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REVIEW PAPER

Pulmonary arteriovenous malformations

Sreeshma Tellapuri[1] · Harold S. Park[1] · Sanjeeva P. Kalva[1]

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Abstract
Pulmonary arteriovenous malformation, a condition most commonly associated with hereditary hemorrhagic telangiectasia, is an abnormal communication between the pulmonary artery and pulmonary vein without an intervening capillary communication. Although asymptomatic in ~50% individuals, it can present with the dreaded complications of stroke or intracranial abscess in high-risk individuals including pregnant women, if untreated. The mainstay of treatment is now endovascular embolization of the feeding artery which can alleviate the symptoms and prevent these complications. In this review, we describe the pathophysiology, methods of screening, diagnostic workup and treatment of these vascular lesions with a particular focus on the currently used embolization techniques and their outcomes.

Keywords Pulmonary arteriovenous malformation (PAVM) · Embolization · Endovascular therapy · Coil · Microvascular plug · Hereditary hemorrhagic telangiectasia (HHT)

Introduction

Pulmonary arteriovenous malformation (PAVM) is an abnormal communication between the pulmonary artery and pulmonary vein without an intervening capillary communication. It may be associated with a venous aneurysm (sac) at the site of the communication. PAVM was initially described by Churton in the nineteenth century, like a walnut-sized lesion filled with a blood clot in a postmortem child [1]. PAVMs have also been addressed as pulmonary arteriovenous fistulae, pulmonary arteriovenous aneurysms, cavernous angiomas of the lung and pulmonary telangiectasias. PAVMs are usually asymptomatic, and the majority is detected incidentally. When large or multiple, however, they may become symptomatic due to the right-to-left shunt effect. Life-threatening complications of PAVM include stroke, transient ischemic attack, cerebral abscess, massive hemoptysis, and spontaneous hemothorax [2–4]. Prompt treatment, therefore, is essential to minimize patients' morbidity and mortality.

✉ Sreeshma Tellapuri
sreeshma.tellapuri@utsouthwestern.edu

[1] Division of Interventional Radiology, Department of Radiology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Epidemiology

PAVMs were first associated with Hereditary Hemorrhagic Telangiectasia (HHT) in 1938 [5]. HHT, also known as Osler–Weber–Rendu syndrome, is an autosomal dominant disorder prevalent in more than 1 in 10,000 individuals [6–8]. HHT is characterized by a triad of epistaxis, mucocutaneous or visceral telangiectasia and family history of PAVM. Endoglin (ENG) gene on chromosome 9 (HHT1 phenotype), activin receptor-like kinase-1 ACVRLI/ALK1 gene on chromosome 12 (HHT2 phenotype) and SMAD4 gene on chromosome 18 have been linked to the inheritance of the disease [9]. Around 15–50% of patients with HHT have PAVM [2, 10, 11]. Around 70% of PAVM are a part of HHT syndrome, and the rest are sporadic [2, 12]. PAVMs are more common and have a larger shunt when associated with ENG mutation (58%) versus ACRVL1 mutation (18%) on chromosome 9 [13]. The estimated prevalence of PAVMs is 38/100,000 individuals [14]. PAVMs are known to have a female preponderance [14, 15], and with pregnancy being a risk factor for complications from PAVMs, it is important to screen high-risk individuals [10, 16]. Acquired PAVM occur in individuals with prior cavopulmonary shunt procedures for congenital heart diseases, chronic liver disease or history of tuberculosis or actinomycosis infections [17, 18].

Pathophysiology

Mutations of the ENG and ACRVL1 alter the ligand-receptor interactions at the endothelial surface while the SMAD4 mutation interferes with the intracellular signaling within the endothelium. The imbalance between the proangiogenic vascular endothelial growth factor (VEGF) and the antiangiogenic transforming growth factor-β (TGF-β) leads to the formation of persistent thin walled direct arteriovenous conduits exposed to arterial blood flow and increased shear forces [19]. In rare cases, the fragile walls of PAVMs may rupture and cause hemothorax and hemoptysis. 65% of PAVMs favor lower lobes probably due to the increased pulmonary blood flow and pressure which is the cause of platypnea, i.e., dyspnea relieved on lying flat and orthodeoxia, i.e., desaturation in an upright position [20]. Around 90% of PAVMs have a single feeding artery and are characterized as "simple" [20, 21] (Fig. 1). Five percent are "complex" PAVMs with two or more feeding arteries from different segments. Another five percent are "diffuse" PAVMs with many feeders [22, 23].

Clinical features

Approximately 13–56% affected individuals with PAVMs are asymptomatic [24]. A careful physical examination may detect 75% of cases in the high-risk populations [25]. The presence of symptoms best correlates with the size of the PAVMs rather than the number of the lesion [24]. The presenting symptoms may include dyspnea, intrapulmonic hemorrhage, neurological symptoms/deficits, palpitations, cough, and chest pain. Signs which may be present on physical examination may include bruit/thrill, clubbing, telangiectasia, polycythemia, cyanosis or a systolic murmur. Complications associated with PAVMs typically arise from two mechanisms. The first results from the decreased O_2 partial pressure and oxygen saturation in the systemic arterial supply. The sequela of this abnormal phenomenon can lead to hypoxemia, anemia, hemoptysis, hemothorax, and pulmonary hypertension. The second mechanism involves anomalous venous drainage. This abnormal arterio-venous communication can lead to pulmonary artery hypertension, but more commonly, complications from paradoxical embolization such as transient ischemic accidents or stroke, cerebral abscesses, endocarditis, or visceral or extremity ischemia/infarction.

Screening

Physical examination including thorough ear, nose and throat examination, chest radiography, arterial blood gas measurements, and finger oximetry are essential in screening individuals with suspected PAVMs [26]. Transthoracic

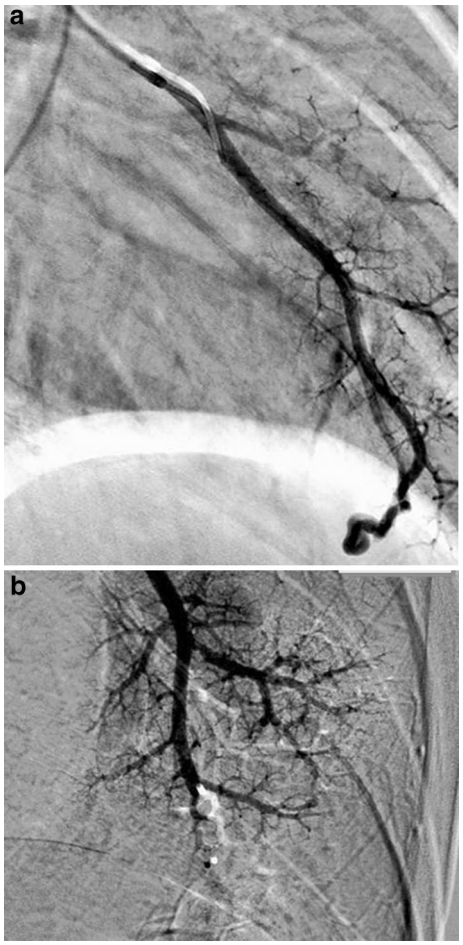

Fig. 1 **a** Simple PAVM in the lingula in a 17-year-old male patient. **b** Post embolization angiogram of the PAVM with Amplatzer plug

contrast echocardiography (TTCE) is the recommended initial screening test for PAVM detection in high-risk patients [27]. The principal behind TTCE in the detection of shunts is dependent on the signal produced by agitated saline which produces numerous microbubbles. Newer ultrasound contrast agents developed recently have facilitated increased duration of the contrast material in the blood pool, i.e., Lumason (Bracco Diagnostics). TTCE is considered positive if there is the detection of any bubbles in the left atrium. Around 44–60% of individuals with HHT may have positive contrast echocardiography indicative of an intrapulmonary shunt [28, 29]. Positive screening can be confirmed with non-contrast multidetector thoracic CT with thin-slice (e.g. 1–2 mm) reconstructions. In children, screening tests may include a physical exam (for cyanosis, dyspnea, clubbing), supine and upright pulse oximetry, chest radiography and/or TTCE. A combination of a chest radiograph and contrast echocardiography achieves nearly 100% sensitivity and negative predictive value [11, 30]. In high-risk patients with negative initial screening, repeat screening should be

considered after puberty, after pregnancy, within 5 years preceding planned pregnancy and otherwise every 5–10 years [27]. With the advancement of genetic mutation testing and family mapping, 80% of affected individuals can be identified by testing for the three most common mutations [31].

Diagnosis and work-up

Patients with HHT are diagnosed based on the Curaçao Criteria [32] (Table 1). Comprehensive blood evaluation, electrocardiography, CT pulmonary angiography, contrast-enhanced echocardiography or radionuclide angiocardiography (to avoid angiography in nonsurgical cases and atypical cases) are the necessary investigations [24]. Optional investigations include catheter-directed angiography, perfusion lung scan, cardiac catheterization, and shunt evaluation procedures.

On chest radiograph, PAVMs appear as homogeneous sharply demarcated pulmonary lesions, with associated curvilinear opacities demonstrating the feeding artery and a draining vein coursing towards the hilum [25, 33]. PAVMs may also appear as a more complex plexiform mass of dilated vascular channels or as dilated tortuous direct communication between an artery and vein [34].

TTCE is minimally invasive initial screening modality with high sensitivity for detecting shunts in the lungs. A grading system (from 0 to 3) has been proposed and studied as a screening tool for PAVMs in HHT patients. The grade is determined by the appearance and concentration of bubble contrast in the left atrium after a minimum of three cardiac cycles, wherein, Grade 0, no bubbles; Grade 1, occasional filling with < 20 bubbles; Grade 2, moderate filling; Grade 3, complete opacification. The overall diagnostic performance was found to have a sensitivity of 1.00, specificity of 0.49, positive predictive value (PPV) of 0.32 and negative predictive value (NPV) of 1.00 [35].

CT pulmonary angiography is considered the gold standard for diagnosis of PAVMs. At our institution, PAVM surveillance and follow-up are performed with CT angiograms following a pulmonary embolism protocol. We recommend a helical scan using 0.63 mm collimation with 1 mm and 3 mm axial reconstructions. We image after injecting 90 cm^3 of contrast at a rate of 5 cm^3/s with bolus tracking over the main pulmonary artery. 2 mm coronal and sagittal multiplanar reformatted (MPR) images, as well as 5×5 and 7×2 coronal and axial maximum intensity projections (MIPS), are also submitted. In particular, the MIP images provide a more sensitive means to detect smaller PAVMs. Employing 3D reconstruction software can depict the angioarchitecture of the feeding arteries and draining veins (number, size, and orientation of the vessels) which can serve as a roadmap for selective embolotherapy and also helps estimate the size of the PAVM before and after embolotherapy [36, 37]. Given the possibility of multiple and bilateral PAVMs, imaging with CT is extremely valuable to both assess the extent of the condition as well as to plan endovascular treatment. Because of this, emergent embolotherapy without a CT is exceedingly rare.

Magnetic Resonance Imaging (MRI) has seen greater usage in detecting, pre-embolization planning and evaluating treated PAVMs. MRI, compared to CT, has the benefit of avoiding ionizing radiation as well as the use of iodinated contrast, particularly in a patient with allergies or renal insufficiency [38, 39]. A study comparing the detection rates of contrast-enhanced MR angiography (CE-MRA) with conventional pulmonary angiography concluded that CE-MRA could detect PAVMs as small as 2 mm and can potentially be used as a screening tool for detecting PAVMs [40]. A suggested protocol for performing dynamic contrast-enhanced MR angiogram includes a three-dimensional T1-weighted spoiled gradient echo sequence after intravenous injection of 0.1–0.2 mmol/kg gadolinium at a flow rate of 2–5 cm^3/s to shorten T1. Scan acquisition commences at the peak of the contrast enhancement by centric elliptic phase encoding and can be completed in two breath holds [41].

Management of PAVM

Before 1978, surgery was the only option to treat PAVMs, and this entailed local excision, segmental resection, lobectomy, or pneumonectomy to reduce complications in symptomatic patients [24]. Initial reports of embolotherapy were

Table 1 Curaçao criteria

Definite HHT	If 3 are present
Possible or suspected HHT	If 2 are present
Unlikely HHT	If fewer than two are present
Criteria	
Epistaxis	Spontaneous recurrent nose bleeds. Night time bleeds are more suspicious
Telangiectasia	Multiple at characteristic sites—lips, oral cavity, fingers, nose
Visceral lesions	Gastrointestinal telangiectasia (with or without bleeding, PAVM, Hepatic AVM, Cerebral AVM, spinal AVM)
Family history	A first degree relative with HHT according to these criteria

published in 1978 [42] and 1980 [43]. However, the International Guidelines by an expert panel now agree that surgical management of PAVMs plays a minimal role, other than in the management of life-threatening bleeding in a center where there is no expertise in embolotherapy [27].

"Single-session outpatient embolotherapy" is the ideal approach to managing PAVM patients with four or fewer lesions [44]. Patients with multiple lesions may require multiple sessions of outpatient therapy (Fig. 2). Treatment of patients with PAVMs is recommended for both symptomatic adults and children and asymptomatic adults. The decision to treat asymptomatic children should occur on a case-by-case basis, and embolotherapy is considered as safe and effective as in adults in children [27, 45]. Although the majority of children with HHT and PAVM are asymptomatic, they require continued follow-up as the PAVMs enlarge with time and may cause complications [46, 47]. It is now recommended that all PAVMs detected by CT should be treated if possible. The previous guideline of treating PAVMs with a feeding artery 3 mm or larger is no longer generally accepted [3, 20, 48].

The pre-procedural multi-disciplinary comprehensive workup typically includes a diagnosis of PAVM by contrast echocardiography or CT pulmonary angiography, electrocardiography to rule out left bundle branch block (LBBB), serum creatinine to prevent contrast nephrotoxicity in patients with acute and chronic renal insufficiency and resting and exercise pulmonary arterial oxygen saturation [49].

Principles of embolotherapy

The feeding artery should be occluded as close to the fistulous communication as possible to preserve normal perfusing lung parenchyma. It is essential to achieve adequate occlusion of all the feeding arteries, while the nidus or venous outflow need not be occluded. Intravenous heparin can be given during the procedure to prevent intraprocedural paradoxical embolism [44]. Holding the breath in deep inspiration aids to include the lung bases in the field of view during the arteriography and permits the evaluation of lesions at the lung bases without overlap. Also, this may also aid in straightening otherwise angled, tortuous vessels. Employing a closed flush system or the double flush technique helps to prevent air suction in the catheter and thus air embolism.

Technique of embolization

In general, treatment is performed under moderate sedation unless the patient has a condition that prevents them from tolerating the procedure, i.e., significant comorbidities, inability to protect the airway, inability to tolerate lying flat, in which case general endotracheal anesthesia can be employed.

When initially placing any vascular sheath during these procedures, it is paramount to place a filter for the flush bag attached to the sheath to prevent introducing air bubbles into the system. Following femoral vein or internal jugular vein access, a 6 Fr angled pigtail catheter/Grollman catheter (Cook, Bloomington, Indiana, USA) or a regular 6 Fr pigtail catheter is advanced into the pulmonary artery and the right or left main pulmonary artery is selected. Pulmonary arterial pressures are measured via a catheter-based transducer system (normal—25/8 mmHg, mean—15 mmHg). At our institution, selective digital subtraction angiography (DSA) in the main pulmonary arteries (half strength contrast material injected at a rate of 15 cm^3/s with a total volume of 30 cm^3/s while imaging at 6 frames/s) is performed in anterior–posterior (AP), ipsilateral and contralateral oblique views to identify PAVMs and determine the feeding vessels. The feeder vessels are then identified, mapped, and a coaxial system (8 Fr guiding catheter with an inner longer 6 Fr angle-tipped catheter combination such a Lumax system—Cook, Bloomington, Indiana, USA) is advanced over an exchange-length Rosen wire. After occluding a feeding artery of a PAVM, care must be taken to identify any additional feeding arteries in a complex PAVM. A more proximal selective DSA can confirm successful embolization of the PAVM (Figs. 1b and 2e). One can treat any number of PAVMs in a single session, but the complexity of the procedure, radiation dose to the patient and the amount of contrast material utilized delimit the number of PAVMs treated in a single session. The venous access sheath is removed after the procedure, and manual pressure is applied at the access site to attain hemostasis. After few hours of monitoring and recovery, the patient is discharged home. Acetaminophen is preferred over NSAIDs for immediate post-procedure pain as is associated with decreased risk of bleeding or epistaxis.

Among the various embolic materials available, coils (Fig. 2) and vascular plugs (Figs. 1 and 3) are the most commonly used for occluding PAVMs. The long-term effects of these embolic materials vary with the type and combination of materials used, the site of embolization proximal to the arteriovenous communication and the size of the feeding vessel. In general, coils are associated with a 20% recanalization rate and 5% for vascular plugs [31]. A single-center retrospective analysis study has suggested that coils in combination with a type I Amplatzer vascular plug can prevent recanalization [50]. Recently, polytetrafluoroethylene-covered nitinol plugs, or microvascular plugs (Medtronic), are being used for the treatment of PAVMs. Our experience (unpublished) suggests a recanalization rate of $< 5\%$ with these plugs. At present, no randomized control studies are comparing

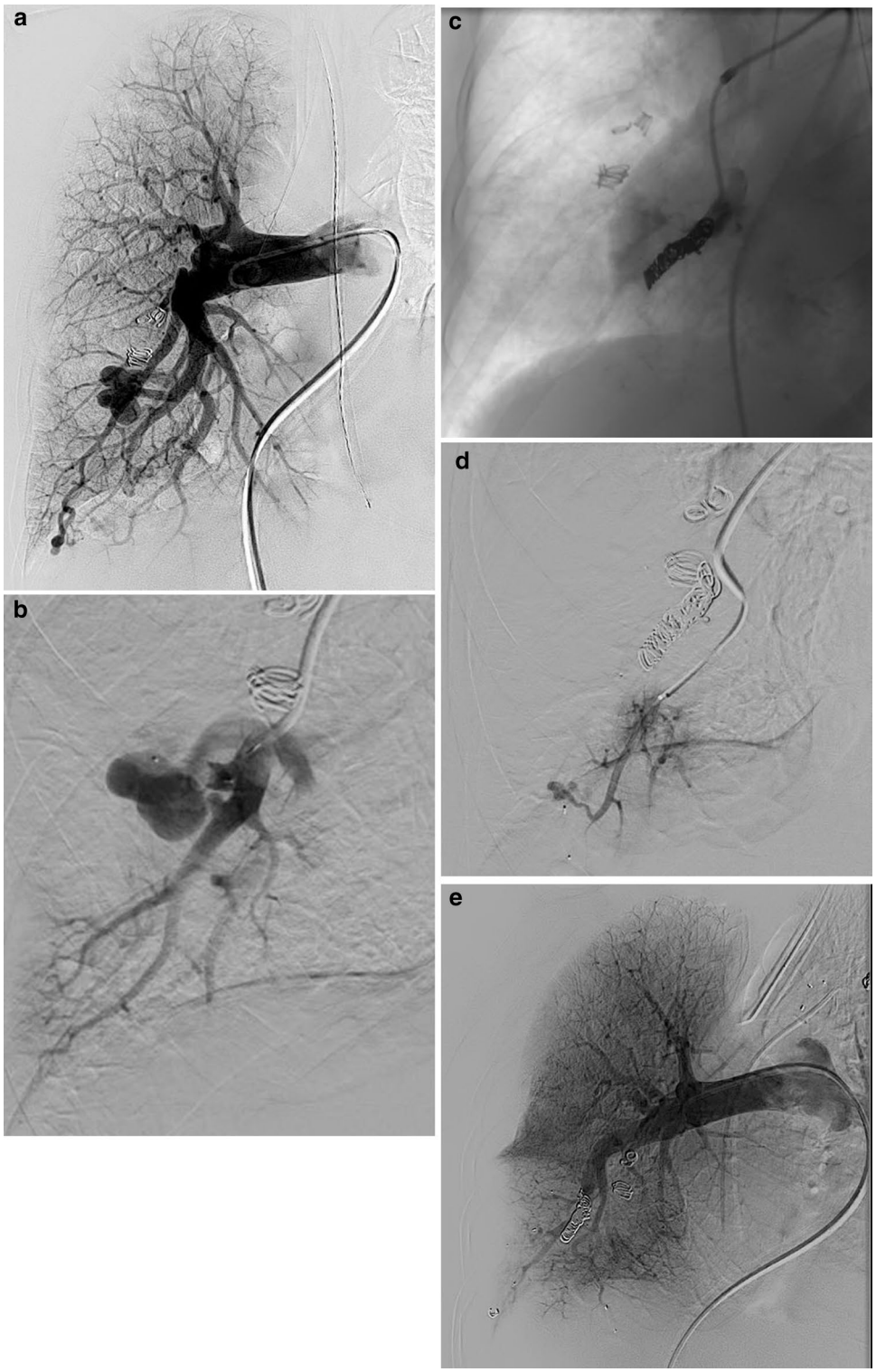

Fig. 2 **a** Right pulmonary angiogram is demonstrating multiple PAVMs in the right lower lobe in a 60-year-old female patient with multiple bilateral PAVMs. The patient subsequently underwent three sessions of transcatheter embolization with coils and microvascular plug. **b** Selective angiogram demonstrates the feeder vessel. **c** Angiogram demonstrates coil deployment in the feeding vessel. **d** Another PAVM demonstrated in the right basal segment of the same patient. **e** Post-embolization proximal angiogram demonstrates no residual PAVM

different embolization techniques or devices. The choice of an embolic device is based mainly on an individual or institutional preference. It should be noted that without regard to the 3 mm "rule," studies have found up to 70% of patients may have residual untreatable PAVMs [51].

Benefits of embolization

Embolization of PAVMs has been shown to improve oxygenation, decrease shortness of breath and increase

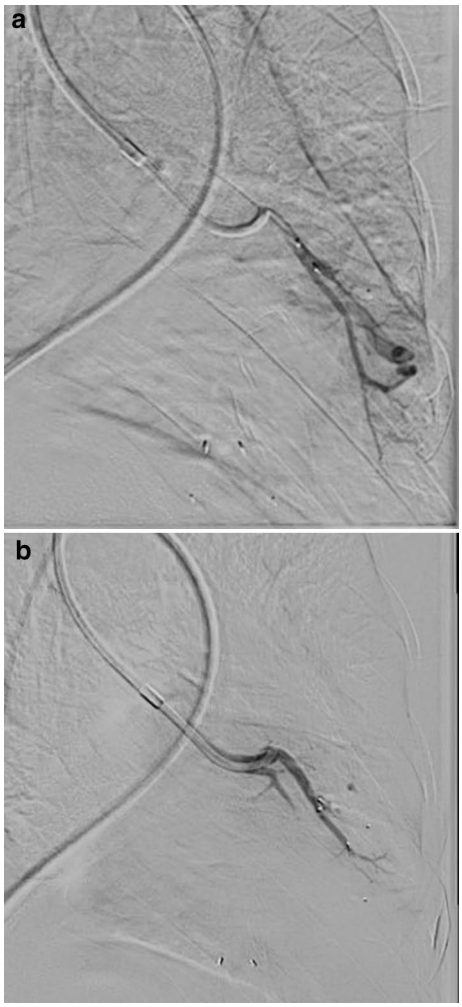

Fig. 3 **a** PAVM in the left lower lobe segment in a 60-year-old female with known HHT. **b** Post-embolization angiogram demonstrating successful occlusion of the feeding vessel with a microvascular plug

exercise tolerance [52]. It has also been reported to decrease the probability of paradoxical embolism and stroke, improves migraines, and decreases pulmonary hemorrhage. A multicenter retrospective study in 42 individuals who were less than 18 years diagnosed with PAVM reported that embolization is a safe and efficacious procedure in this age group and recommended that children with cyanosis, exercise intolerance, growth delay or previous complications from PAVM will benefit from the procedure [45].

Follow-up

Multidetector thoracic CT angiogram is recommended within 6–12 months after embolization and then approximately every 3 years after embolization [27]. In small untreated PAVMs and suspected microscopic PAVMs (e.g., detected on TTCE but not detectable on CT), the follow-up period should be determined on a case-by-case basis (approximately every 1–5 years) with CT angiogram, while considering radiation dose limitations and patient age. PAVM management requires life-long follow-up and continued vigilance observing for PAVM growth or recanalization [31, 53]. Several risk factors have been suggested for failed embolotherapy. These include the presence of gastrointestinal tract and/or hepatic arteriovenous fistulas at the time of initial diagnosis, pulmonary hypertension, large feeding artery diameter, smaller numbers of coils resulting in insufficient mechanical occlusion, lack of dense coil packing, under sizing coils or plugs, and embolization greater than 1 cm proximal to the nidus [49, 54].

Conclusion

Endovascular embolization of the feeding artery can prevent the complications associated with PAVMs. The procedure is minimally invasive, associated with minimum morbidity and high success rates. With the advancements in the development of newer techniques and embolization materials, recanalization rates of PAVMs are expected to decrease. However, given the chronic nature of the disease, affected patients need life-long follow-up for potential growth or recanalization of previously treated lesions to prevent the life-threatening complications associated with PAVMs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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