	3 4	Simple Simple	Fistula Plexiform	0§	-	-
12	1	Lingula#	1	3	Simple	Fistula	1	-	-
13	2	LLL# LLL#	1 2	5 5 7	Simple Simple	Plexiform Plexiform	1	-	-
14	1	RLL#	1	6	Simple	Fistula	1	-	-
15	1	LLL#	1	3	Simple	Fistula	1	-	-
16	1	RML#	1	6	Simple	Fistula	1	-	-
17	1	RLL#	8	3–13	Complex	Fistula	1	+	-
18	1	RLL#	10	2–8	Complex	Plexiform	3	+	+##
19	1	RUL#	10	3 (each)	Simple	Plexiform	2	-	+
20	1	RUL	1	2	Simple	Fistula	0f	-	-

RLL: right lower lung; LLL: left lower lung; LUL: left upper lung; RUL: right upper lung; NA: not applicable; -: absent; +: present. #: embolisation performed; ¶: spontaneous thrombosis of feeding artery; §: declined treatment and follow-up; f: feeding artery too small for treatment; ##: initial embolotherapy performed at another centre (patients entered our study when reperfusion was detected and an additional embolisation session was required).

TABLE 3 Comparison of clinical manifestations in our series to other pulmonary arteriovenous malformation series

	Present study	First author [ref.]				
		Swanson [16]	Gupta [3]	Mager [4]	Pollak [5]	Cottin [17]
Patients n	20	93	66	112	155	126
Age yrs mean±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
Dyspnoea %	50	53	56		59	56
Cyanosis %	0	29	29			18
Polycythaemia %	5	13	27			
Migraine %	30		38		46	16
Haemoptysis %	20	15	9	1	3	12
Haemothorax %	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

HHT: hereditary haemorrhagic telangiectasia; CVA: cerebral vascular accident.

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 with <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. First, patients with idiopathic PAVMs might have a lower incidence of platypnoea and orthodeoxia that usually results from increased ventilation–perfusion mismatching in an upright position, an observation usually seen in lower lobe preponderance. Secondly, MAGER *et al.* [4] showed in their study that patients with solitary PAVMs were more likely to have a favourable outcome after embolotherapy than those with multiple PAVMs. 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 polycythaemia (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 shown in table 2. There were no major complications from the procedure, such as paradoxical embolism or haemoptysis, and no long-term symptoms or sequelae. During an average 3-yr follow-up period after embolisation, all patients reported improved dyspnoea and none developed serious PAVM-related complications.

The prevalence of HHT in patients with PAVMs has historically ranged between 50 and 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 trend towards higher prevalence of HHT as the underlying diagnosis is probably 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 centres reporting PAVM series are HHT tertiary referral centres, 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-characterised 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 ~80% sensitive [31]. This is because introns (noncoding 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 unrecognised causative mutation.

It remains possible that some of the patients in our series have unrecognised HHT, with this being especially plausible for the seven patients who had epistaxis, mucocutaneous telangiectases or hepatic shunt. HHT is often unrecognised in children and young adults, as the clinical expression of HHT is age-related [35]. For example, <50% of children with HHT have epistaxis or telangiectasia [36] but ~90% of adults >50 yrs of age have recurrent epistaxis [35, 37]. However, given that the mean age in our group of ''possible'' patients is >50 yrs, none had a family history of HHT and all (six out of six) 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. They were later excluded from our study when they re-presented to the clinic 6 yrs 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 an *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 a 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.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

None declared.

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