Management of Pulmonary Arteriovenous Malformations

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ABSTRACT

Pulmonary arteriovenous malformations are rare lesions with significant clinical complications. These lesions are commonly seen in patients with hereditary hemorrhagic telangiectasia (formerly Osler-Weber-Rendu syndrome). Interventional radiologists are a key part of the treatment team in this complex disease, and a thorough understanding of the disease process is critical to providing good patient care. In this article, the authors review the disease course and its association with hereditary hemorrhagic telangiectasia, discusses the clinical evaluation and treatment of these complex patients, and outlines complications and follow-up.

KEYWORDS: Pulmonary arteriovenous malformation, embolotherapy, arteriovenous malformation, telangiectasia

Objectives: Upon completion of this article, the reader should be able to identify the criteria for diagnosing hereditary hemorrhagic telangiectasia and recall the evaluation, treatment, and complications of this disease process.

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Pulmonary arteriovenous malformations (PAVMs) are direct high flow, low-resistance fistulous connections between pulmonary arteries and veins (Fig. 1). The resulting right to left shunt can be clinically silent in small malformations, but often results in hypoxia or a variety of neurologic sequelae in larger malformations. PAVMs are rarely sporadic. Between 60 and 90% are congenital manifestations of the autosomal dominant syndrome hereditary hemorrhagic telangiectasia (HHT), sometimes referred to as Osler-Weber-Rendu syndrome. Rare acquired causes include trauma, malignancy, hepatopulmonary syndrome, and cardiac surgery. PAVMs in hepatopulmonary syndrome relate to the lack of the liver's

ability to clear vasoactive substances such as prostaglandins. Similarly, hepatic clearance has been blamed for the development of PAVMs in children following shunt procedures for congenital cardiac anomalies (Fig. 2). However, there are case reports of PAVMs developing in patients who have maintained balanced hepatic venous flow from the liver following cardiac shunt procedures.¹

The natural history of PAVMs has historically been poorly understood. Symptoms reflect the consequence of right to left shunt physiology. Patients may present with hypoxia as unoxygenated blood shunts to the systemic circulation. Shunting of micro emboli bypasses the filtration function of the lungs and may

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Figure 1 Posteroanterior (A) and lateral (B) chest of a child show a large round soft tissue mass in the left midchest with connection to the pulmonary vasculature diagnostic of a pulmonary arteriovenous malformation.

result in development of transient ischemic attacks (TIAs), a cerebrovascular accident (CVA), or a brain abscess. Multiple literature reviews of untreated patients list a PAVM associated mortality ranging from 0–55%.² Gossage combined recent studies of untreated patients

and calculated a stroke incidence of 11.4%, a brain abscess incidence of 6.8%, and total morbidity and mortality at 23%.² A review of the Mayo Clinic experience suggested a morbidity of 26–33% and mortality of 8–16% in untreated patients.³ In his patients prior to treatment, White reported migraine headaches in 43%, TIAs in 37%, stroke in 18%, brain abscess in 9%, and seizures in 8%.⁴ Because a substantial number of patients with PAVMs present with multiple malformations, investigators have evaluated lesion characteristics in hopes of determining which malformations present the greatest danger to patients. White has suggested that patients become at risk for central nervous system complications when feeding vessels are > 3 mm. Most investigators believe that all such malformations should be treated regardless of symptoms.^{5,6} Because of the association between PAVMs and HHT, the interventional radiologist who plays an important role in the clinical management of PAVM patients should be familiar with HHT, its genetics, its clinical manifestations, and the appropriate workup of family members of patients who present with either PAVMs or other evidence of HHT.

Figure 2 Coronal maximum intensity projection of a contrast-enhanced computed tomography scan in a child with multiple pulmonary arteriovenous malformations in the right lower lobe following formation of Blalock-Taussig shunt (right subclavian to pulmonary artery).

HEREDITARY HEMORRHAGIC TELANGIECTASIA

Formerly called Osler-Weber-Rendu, HHT is an inherited disorder of the vasculature associated with

AVMs and telangiectasias. The prevalence of HHT is 1 in 5,000 to 10,000 patients.⁷ HHT is inherited in an autosomal dominant fashion. Diagnosis of HHT is based upon the presence or absence of four specific clinical criteria often referred to as the Curacao criteria.⁸ Although sensitivity and specificity data are not available for these criteria, they are felt to be the best available assessment tool.⁶ If three criteria (Table 1) are present, the diagnosis is definite. If two criteria are present, the diagnosis of HHT is probable. If less than two criteria are present, the diagnosis is unlikely. Eighty to ninety percent of patients with pulmonary AVMs have HHT.^{3–5} However, only 15–25% of patients with HHT have pulmonary AVMs. This relates to the different genetic mutations responsible for the disease. The HHT1 subtype is associated with an endoglin gene mutation and has a higher rate of pulmonary involvement than the HHT2 subtype, which is associated with an activin receptor like kinase gene mutation.⁷ Both the endoglin and activin receptor like kinase genes are associated with transforming growth factor-beta (TGF- β). On endothelial cells, TGF- β controls cellular adhesion, migration, and proliferation. Abnormal endothelial cells form the malformations and telangiectasias characteristic of the disease. Ten percent of patients who test negative for the HHT1 and HHT2 subtypes will have a SMAD4 gene mutation, which causes a combination of juvenile polyposis and HHT.⁶

HHT is a familial disease. Because, the disease is often clinically silent but places patients at risk for sudden and debilitating insult, it is critical that family members of patients with HHT be screened for pulmonary AVMs to allow preventative intervention. Up to 35% of first-degree family members will have PAVMs. In a family with a known genetic mutation, the remainder of the family can be tested for that mutation sparing non-HHT family members from invasive testing and radiation exposure. In cases where genetic testing is not available or financially prohibitive, rigorous clinical screening is recommended and is detailed later in this article.

HHT Presentation

Epistaxis is the main presenting symptom in patients with HHT. Spontaneous nocturnal epistaxis is considered the classic presentation for HHT. The average age of onset is 12 years. Fifty percent of HHT patients will

have had spontaneous epistaxis by age 20 and 90% by age 45. Epistaxis in these patients is secondary to mucosal telangiectasias. Dyspnea is a common complaint of patients with PAVM, but does not typically lead patients to seek care. Platypnea (dyspnea which is relieved by lying down) and orthodeoxia (decreased O₂ seated in an upright vs recumbent position) can be seen in patients with PAVMs. Patients are not usually symptomatic from hypoxemia unless lesions are ≥ 2 cm. In addition, the slowly progressive nature of the disease often allows for adequate compensation. Patients may present with other symptoms related to hypoxemia such as clubbing or cyanosis. Compensatory polycythemia does occur, but is frequently masked by chronic gastrointestinal (GI) bleeds or recurrent epistaxis. Hemoptysis drives some patients to seek medical attention and was the most common presenting symptom in the review of Mayo's clinical experience,³ but it has been more infrequently noted in other series. Fatal or massive hemoptysis or hemothorax is uncommon (< 8%), but has been reported.⁹ Pregnancy may be a risk for hemoptysis in patients with PAVMs. Three of the seven women in Ferenc's review with massive hemoptysis were pregnant.⁹ Pregnancy causes growth of PAVMs (particularly in the last trimester) due to increased cardiac output, blood volume, and hormone-related changes of the vasculature. Neurologic sequelae of the right-to-left shunt are common and dreaded presenting signs of PAVMs and HHT. Thirty to 40% of patients with feeding vessels > 3 mm present with TIAs, stroke, or a brain abscess.^{2,4,5}

In patients with HHT, GI bleeding related to telangiectasias may be the presenting symptom and is present in 15–30%. Telangiectasias also occur on the patient's skin and mucosal surfaces. Visceral vascular malformations may be present and are often found in the liver. These lesions range from discrete focal malformations, such as a hepatic artery to hepatic vein, to diffuse perfusion abnormalities.

Evaluation

Because PAVMs are uncommon lesions, a high index of suspicion is helpful when patients present with difficult to explain clinical syndromes. For example, PAVM should be considered in the evaluation of young patients who present with cerebral abscess, TIAs, or stroke unassociated with a clear etiology. PAVM should also

Table 1 Curacao Criteria for Diagnosis of Hereditary Hemorrhagic Telangiectasia (HHT)

Epistaxis	> 1 Episode of spontaneous bleed (nocturnal bleeding is particularly suspicious)
Multiple telangiectasias	Common sites include the lips, oral cavity, fingers, and nose
Visceral lesions	Common sites include pulmonary AVM, hepatic AVM, cerebral AVM, spinal AVM, and GI telangiectasias
Family history	A first-degree relative with HHT diagnosis made by these criteria

AVM, arteriovenous malformation; GI, gastrointestinal

be a consideration in the evaluation of patients with unexplained hypoxia or cyanosis.

In patients diagnosed with HHT, the interventional radiologist must be prepared to diagnose and appropriately manage PAVMs.

Patients with suspected HHT should undergo a complete history and physical evaluation to identify the nature and extent of the disease. Pertinent historical positives include a personal or family history of spontaneous epistaxis, neurologic symptoms (including headache), dyspnea, or GI bleeding. A careful cardiac and respiratory history should be obtained for any signs or symptoms of high output heart failure. The physical examination is designed to elicit evidence of vascular malformations. The mucosal surfaces, trunk, and fingertips should be inspected for telangiectasias. Telangiectasias are red ~2-mm nonblanching lesions that will be present in 50% of patients by the third decade and occur ~10 years after the onset of epistaxis. The presence of PAVMs can occasionally be demonstrated as an audible bruit on examination of the chest. A complete neurologic examination is critical as 23% of HHT patients will have cerebral vascular malformations or spinal vascular malformations in addition to the ischemic sequelae of the right-to-left shunt.

Detection of hypoxia is an important clue to the presence of shunt physiology. Seated, recumbent, and postexercise pulse oximetry may show a decreased oxygen saturation on room air. Orthodeoxia, which is a decrease in oxygen saturation upon standing, can also be seen. One study of 53 patients demonstrated a mean recumbent oxygen saturation of 89%, which decreased by a mean of 6% on standing.¹⁰ An arterial blood gas on room air with a PaO₂ of > 90 mm Hg rules out a significant shunt whereas a PaO₂ < 85 mm Hg suggests that a significant shunt (> 5%) is likely. If blood gases reveal hypoxemia, quantification can be estimated with several techniques including the 100% O₂ method, macroaggregated serum albumin (MAA) nuclear medicine study, and transthoracic contrast bubble echocardiography, which is recommended by the HHT consensus panel.^{6,11}

The imaging evaluation is designed to detect visceral malformations and should be driven by the history and physical examination and blood gas findings. Although many PAVMs can be identified on plain chest x-ray, fine-cut computed tomography (CT) of the chest is substantially more accurate. Sensitivity and specificity of PAVM detection in contrast-enhanced 16-detector CT has been reported at 83% and 78%, which compares favorably with digital subtraction pulmonary angiography of 70 and 100%.¹² Contrast-enhanced breath-hold magnetic resonance angiography (MRA) also has high sensitivity and specificity and should be considered in young patients where radiation exposure will be of greater concern.¹³

Contrast magnetic resonance imaging (MRI) should be used to evaluate any patient who has a neurologic deficit. The use of MRI for screening for cerebral vascular malformations in asymptomatic patients is of uncertain benefit given the limited treatment options for such lesions. Gastric and small bowel telangiectasias are very common in HHT patients over 50 years of age; however, these lesions only cause bleeding in 25–30% of patients. Bleeding is twice as likely to occur in females compared with males. Endoscopy is only recommended to evaluate and treat the lesions if the patient is actively bleeding or anemic from GI blood loss; there is no need to screen asymptomatic patients with endoscopy. Vascular malformations of the liver are present in up to 78% of people who undergo screening, but only 10% are symptomatic. Liver function tests should be obtained. The gamma glutamyl transpeptidase (GGT) test is commonly slightly elevated. The clinician should look for signs and symptoms of liver failure, portal hypertension, mesenteric ischemia (usually from steal), biliary abnormalities, and hepatic encephalopathy. In patients with laboratory or clinical abnormalities related to the liver, triphasic contrast-enhanced CT or Doppler ultrasound is recommended. There is a significantly increased incidence of focal nodular hyperplasia in HHT patients. Biopsy is not recommended as there is a significantly increased risk of bleeding.⁶

Treatment

PAVMs were historically treated with surgical resection. As endovascular techniques developed, embolization became the mainstay of treatment. Coils and a detachable occlusion balloon were used extensively. Today, there are no commercially available detachable balloons and coils have become the main tool utilized in malformation occlusion. Multiple studies report > 95% success rate with embolization^{2,3,5,6}; although recanalization can occur.

PAVMs are classified as simple or complex.⁵ The simple type has a single segmental artery feeding the malformation. This feeding segmental artery may have multiple subsegmental branches that feed the malformation, but must have only one single segmental level (Fig. 3). Complex malformations have multiple segmental feeding arteries. There is a rare, diffuse form of the disease characterized by hundreds of malformations. The diffuse form is seen in an estimated 5% of PAVM patients. Patients can have simple and complex AVMs within diffuse lesions. Diffuse lesions are difficult to treat with endovascular techniques and are often referred for lung transplant. Classifying the lesions is helpful in planning the embolization procedure, in determining which lesions are embolized and what form of therapy is most appropriate. Lesion classification also helps direct postintervention evaluation. For complex lesions,

Figure 3 Digital subtraction angiography of a single segmental feeding vessel to a simple-type pulmonary arteriovenous malformation (PAVM) in the right lower lobe of a patient with hereditary hemorrhagic telangiectasia. There are multiple small subsegmental branches feeding the PAVM. Because they all arise from one segment, this is classified as a simple-type lesion.

it is critical that the postembolization angiogram be performed from a more central location to allow visualization of other feeding arteries.

The angiographer approaching PAVMs should employ meticulous technique. A tiny air embolus that might be tolerated in the systemic arterial circulation can be catastrophic in patients with PAVMs. We utilize closed flush systems for all PAVM interventions to minimize the risk of iatrogenic air or particle embolus. We utilize air filters on all peripheral intravenous (IV) lines. Further, we teach our patients to instruct other healthcare professionals to exercise care with peripheral IV access.

Prior to PAVM intervention, we assess the patient for any risks related to right heart and pulmonary artery catheterization.¹⁴ In addition to standard laboratory evaluation, we review the patient's electrocardiogram (ECG) to exclude left bundle branch block. If identified, we prepare to externally pace the patient. We use a standard right femoral approach with a MONT-1 Montefiore pulmonary artery catheter (Cook, Bloomington, IN) for diagnostic angiogram and pressure measurements. Most patients with PAVMs have pulmonary pressures that are normal or low. Rarely, pulmonary artery hypertension can be identified. If so, contrast injections are adjusted appropriately. The initial diagnostic angiogram should be performed in the anteroposterior (AP) projection and ipsilateral 40-degree oblique. This projection places the heart over the injected lung and spreads the basal segments.

After main right and left pulmonary arteriography (if indicated), selective catheterization is performed. We

exchange our diagnostic pulmonary catheter over a Bentson exchange wire (Allwin Medical, Anaheim, CA) for a White Lumax[®] catheter system (Cook, Bloomington, IN). The White Lumax[®] catheter set includes a 7F guiding sheath with a 5F angle tipped working catheter. Lower lobe vessels are usually easily accessible utilizing the White Lumax[®] 5F catheter or a curved "hockey" stick catheter such as a Berenstein catheter (Boston Scientific, Natick, MA) and either a Bentson (Allwin Medical, Anaheim, CA) or glidewire (Boston Scientific, Natick, MA). Lower lobe access can often be facilitated by "flopping" the Bentson wire down into the lower segments. Alternatively, they may be accessed with a hockey stick diagnostic catheter and glidewire. Access to the middle and upper lobes can be challenging and is facilitated by the use of a right coronary or internal mammary catheter. Once a feeding segmental artery is catheterized, we place the guiding catheter in the parent segmental vessel and advance the embolization catheter into the vessel that feeds the malformation. We attempt to selectively catheterize and embolize all feeding vessels > 3 mm in diameter. Our coil of choice is the 0.035 Nestor coil (Cook, Bloomington, IN). These coils are available in 4 mm, 6 mm, 8 mm and 10 mm diameters. Coil size is an important consideration. Undersized coil are at risk to pass through the malformation and becoming an embolic agent. We oversize the initial coil to the feeding vessel by 20%. We favor the "anchor" technique of embolization. The coil tip is purposely anchored in a small side-branch proximal to the actual malformation and the body of the coil then prolapses into the feeding vessel. By securing the tip in a side-branch, the risk of inadvertent coil dislodgment is minimized (Fig. 4). Detachable coils can be used in more challenging situations, but are rarely necessary. In certain circumstances, a microcatheter may be utilized to deliver 0.018 coils.¹⁵ After embolization a more central pulmonary angiogram should be repeated to evaluate for other feeding vessels that may have been missed on the initial planning run.

Although coils are the standard endovascular treatment, successful occlusion has been performed with the AMPLATZER[®] Vascular Plug (AGA Medical, Golden Valley, MN).¹⁶ The AMPLATZER[®] is a malleable nitinol basket that forms to the shape of the vessel. It is detached from the delivery device by a screw mechanism, which allows for precise deployment and repositioning of the plug in difficult to coil lesions (Fig. 5). The nitinol device is MRI compatible. Packing of the aneurismal sac with coils is not typically necessary. The sac will involute if the feeding vessels are appropriately occluded. Some fistulas demonstrate dilated feeding arteries that cannot be coiled safely or treated with AMPLATZER[®]. In these rare occasions, a framing coil can be placed in the aneurysm sac and then packed

Figure 4 Images of a right middle lobe pulmonary arteriovenous malformation (PAVM) demonstrating the anchor technique. (A) The feeding pulmonary artery in the lateral segment of the right middle lobe. (B) The tip of the coil mass in a side branch of the main feeding vessel with the bulk of the coil mass prolapsed into the main feeding artery and no flow identified in the PAVM.

similar to treatment of intracranial aneurysms. This is not the preferred method as the fistula can rupture or continue to enlarge if complete thrombosis of the feeding artery is not achieved.

On occasion we have encountered challenging malformations where the malformation arises as a side-branch of a larger parent vessel with a very short feeding vessel. In these instances, we have successfully excluded the malformation with a stent graft (Fig. 6). In patients with HHT and numerous lesions, care must be taken to avoid radiation overexposure and contrast nephropathy.

Figure 5 Posteroanterior chest x-ray of the child in Fig. 1 following occlusion of the feeding pulmonary artery with an AMPLATZER® device. The soft tissue mass (pulmonary arteriovenous malformation) previously seen in the left mid-chest is no longer visualized.

Multiple planned treatments can be performed to limit procedural risk.

Treatment Follow-Up

After a patient's PAVMs have been treated, we see them in clinic at 3 months, evaluate oxygenation, and evaluate the coils and feeding vessels with CT. On routine cases, we then follow the patient in clinic, evaluate oxygenation, and obtain CT 6–12 months later and every 3 years thereafter unless the patient's symptoms change. If the draining vein does not decrease in size or a persistent soft tissue mass remains associated with coils, then recanalization or incomplete embolization should be suspected and repeat angiography should be performed. Coil recanalization occurs in 12–15% of cases; AMPLATZER® recanalization rates are not completely understood, although some investigators suspect that recanalization is less common with this device. Enlargement of PAVMs occurs over time and is exacerbated by hormones and pregnancy. Pregnant and pubescent patients should be followed and imaged more frequently. As part of our clinical role in managing this disease, we assume the responsibility to counsel our patients on the need for prophylactic antibiotics for dental and medical procedures, the need for air filters on IVs, and the dangers associated with scuba diving.

Treatment Complications

Pleurisy is the most common side effect of embolization occurring in 14–31% of patients.^{2,5} When it occurs in the periprocedural period, it is usually short-lived and relieved by over-the-counter medications. White reported a group of patients that presented with late-onset (4–6 weeks postprocedure), severe pleurisy, and fever.⁵ The most feared complication of PAVM embolization is coil

Figure 6 Digital subtraction angiography of a left upper lobe pulmonary arteriovenous malformation (PAVM) prior to (A) and following (B) treatment using a stent graft to occlude the feeding vessel. (A) The feeding vessel originates as a side branch making direct coiling difficult. (B) The stent graft is in place with successful occlusion of the PAVM by covering the feeding side-branch.

migration into the systemic arterial circulation. Most reported cases of detachable balloon or coil migration are snared without consequence to the patient. For example, Gupta reported a case of embolization of a 5-mm coil into the left popliteal artery with successful snare retrieval.¹⁷ White reported a case of coil migration into the left carotid artery with successful uneventful snare retrieval.⁵ Even with careful technique, air embolus is not infrequently encountered (< 5% of cases). Small air emboli have a propensity to enter the anteriorly situated left coronary artery causing acute chest pain, bradycardia, and temporary ECG changes. This usually resolves with sublingual nitroglycerin; atropine should be immediately available to treat bradycardia if it occurs. The pulmonary artery pressures are usually normal or low in patients related to the shunting from the fistula. Rarely, pulmonary hypertension develops in patients who have undergone embolization of PAVMs. In patients with pulmonary hypertension, cardiac failure can develop.

CONCLUSION

PAVMs are rare, but potentially dangerous anomalies associated with HHT. They are poorly understood by much of the primary care medical community. The clinical interventional radiologist is well suited to assume an increasing role in the identification, evaluation, and management of patients with PAVMs and HHT. It has been our experience that patients have often wandered from physician to physician in varying degrees of frustration until they have come to our practice. Because of the disparate organ systems involved and the numerous presentations possible in patients with HHT, we believe that a multidisciplinary team should be involved in the full evaluation of these patients. Such a team includes geneticists, otolaryngologists, interventional radiologists, interventional neuroradiologists, pulmonologists,

and gastroenterologists. With proper evaluation and management, patients with HHT and PAVMs and their asymptomatic family members can be reliably and effectively identified. With meticulous angiography utilizing modern coaxial catheters, coils, and other embolic devices, almost all PAVMs can be successfully treated, thereby preventing the devastating outcomes too frequently seen in the past.

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