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Update on pulmonary arteriovenous malformations

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ABSTRACT

This review aimed to provide an overview of pulmonary arteriovenous malformations, including the major clinical and radiological presentations, investigation, and treatment algorithm of the condition. The primary etiology of pulmonary arteriovenous malformations is hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, with mutations in the *ENG* gene on chromosome 9 (HHT type 1) or in the *ACVRL1/ALK1* complex (HHT type 2). Epistaxis should always be evaluated when repeated, when associated with anemia, and in some cases of hypoxemia. In the investigation, contrast echocardiography and chest CT are essential for evaluating this condition. Embolization is the best treatment choice, especially for correction in cases of hypoxemia or to avoid systemic infections. Finally, disease management was addressed in special conditions such as pregnancy. CT follow-up should be performed every 3-5 years, depending on the size of the afferent and efferent vessels, and antibiotic prophylactic care should always be oriented. Ultimately, knowledge of the disease by health professionals is a crucial point for the early diagnosis of these patients in clinical practice, which can potentially modify the natural course of the disease.

Keywords: Telangiectasia, hereditary hemorrhagic; Arteriovenous malformations; Lung.

INTRODUCTION

Pulmonary arteriovenous malformations (PAVMs) are abnormal communications between the pulmonary artery and veins.[1] These alterations can be related to hereditary diseases, such as hereditary hemorrhagic telangiectasia (HHT, also known as Osler-Weber-Rendu syndrome),[2,3] or be classified as idiopathic if no specific etiology is discovered.[1] There are different clinical presentations, such as hypoxemia, hemorrhages, and complications from distant embolization, including stroke and brain abscesses.[4]

PAVM was first described in 1864 by the British pathologist Henry Gawen Sutton.[5] Subsequently, Benjamin Guy Babington published a series of cases of epistaxis occurring in five generations of the same family.[6] In 1896, epistaxis was distinguished from hemophilia by the French doctor Henri Jules Louis Marie Rendu,[7] who reported the presence of skin lesions in a patient's mother and brother. Five years later, William Osler established that that was a hereditary disease, describing three cases of individuals with epistaxis and skin lesions and making it clear that it was not related to hemophilia.[8] In 1907, Frederick Parkes Weber described a series of cases after noticing lesions on the fingers and under the nails that were similar to those described by Osler and invited him to see his patients.[9] In 1909, Hanes coined the term HHT; however, the eponym Rendu-Osler-Weber is still widely known and accepted.[6,10]

The prevalence of PAVMs in the general population remains unclear. In a study performed using thoracic CT for lung cancer screening, it was estimated that the detection rate of PAVMs by CT was 0.038%, with a prevalence of 38 per 100,000 population, that is, 1 case in 2,600 individuals.[11] Usually, pulmonary fistulas are characterized by their anatomy; approximately 85% are simple, directly connecting an artery to the pulmonary vein.[12] Some patients could have a complex fistula with multiple arterial feeder vessels that connect with more than one pulmonary segment. In a small proportion of cases, pulmonary fistulas may be multiple, with widespread involvement of lung segments. In more rare cases, microscopic lesions are usually suspected in patients with hypoxemia, as revealed by an echocardiogram with bubbles suggestive of an intrapulmonary shunt and by the absence of CT findings of PAVMs.[13] Treatment becomes more difficult in patients with multiple complex fistulas, especially with microscopic lesions.

PAVM rupture is a rare complication, except in pregnancy, which can be responsible for up to 1% of cases among women with PAVMs.[4] The treatment of PAVMs was proposed more than 60 years ago; even in patients without many symptoms, intervention should be considered to avoid the risks of serious and potentially fatal complications.[14] Furthermore, the evolution of treatment using percutaneous techniques has decreased the risks of postoperative complications inherent to lobectomy, the length of hospital stay has become shorter, and

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more patients can be treated, even in some situations during pregnancy.[15]

This review aimed to provide an overview of this rare but potentially fatal disease. Clinical presentation findings can help identify these patients, and available diagnostic tools can be used. This study focused on familiarizing more health professionals, especially pulmonologists, with the early identification of cases of PAVMs to reduce the risk of serious or even fatal complications in these patients.

ETIOLOGIES

HHT is an autosomal dominant disorder with a high penetrance and great variability in clinical presentation. Its pathogenesis results from an anomalous sequence in the *ENG* gene on chromosome 9, which produces an endoglin protein, or a mutation in the *ACVRL1/ALK1* gene on chromosome 12.[16] The mutation in the *ENG* gene determines HHT type 1, whereas the mutation in the *ACVRL1/ALK1* gene predisposes to HHT type 2. These mutations result in the dysregulation of the TGF-β pathway, which is responsible for angiogenesis. In the context of tissue inflammation, this dysregulation can alter the vascular endothelium and predispose patients to the formation of fistulous sacs. A third disease-causing mutation has been described in the *SMAD4* gene.[17]

These genotypic alterations imply phenotypic alterations. Patients with HHT type 1 are more likely to have pulmonary and cerebral arteriovenous malformations, whereas patients with HHT type 2 have a higher prevalence of hepatic malformations and pulmonary arterial hypertension (PAH).[18] Nevertheless, a mutation in *SMAD4*, in addition to the characteristic presentation of HHT, could simultaneously cause symptoms such as familial polyposis syndrome.[17] Molecular diagnosis can identify which allele is responsible for HHT, although this is unavailable in clinical practice. In the future, it may be an important tool for the clinical characterization, prognostic analysis, and treatment of these patients.[19]

A first-degree relative of patients with PAVMs and HHT has a 1 in 4 risk of developing PAVM. The risk increases to 1 in 2 if the relative has already been diagnosed with HHT. Currently, three main tests (for *ENG*, *ACVRL1*, and *SMAD4*) are performed for the genetic investigation of HHT. However, other genes still need to be identified. Among these three genes, *ENG* and *SMAD4* are the most prevalent in patients with PAVMs, and a smaller proportion of cases have an impairment in the *ACVRL1/ALK1* gene complex.[20]

In contrast, patients without HHT usually present with a single PAVM of varying etiology, particularly thoracic surgery, trauma, actinomycosis, schistosomiasis, and liver cirrhosis with hepatopulmonary syndrome or hepatocellular carcinoma.[13,20] Another relevant etiology of non-HHT PAVM is the correction of cyanotic congenital heart disease with cavopulmonary anastomosis.[21] The major explanation for this occurrence is the absence of hepatic flow in the pulmonary territory, which induces a reduction in hepatic factors that are responsible for inhibiting the development of pulmonary fistulas.[21]

DIAGNOSIS

Clinical manifestations

Patients with HHT have epistaxis as their main clinical manifestation, usually starting at around 10 years of age and becoming more severe with aging, occurring spontaneously or recurrently.[22] Skin telangiectasias are common and usually multiple, commonly involving the lips, tongue, palate, fingers, face, and conjunctiva.[22] Neurological symptoms such as migraine with aura, brain abscess, seizure, stroke, or transient ischemic attack have been described in these patients and may occur due to the presence of cerebrovascular abnormalities; however, most of these findings are consequences of PAVMs that allow the passage of emboli unfiltered by the pulmonary capillary network to the cerebral circulation.[2]

The clinical manifestations in the gastrointestinal (GI) tract are usually upper or lower digestive tract bleeding, which occurs owing to the presence of arteriovenous malformations, telangiectasias, or angiodysplasias that may occur in the stomach, duodenum, small intestine, or colon. Anemia from chronic blood loss has been described, although uncommon, and may require iron supplementation or multiple blood transfusions.[23] These patients may present with abdominal pain due to mesenteric ischemia caused by stealing blood flow from the hepatic artery to the hepatic or portal veins.[24] GI arteriovenous fistulas promote communication between the hepatic artery and the portal vein, increasing the blood flow and causing portal hypertension and hepatic encephalopathy. Liver involvement occurs in 40-75% of patients, but most of these liver malformations are minor with no clinical repercussions.[2] Among hepatic impairments, the most common are hepatic arteriovenous malformations, which manifest as high-output heart failure through the left-to-right shunt.[22]

In the initial investigation of brain arteriovenous malformation, MRI should be performed. Liver malformations could be investigated at diagnosis using Doppler ultrasound, multiphase contrast CT, or contrast abdominal MRI.[25]

Cyanosis and digital clubbing may be present in hypoxemic patients with PAVMs; cyanosis is often masked by anemia, and the severity of digital clubbing does not appear to be predictable unless the right-to-left shunt is severe.[2] Patients with PAVMs occasionally present with orthodeoxia due to the basal predominance of arteriovenous malformations, but it is usually asymptomatic. Platypnea (dyspnea when one is upright) is uncommon.[26]

PAVM is the major pulmonary manifestation of HHT[13] and is present in 50% of these patients.[27] PAVMs are characterized by an artery connected directly to a vein

by aberrant communication, with saccular or fistulous connections. In most cases, the afferent artery is a branch of the pulmonary artery, and the efferent vein is a branch of the pulmonary vein, with rare cases involving branches of the systemic circulation responsible for the nutrition or drainage of the arteriovenous fistula.[13] These alterations are usually congenital and do not change in size in adulthood, except in the presence of pulmonary hemodynamic changes, such as puberty or pregnancy.[13] There is a predominance in women, and the most prevalent location of PAVMs is the lower lobes in patients with and without HHT.[28]

Most PAVMs are asymptomatic, but their presence can result in serious complications, especially if the artery diameter is > 3 mm.[12,29] The right-to-left shunt allows the occurrence of paradoxical embolic events that can lead to stroke, acute myocardial infarction, and brain or peripheral abscesses.[12,30] These events occur due to the loss of the filtering function of the capillary network and depend on the area and number of pulmonary fistulas.[12]

Other respiratory manifestations in individuals with HHT include hemoptysis or hemothorax, pulmonary thromboembolism, and pulmonary hypertension (PH). Hemoptysis and hemothorax can occur in cases of wall necrosis and fistula rupture.[2] In the presence of hemoptysis without PAVMs, bronchial telangiectasias should be suspected.[12] Despite the high risk of bleeding, these patients have an increased prevalence of pulmonary thromboembolism, especially in the presence of low iron levels and high factor VIII levels.[24]

Diagnostic criteria for HHT

Rendu-Osler-Weber syndrome, or HHT, can be diagnosed using a probability score defined and presented in 2000 by the Scientific Advisory Board of the HHT Foundation International, designated the Curaçao criteria.[31] These criteria facilitate the recognition of clinical findings that are less common than epistaxis, which is the main manifestation of the disease in affected individuals,[23] and allow early recognition in individuals with less classic but potentially serious manifestations, such as PAVMs.

Based on those criteria,[31] the diagnosis can be definitive (when three criteria are present); possible, (if two criteria are present); or suspected (if less than two criteria are present). The criteria are as follows: 1) presence of epistaxis (spontaneous and on more than one occasion); 2) presence of visceral lesions (GI telangiectasia, or pulmonary, hepatic, cerebral, or spinal vascular malformation); 3) presence of mucocutaneous telangiectasia in a typical location; and 4) first-degree family history (or presence of the genetic mutation). In families with individuals with HHT, the diagnosis can be made from the findings of two sites with visceral lesions.[31] These criteria have a positive predictive value of 100% and a negative predictive value of 97% in comparison with genetic testing.[32]

Despite the genetic knowledge of the molecular pathways damaged to generate the disease, there is great heterogeneity in the locus of these genes, which makes it difficult for the diagnosis to be established by molecular criteria in the general population, although they may be useful in individuals with possible/suspicious diagnosis.[31]

COMPLEMENTARY EXAMINATIONS

Transthoracic contrast echocardiography

Transthoracic contrast echocardiography (TTCE) is an important diagnostic modality. It is considered positive if bubbles are detected in the left atrium after the infusion of saline solution with microbubbles in the peripheral vein.[33] The passage of bubbles after the third beat suggests PAVMs, differently from intracardiac shunts. In this case, the test is considered positive when the passage occurs up to the third beat. Also, healthy people may have some degree of shunting.[25]

TTCE can predict the size of and need for therapeutic intervention for PAVMs.[12] In addition, the risk of cerebrovascular events can be evaluated based on the estimated pulmonary shunt calculation, in which the finding of 30 microbubbles on the TTCE is not related to the increased prevalence of central nervous system events, whereas that of more than 100 microbubbles is a strong independent predictor of brain abscess and cerebrovascular events.[12,13,34] Finally, TTCE performed using infused saline with microbubbles is capable of diagnosing microscopic lesions when there is a positive finding of shunt on the test but an absence of arteriovenous fistulas on CT of the chest and abdomen.[12]

Chest radiography

Chest radiography is simple and easy and results in low radiation exposure. However, there is low sensitivity for identifying small PAVMs.[35] The most common finding on chest radiography is a pulmonary nodule.[36] Nevertheless, when the fistulous sac is large, it can be confused with a pulmonary mass (Figure 1). Chest radiography may be useful for follow-up.

Chest CT

The presence of chest CT radiological findings consistent with PAVMs is the gold standard for the diagnosis of these malformations.[20] The most common radiological presentation is the presence of well-defined peripheral nodules. The use of intravenous contrast is not mandatory, but it can allow better definition of PAVM angioarchitecture to plan endovascular therapy.[12] Differential diagnoses of PAVMs (Chart 1) based on radiological findings are true pulmonary artery aneurysms or true aneurysms secondary to syphilis, connective tissue diseases, Behçet's disease, Takayasu's arteritis, chronic thromboembolic pulmonary hypertension, idiopathic PH, or hepatopulmonary syndrome; false aneurysms secondary to tuberculosis,

or septic embolism; and even nonvascular changes such as bronchocele or tumors.[36]

Morphological classification is based on radiological findings from chest CT or angiography and is relevant in planning endovascular interventions.[12,20] Simple PAVMs are those in which only one supplying artery is connected to one or more of the draining veins. Complex PAVMs are lesions in which two or more supplying arteries are connected to multiple drainage veins by a septate aneurysmal sac. The latter are rarer, corresponding to 20% of the cases. Complex PAVMs radiologically present as ground-glass areas connected by nourishing and draining vessels.[13] Diffuse fistulas are characterized by the involvement of an entire lung segment and may even affect the entire lung.[37]

Other examinations

Chest magnetic resonance angiography is an accurate method for detecting PAVMs and analyzing fistula patency, which are important in embolization therapy planning.[38]

Despite not being routinely used for the diagnosis of pulmonary arteriovenous fistulas (sensitivity = 60%), catheter angiography can be used for therapeutic programming because of its accurate assessment of the distribution of nourishing and drainage vessels of the PAVM.[13] Angiography is also relevant for guiding embolization.

Screening for PAVMs should be performed for all individuals older than 16 years of age with a suspected or established diagnosis of HHT. Chest radiography cannot exclude the presence of PAVM, even in asymptomatic patients with normal oxygen saturation, since it has a low sensitivity for detecting small PAVMs.[20] However, chest radiography can sometimes reveal alterations.

The use of TTCE for screening is not a consensus in the literature.[13,20] It is a safe and noninvasive test with a low rate of false negatives and high sensitivity[13]; however, it is operator-dependent and not available in all centers.[20] In specialized services, it is recommended that TTCE be a part of the screening algorithm (Figure 2). Chest CT can exclude pulmonary fistulas in the absence of compatible radiological findings. Repeat chest CT is

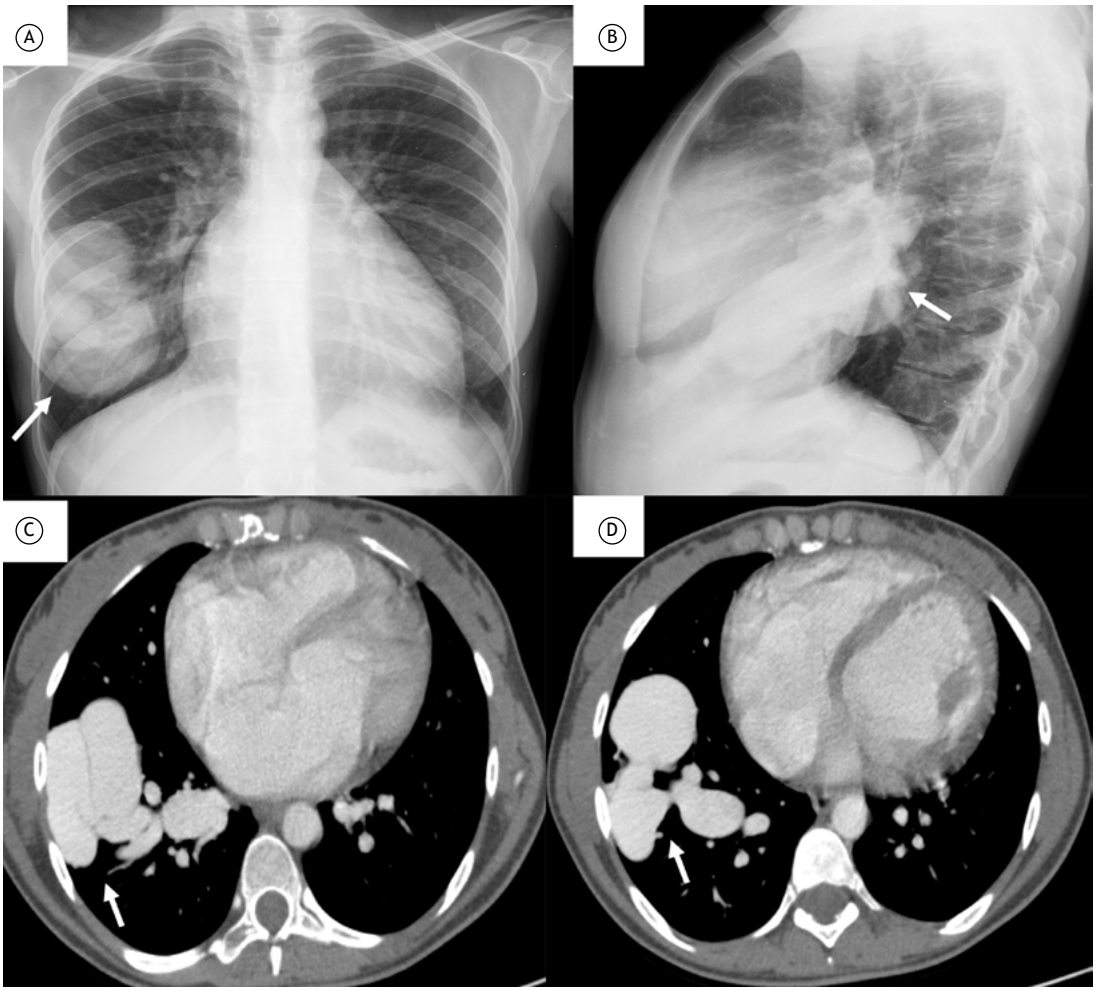


Figure 1. In A and B, chest radiographs showing a large pulmonary arteriovenous malformation/fistulous sac (white arrows). In C and D, CT scans demonstrating a large arteriovenous malformation (white arrow).

Chart 1. Differential diagnoses.

Vascular		
Pulmonary aneurysmal disease	True aneurysms	Idiopathic Secondary to syphilis; connective tissue diseases; Behçet's disease; Takayasu's arteritis; CTEPH; IPH; hepatopulmonary syndrome
	False aneurysms	Secondary to tuberculosis; pneumonia; septic emboli; connective tissue diseases
Pulmonary varices	Congenital	
	Acquired	Associated with mitral valve disease Secondary to chronic tuberculosis or sarcoidosis
Pulmonary artery collaterals	Associated with IPH and CTEPH	
Nonvascular		
Bronchocele	Congenital Acquired	Congenital bronchial atresia Foreign body; endobronchial tumor; bronchiectasis of any cause
Tumors	Primary carcinoid Metastases	

Adapted from Boussel et al.[38] CTEPH: chronic thromboembolic pulmonary hypertension; and IPH: idiopathic pulmonary hypertension.

not routinely indicated due to high radiation exposure, and screening with TTCE is recommended every 5-10 years, or after pregnancy, which can increase the risk of PAVM rupture.[12] An investigation algorithm option may be through SpO_2 in a patient with suspected or confirmed HHT. When SpO_2 > 95%, we should start with TTCE; if positive, perform chest CT. When SpO_2 ≤ 95%, the initial option is chest CT, which may or may not confirm the presence of PAVMs (Figure 2).

TREATMENT MANAGEMENT

Epistaxis and GI bleeding

Epistaxis is the main symptom presented by patients with HHT, and it is also very impacting on daily activities of patients with the disease. This results in social isolation and difficulties in work and travel.[39] Initial treatment recommends the use of medications that promote humidification of the nasal mucosa.[33] Another alternative is surgical treatment.[33] However, the Second International Guidelines for the Diagnosis and Management of HHT[25] propose the use of systemic medications to reduce bleeding. In 2014, two randomized clinical trials[40,41] demonstrated the benefits of tranexamic acid, which is an oral antifibrinolytic agent that has been shown to reduce nosebleeds, although it does not increase hemoglobin levels. Thus, tranexamic acid has become the first choice when the use of other medications is unable to control the bleeding.[42]

Recently, animal models have shown that VEGF leads to telangiectasias and arteriovenous malformations, and the normalization of its levels inhibits the formation of abnormal vascular structures.[43] These findings have stimulated the development of systemic antiangiogenic agents that directly or indirectly inhibit VEGF to treat epistaxis and GI bleeding in HHT. Two drugs with potential use in patients are bevacizumab (Avastin; Genentech, San Francisco, CA, USA) and thalidomide (Thalomid; Celgene, Summit, NJ, USA).[44] The latter has immunomodulatory effects and potentially inhibits VEGF; some adverse effects, such as neuropathy, have limited its long-term use.[45] Bevacizumab exhibits antiangiogenic action, showing the greatest potential for the treatment of HHT. With promising results and low adverse event rates, bevacizumab has the potential to treat both epistaxis and GI bleeding. Argon plasma coagulation could also be a therapeutic option in emergencies for this type of bleeding.[42]

Iron deficiency and anemia

Iron replacement therapy is recommended when there is deficiency, as well as in situations where there is impairment in iron absorption, such as in inflammatory bowel disease. Iron levels should be monitored after the initiation of oral therapy. After normalization, this therapy must be discontinued.[20]

PAVM embolization

Embolization is the standard of care for PAVMs,[12,46] with substantial improvement in oxygenation and reduction in the risk of embolic events.[3,47] When all arteries are obliterated, the sac regresses within 6 months after the procedure. However, if not all supplying arteries are embolized, the fistulous sac may not regress, indicating the possibility of recanalization.[48,49]

Persistence of blood flow after embolization is present in up to 25% of cases, and this can occur by recanalization or reperfusion.[12] In the former, flow occurs through an already embolized fistula. Although controversial, it is believed that the risk of complications is lower in this situation, which is present in 88-91% of cases.[50,51] In the latter, there is rupture of an accessory artery. In both situations, the preferred treatment is new embolization. The results were better for recanalization than for reperfusion.[50]

Ideally, embolization should be performed before any complications due to the presence of fistulas.[37]

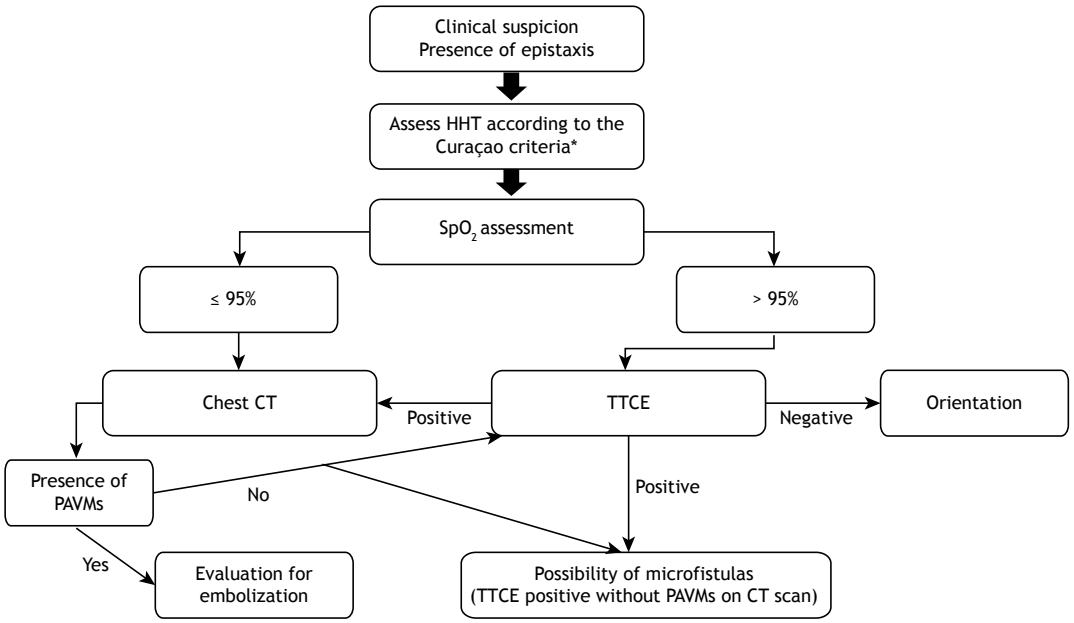


Figure 2. Investigation algorithm. HHT: hereditary hemorrhagic telangiectasia; PAVMs: pulmonary arteriovenous malformations; and TTCE: transthoracic contrast echocardiography. Adapted from Saboo et al.[13] *Shovlin et al.[31]

Several devices are available, such as fibered steel coils (Figure 3), fibered platinum coils (Nester embolization coils), fibered microcoils, hydrophilic coils, and self-expandable nitinol plugs (Amplatzer vascular plugs). The anchoring technique is used for coils and consists of locking the spring within a small collateral branch of the main supply artery immediately upstream of the arteriovenous malformation, allowing for optimal occlusion of the cross-section and preventing further accidental mobilization of the device and distal migration into the left circulation.[35] However, coils cannot be relocated in the event of unsatisfactory deployment on a vessel. In contrast, Amplatzer plugs are anchored in the candidate vessel without the need to occlude adjacent normal vessels (Figure 4).[52] Sometimes, both coils and Amplatzer plugs can be used (Figure 5). One study comparing the use of coils vs. Amplatzer plugs showed that the coils had a higher rate of recanalization.[52]

Surgery

The performance of lobectomy or segmentectomy is restricted to cases with complex or multiple PAVMs when catheter embolization is not possible.[26] Lung transplantation is also performed in selected cases, because the survival of these patients, despite the hypoxemia and infectious risks related to the disease, is greater in many cases than in transplanted individuals.[53]

Anticoagulation and antiplatelet therapy

Although HHT is a bleeding disorder, there is no protection against thromboembolic events.[42] In fact, these patients may have an increased risk of embolic events due to iron deficiency and consequently increased levels of factor VIII.[54,55] According to current guidelines, the use of (prophylactic or therapeutic) anticoagulant medications or antiplatelet agents is rare and recommended when arterial or venous embolic events occur. However, the risk of bleeding should be considered. These medications are tolerated by most patients, and there should not be an absolute contraindication to their use. Furthermore, patients should be closely monitored.[56] One exception is the concomitant use of two antiplatelet medications or the combination of antiplatelets and anticoagulants, which should be avoided.[42]

Antibiotic prophylaxis

Although controversial, some procedures that involve transient bacteremia and the use of prophylactic antibiotics are recommended in the general population. However, prophylactic antibiotic therapy is mandatory in patients with PAVMs.[20,26] Based on recommendations, prophylactic medication should be administered 1-2 h before a dental or surgical procedure, and another dose should be taken after the procedure. Amoxicillin/clavulanic acid is the preferred agent,[57] and metronidazole or clindamycin may be used in patients who cannot receive β-lactams.[58] In other procedures such as endoscopy, prophylactic antibiotics are recommended to avoid brain abscesses.[20] Prophylaxis is recommended if TTCE is positive, even in the absence of CT findings suggestive of PAVM.[59]

General measures

Long-term oxygen therapy is used to improve hypoxemia, especially when the alveolar-capillary membrane is compromised. However, in PAVMs, there is a direct shunt in which the use of oxygen is controversial, and the indication is more based

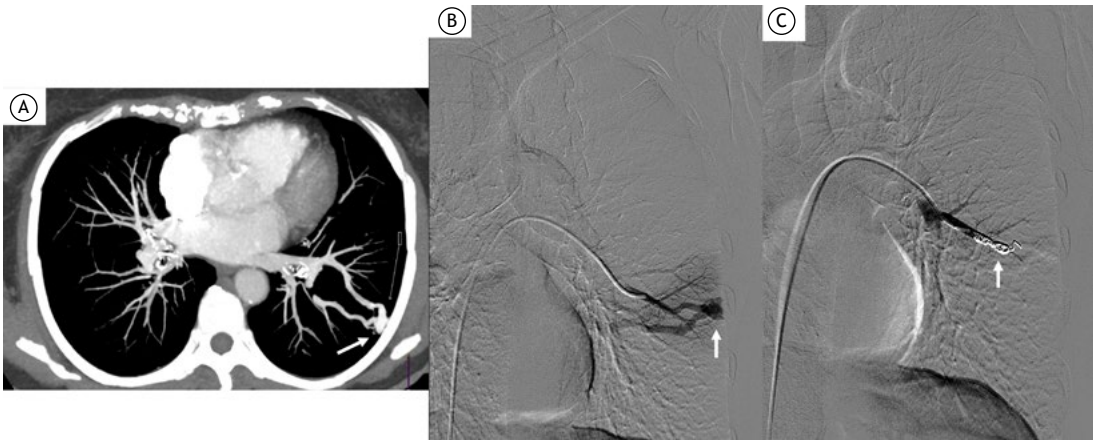


Figure 3. In A, a CT scan demonstrating peripheral pulmonary arteriovenous malformations (white arrow). In B, localization of the malformation by pulmonary angiography (white arrow). In C, embolization with coils (white arrow).

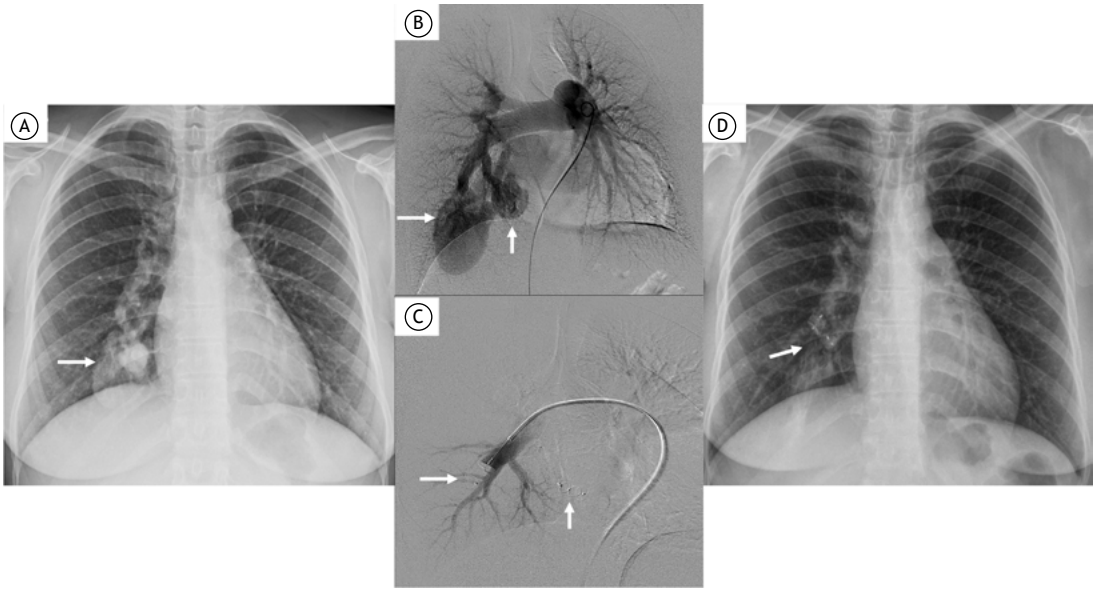


Figure 4. In A, a chest radiograph showing pulmonary arteriovenous malformations (white arrow) before embolization. In B, localization of the malformations by pulmonary angiography (white arrows). In C, embolization with Amplatzer vascular plugs (white arrows). In D, a chest radiograph after embolization (white arrow).

on symptoms than on SpO_2. In travels, there is no evidence that using supplemental oxygen modifies the risk of complications. Long-term oxygen therapy may be indicated in patients with comorbidities such as heart disease or neurological disorders. There is no formal indication for phlebotomy.[20]

FOLLOW-UP

Follow-up of patients with HHT should be performed every 5 years in those whose initial evaluation is negative for the presence of a shunt.[12]

The guidelines recommend follow-up every 3-5 years in patients with small fistulas (diameter < 3 mm). However, two recent studies have demonstrated that the growth of these fistulas is slow and infrequent,[60,61] and they recommend follow-up CT every 5 years (Figure 6).

In cases treated with embolization, the initial recommendation is to repeat CT 6-12 months after treatment. Thereafter, CT can be repeated every 3-5 years.[33] In patients with complex PAVM, follow-up can be performed earlier; in those with simple fistulas with no sign of shunt, control can be repeated after a longer time.[12] Treatment is considered successful when there is 70% regression of the drainage vein or of the fistulous sac within 3-6 months.[12,50,51] It is worth mentioning that TTCE remains positive in 80-90% of successfully treated patients.[35,62]

When cerebral malformations are diagnosed, treatment with embolization should be considered. In cases of GI bleeding, both endoscopy and colonoscopy can be used if there is major bleeding. Liver transplantation is a perspective in specific situations, such as refractory high-output cardiac failure, biliary ischemia, or complicated portal hypertension.[25]

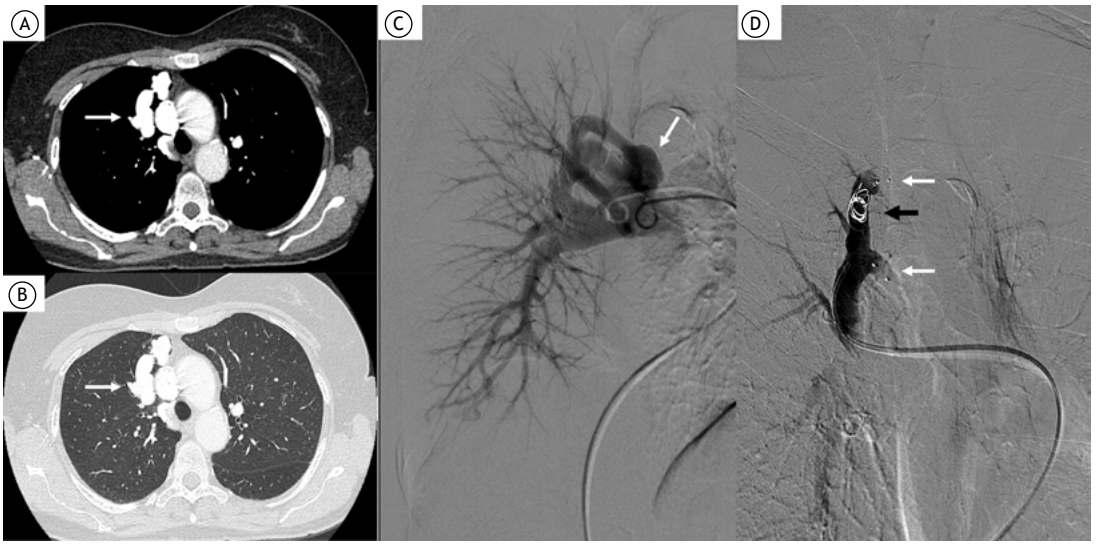


Figure 5. Combined coils and Amplatzer embolization In A and B, respectively, CT scans of the chest with mediastinal and lung window settings showing the pulmonary malformation (white arrows). In C, localization of the malformation by pulmonary angiography (white arrow). In D, embolization with coils (black arrow) and Amplatzer vascular plug (white arrow).

Recently, initial studies have recommended the use of MRI for the follow-up of patients who underwent embolization.[63,64] This choice involves excessive exposure to radiation and the use of contrast CT.[65] Nonetheless, MRI equipment and trained personnel should be available for its routine use.

FUTURE PERSPECTIVES

In addition to the abovementioned VEGF inhibitors, other antiangiogenic medications are being studied. Antiangiogenic therapies using tyrosine kinase inhibitors can also act by inhibiting VEGF, and consequently, decrease the formation of telangiectasias and arteriovenous malformations.[66] Among these medications, two were tested in murine models, sorafenib and a pazopanib analog, both of which improved hemoglobin levels and reduced GI bleeding but did not prevent skin telangiectasia.[67]

Nintedanib, a tyrosine kinase inhibitor that targets PDGF, FGF, and VEGF receptors, was used in a patient with HHT and idiopathic pulmonary fibrosis, with a reduction in nasal bleeding, showing potential for use in patients with HHT.[68]

Another potential therapy is anti-ANGPT2 antibodies and PI3-kinase inhibitors, which would act on genes encoding components of the BMP9/BMP10 signaling pathway. Tacrolimus and sirolimus have the potential for future use in patients with HHT.[66]

SPECIAL SITUATIONS

Diffuse PAVMs and microscopic arteriovenous connections

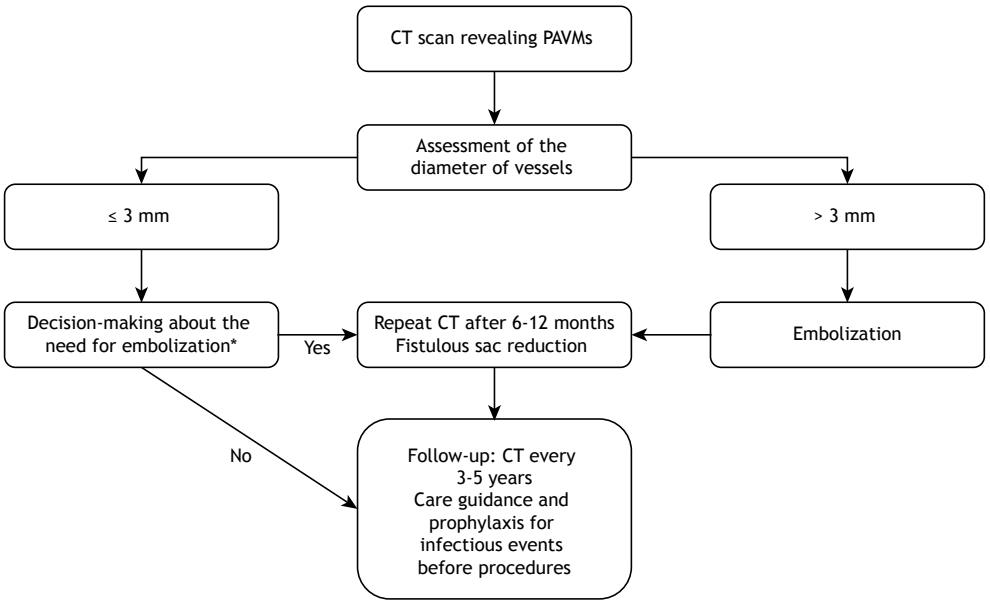
Diffuse pulmonary fistulas affect several segments or subsegments.[13] These are considered complex subtypes of PAVMs.[12] These patients are at an increased risk of hypoxemia and central nervous system complications.[13] One of the most important difficulties in these cases is embolization. Some authors have performed this procedure in patients with diffuse fistulas, treating those with the largest caliber (> 3 mm), while leaving the others untreated. A decrease in neurological complications was observed, but there was no improvement in hypoxemia.[37,69]

Microscopic arteriovenous connections are difficult to manage. This situation can occur when there are hypoxemia and right-to-left shunt on TTCE, but normal results on CT scans.[13] In the evolution phase of this type of alteration, CT scans can reveal images such as nodular ground-glass opacities after the connection between the precapillary pulmonary artery and the postcapillary venules and definitive formation of a PAVM, which is composed of an aneurysmal connection between the dilated drainage vein and the supplying pulmonary artery with concomitant disappearance of the ground-glass lesion.[13]

Diffuse PAVMs remain a diagnostic and treatment challenge. The evaluation of lung transplantation remains controversial for these patients, because survival tends to be long and long-term outcomes are still uncertain.[69] In these cases, an individual decision should be made, and an experienced transplant team should define the treatment of choice.[53]

PREGNANCY

HHT is a rare disease, and there are few data in the literature regarding pregnancy-related care. Dupuis et al.[70] estimated that the spontaneous abortion rate was between 14.4-20.0% and the prematurity rate was up to 13.8%; the data do not differ from those found in



*Discussion with the interventional radiology team

Figure 6. Follow-up recommendations. PAVMs: pulmonary arteriovenous malformations. Adapted from Lee et al.[62] and Kawai et al.[63]

the general population. However, in the same study, the maternal mortality rate was 1.2% in those with HHT, and the rate of serious complications was between 2.7-6.8%, both of which are higher than are those in the control population.[70] Therefore, all pregnancies in HHT patients are at high risk due to the prevalence of severe complications.[15] These complications can occur near the 26th week of pregnancy and have PAVMs as the main etiology.[70]

During pregnancy, there is a reduction in systemic vascular resistance and an increase in cardiac output by 40%, especially due to the effects of estrogen and relaxin during the second and third trimesters of gestation.[71] These vascular changes (Figure 7) can be particularly important in patients with HHT, because they can increase the shunt in anomalous vessels.[70] Most gestational complications occur during this period with more significant hemodynamic changes, corroborating the hypothesis that these complications are related to physiological alterations. However, they are not associated with specific vascular effects in HHT patients.[15]

The most common complications are hemothorax, hemoptysis, hypoxemia, cerebral abscess, or cerebral ischemia. There may be an increase in the frequency of epistaxis and emergence of new telangiectasias. Although rare, hepatobiliary necrosis and cholangitis have been reported in these patients. Complications during childbirth, such as uterine bleeding, occur in 5% of deliveries.[72]

Regarding the management of these patients, a cohort study with prospective and retrospective components and analysis of family data carried out between 1999 and 2005 with data from 262 pregnancies in 111 women with HHT and PAVMs conducted by Shovlin et al.,[15] revealed that these events are more common in women who were unaware of their diagnosis of HHT before pregnancy, raising the hypothesis that counseling about gestational risks is important to reduce complications. The health care service responsible for the care of these patients must also be prepared to recognize warning signs and refer complex cases to more experienced centers.[15]

Screening and treatment of PAVMs should be performed before pregnancy. Women diagnosed with HHT or hypoxemia without a defined etiology should be investigated for pulmonary artery malformation. If the patient has never been screened before, prompt investigation reduces the complications during pregnancy.[12]

The literature regarding the treatment of arteriovenous fistulas during pregnancy is controversial, especially if the patient is asymptomatic, due to the high ionizing load of the imaging techniques and the risks of the endovascular embolization procedure.[12,73] Nevertheless, according to the Second International Guidelines for the Diagnosis and Management of HHT,[25] due to the high risk of complications during pregnancy, the recommendation is to perform embolization in the second trimester of pregnancy (Figure 7).

In relation to cerebrovascular malformations, screening with cranial MRI is unnecessary, except in patients with a positive family history or in the presence of specific symptoms. In relation to spinal vascular malformations, screening is controversial in the literature due to its low incidence,[72] and some authors suggest screening if regional anesthesia has been programmed.[15]

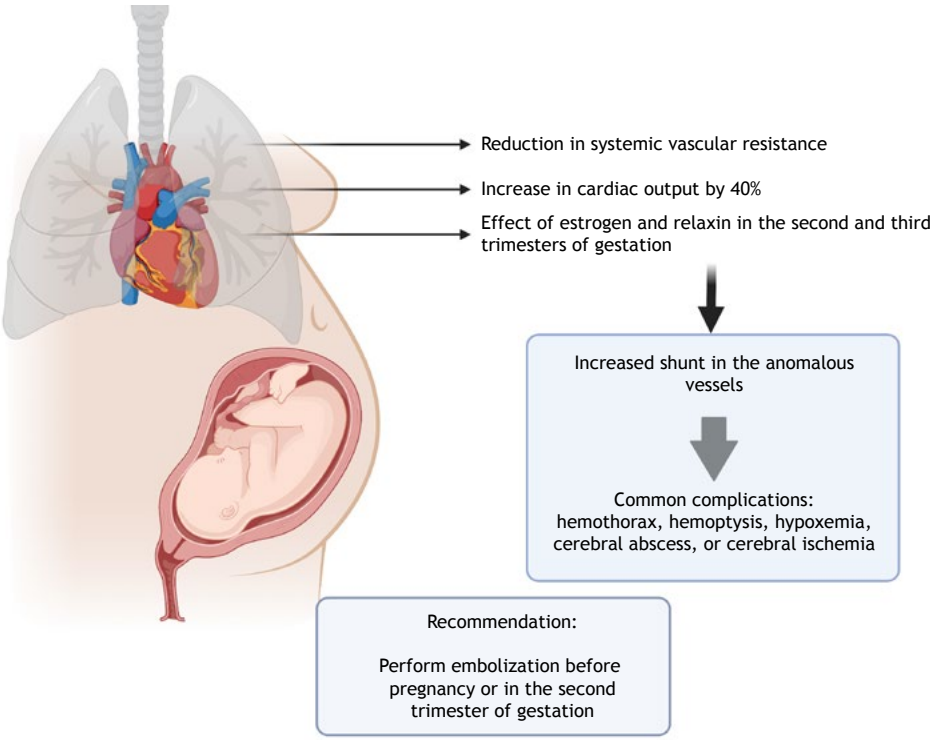


Figure 7. Pathophysiological mechanism in pregnancy and treatment recommendation. Created with BioRender.com (2022). Adapted from Geisthoff et al.,[41] de Gussem et al.,[72] and Bari et al.[73]

General care during childbirth also includes the administration of antibiotics due to the risk of septic embolism in cases of transient bacteremia, as well as avoidance of prolonged childbirth in cases where the presence of cerebral arteriovenous malformations has not been excluded.[15]

PH

PH can occur in these patients, with an estimated prevalence of 13%.[74] Most cases of PH are due to hepatic arteriovenous malformations in addition to anemia, generating postcapillary PH due to increased blood flow in the pulmonary artery territory in association with left ventricular failure because of high output.[2] Precapillary PH has a low prevalence. This is more common in the presence of endoglin or ALK1 receptor mutations and is characterized by the remodeling of the pulmonary arteries, similarly to what occurs in idiopathic PAH, resulting in elevated pulmonary vascular resistance.[18]

The coexistence of PH and PAVM may initially be protective due to the reduction in pressure in the pulmonary artery; however, as the disease progresses, the increase in pressure in the pulmonary artery can lead to the rupture of the fistulous tract.[13]

Differentiation between the presentations of PH depends on the right heart catheterization findings.[18] If PH is associated with hepatic arteriovenous malformations, high cardiac output, high pulmonary artery occlusion pressure, and normal pulmonary vascular resistance can distinguish high output heart failure in patients with PAH.[2] The initial treatment is diuretics, and the correction of anemia helps reduce the overload of the right ventricle.[2]

There have been no studies on drug treatment of patients with PAH-HHT. Initially, the management of these patients should be the same as that of those with PAH without HHT. However, there are only case reports available in the literature, one of which demonstrated the benefit of using bosentan (an endothelin receptor antagonist), with improvement in hemodynamic parameters, exercise capacity, and brain natriuretic peptide levels.[75] In another study, sildenafil was initiated.[76] The most crucial step in deciding on the initial treatment with specific medications is distinguishing between PH associated with hepatic vascular malformations and PAH.[2]

Secondary to chemotherapy (trastuzumab)

Trastuzumab is a new chemotherapeutic agent used to treat HER2-positive breast cancer that does not respond to previous lines of treatment.[77] A case report described the appearance of skin telangiectasia and PH after the use of this medication. The emtansine component of trastuzumab may explain the occurrence of mucocutaneous telangiectasia and vasculopathy of distal small vessels, eventually leading to PAH. These findings resolved after drug discontinuation.[78]

FINAL CONSIDERATIONS

Early identification of PAVM cases is of paramount importance for the prognosis of patients with this

alteration. Although rare, the consequences of these malformations can be catastrophic and lead to fatal situations. Performing embolization has the potential to protect patients from complications. Embolization has the advantage of preserving lung parenchyma when compared with surgical resection.[79]

The association between PAVMs and HHT is common; in this case, the finding of recurrent epistaxis can be an important warning sign in the history of these patients and deserves care in clinical evaluation.[80]

Identifying and treating patients with PAVM remains a challenge, but there have been advances in imaging tests and embolization techniques. In the future, we will be able to see fewer patients being diagnosed only when they present with a major complication, such as hemothorax, bleeding from the central nervous system, or infectious complications such as abscesses.

When there is a clinical suspicion of PAVMs or HHT, referral to a center specializing in treating this type of pathology can be helpful for better management of these patients.

AUTHOR CONTRIBUTIONS

WSF and MTF: study design and conception. WSF and FRO: drafting and revision of the manuscript. MTF: revision of the manuscript. WSF, FRO, and MTF: revision and approval of the final version.

CONFLICTS OF INTEREST

None declared.

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