Case Report

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Hereditary Hemorrhagic Telangiectasia: A Rare Cause of Exertional Dyspnea

L Lopes[1], PG Ferreira[1]

[1]Pulmonology department, ULS de Coimbra, Portugal

*Corresponding Author:
Laura Lopes
Praceta Professor Mota Pinto, Celas, 3004-561 Coimbra

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1. Abstract

Hereditary hemorrhagic telangiectasia (HHT) is an uncommon autosomal dominant vascular disorder, most frequently associated with pathogenic variants in ENG or ACVRL1, resulting in multisystem arteriovenous malformations (AVMs). We report a middle-aged woman with primary antiphospholipid syndrome on chronic enoxaparin therapy who presented with exertional dyspnea. Computed tomography demonstrated bilateral pulmonary AVMs and clinical evaluation revealed mucocutaneous telangiectasias. Genetic testing identified an ENG mutation, confirming HHT type 1 according to three Curaçao criteria. Selective microcoil embolization of pulmonary AVMs with feeding arteries >3 mm led to marked improvement in functional capacity. HHT1 is predominantly associated with pulmonary and cerebral AVMs, whereas HHT2 and JP-HHT involve hepatic and gastrointestinal manifestations. Diagnostic assessment relies on echocardiographic contrast studies and computed tomographic angiography. Embolization represents the standard of care for significant pulmonary AVMs, with periodic radiologic surveillance recommended. This case underscores the importance of early recognition and multidisciplinary management to mitigate HHT-associated complications.

2. Keywords: Hereditary hemorrhagic telangiectasia; Osler–Weber–Rendu syndrome; AVMs; Genetic testing; embolization

3. Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler–Weber–Rendu syndrome, is a rare autosomal dominant vascular disorder characterized by mucocutaneous telangiectasias and visceral arteriovenous malformations (AVMs) [1–3]. The estimated prevalence ranges from 1 in 5,000 to 1 in 8,000 individuals, although underdiagnosis remains common [3]. Clinical manifestations include recurrent epistaxis, gastrointestinal bleeding, iron deficiency anemia, and progressive involvement of visceral organs, most commonly the lungs, brain, liver, and gastrointestinal tract [1,3]. Pulmonary arteriovenous malformations (PAVMs) represent one of the most clinically significant manifestations of HHT and occur in up to 50–60% of patients, particularly in those harboring pathogenic variants in the ENG gene (HHT type 1) [4–6]. PAVMs result in right-to-left shunting and may lead to exertional dyspnea, hypoxemia, paradoxical embolization, ischemic stroke, and brain abscesses, even in patients with preserved resting oxygen saturation [6–8]. The diagnosis of HHT is primarily clinical and based on the Curaçao criteria, which include recurrent spontaneous epistaxis, characteristic mucocutaneous telangiectasias, visceral AVMs, and a first-degree relative with HHT [9]. Genetic testing allows confirmation of the diagnosis, facilitates family screening, and most commonly identifies pathogenic variants in the ENG and ACVRL1 genes [2,4]. Current international guidelines emphasize the importance of systematic screening for visceral AVMs and multidisciplinary management to prevent potentially life-threatening complications [9].

4. Clinical Case

A middle-aged woman with primary antiphospholipid syndrome (APS) and high thrombotic risk, receiving chronic therapeutic anticoagulation with enoxaparin (1.5 mg/kg/day), presented with new-onset exertional dyspnea (mMRC grade 2) and early lower-limb fatigue. Chest computed tomography (CT) revealed bilateral serpiginous opacities consistent with pulmonary arteriovenous malformations, including one lesion in the right upper lobe and two in the left lower lobe, measuring 18 mm and 10 mm, respectively. The patient reported recurrent epistaxis, occurring approximately twice monthly, and episodic lower gastrointestinal bleeding (hematochezia) twice per year. Physical examination showed oxygen saturation of 98% on room air, eupnea, and normal lung auscultation. Oral examination revealed four punctiform erythematous lesions on the tongue and palate, while anterior rhinoscopy demonstrated vascular ectasia in the Kiesselbach area, managed conservatively with topical hemostatic measures. Laboratory evaluation revealed mild microcytosis and hypochromia despite normal hemoglobin levels. Pulmonary function testing showed normal lung volumes, with a diffusion capacity (DLCO) of 79% and transfer coefficient (KCO) of 72% of predicted values. Upper gastrointestinal endoscopy identified a duodenal angiodysplastic lesion. Transesophageal echocardiography revealed a redundant interatrial septum without tunnel-like morphology or Doppler evidence of intracardiac shunting. Agitated saline contrast echocardiography performed at rest and after Valsalva maneuver showed late appearance of a large number of microbubbles in the left cardiac chambers (grade 3), predominantly originating from the left pulmonary veins, consistent with significant intrapulmonary shunting. Mild tricuspid regurgitation allowed estimation of pulmonary artery systolic pressure at 26 mmHg. The patient fulfilled three Curaçao criteria—recurrent epistaxis, oral telangiectasias, and

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pulmonary AVMs. Genetic testing identified a pathogenic ENG mutation, confirming the diagnosis of HHT type 1. She subsequently underwent selective endovascular embolization of the dominant left lower lobe PAVM using microcoils, as the feeding artery exceeded 3 mm in diameter. The procedure was uncomplicated and resulted in improvement of exertional dyspnea. Family screening revealed a history of recurrent epistaxis in her father, who had not previously undergone evaluation for HHT. Two months after embolization, the patient demonstrated clinical improvement, with a reduction in dyspnea severity (mMRC grade 2 to 1) and normalization of gas transfer parameters (DLCO from 79% to 102% and KCO from 72% to 78%). At six-month follow-up, contrast echocardiography revealed a patent foramen ovale with intermediate-risk anatomical features and early passage of more than 20 microbubbles into the left atrium during Valsalva maneuver, as well as persistence of a smaller extracardiac shunt. Given the patient's high thrombotic risk related to APS and prior venous thromboembolism, percutaneous PFO closure was performed. Follow-up echocardiography demonstrated preserved biventricular systolic function, appropriate device positioning without residual shunting, and no clinically significant valvular abnormalities or pericardial effusion. One-year follow-up chest CT demonstrated stable embolized AVMs in the left lower lobe and unchanged small AVMs in the right upper and lower lobes, consistent with expected post-treatment findings.

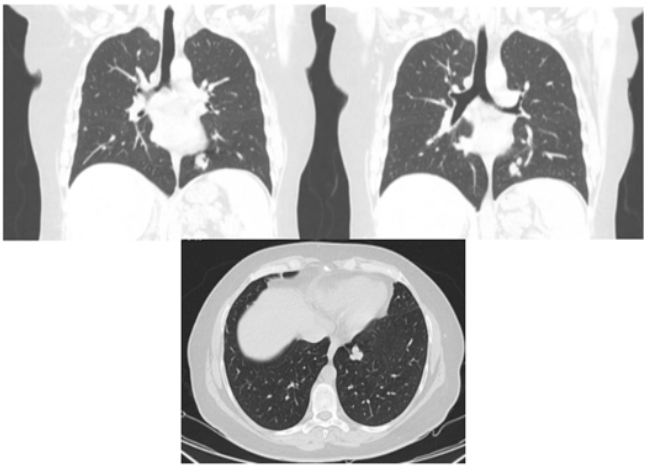

Figure 1: Chest CT scan showing a 18 mm antero-basal left lower lobe AVM with 6mm feeding artery

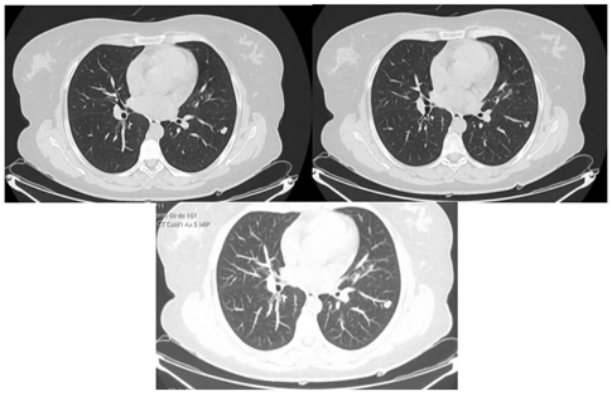

Figure 2: Chest CT scan showing a 10 mm apical left lower lobe AVM with 4mm feeding artery

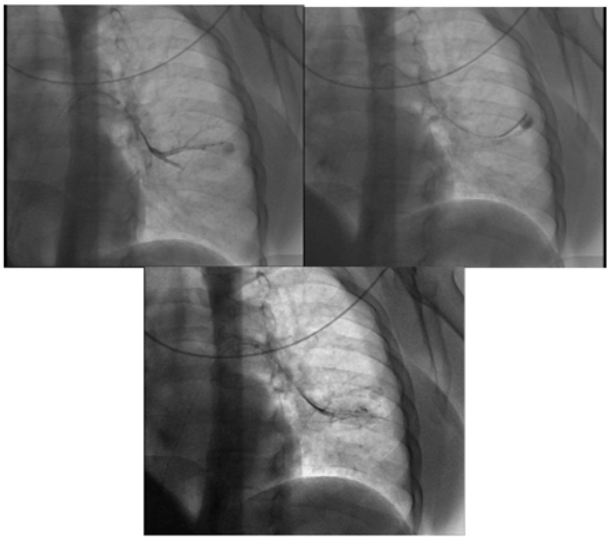

Figure 3: Angioembolization of the apical left lower lobe AVM

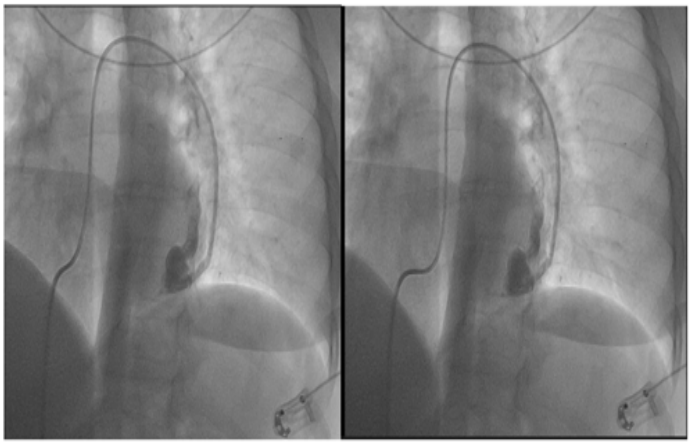

Figure 4: Angioembolization of the antero-basal left lower lobe AVM

5. Discussion

Hereditary hemorrhagic telangiectasia is a multisystem vascular disorder with progressive clinical manifestations that often lead to delayed diagnosis, particularly in patients with comorbid conditions that may obscure its presentation [1,3]. In this case, the diagnosis was established based on fulfillment of three Curaçao criteria and confirmed by identification of a pathogenic ENG mutation, consistent with HHT type 1, which is strongly associated with pulmonary and cerebral AVMs [4–6,9]. Pulmonary arteriovenous malformations are among the most clinically relevant complications of HHT and are a major source of morbidity due to right-to-left shunting and paradoxical embolization [6–8]. Contrast-enhanced transthoracic or transesophageal echocardiography is considered a highly sensitive screening tool for PAVMs, with delayed appearance of microbubbles in the left cardiac chambers serving as a key feature distinguishing intrapulmonary from intracardiac shunts [7,10]. Chest CT remains the gold standard for anatomical

characterization and treatment planning [6,11]. Current international guidelines recommend endovascular embolization for PAVMs with feeding artery diameters ≥2–3 mm, even in asymptomatic patients, to reduce the risk of neurologic complications [9,12]. In the present case, embolization was performed despite ongoing anticoagulation and resulted in symptomatic improvement, supporting previous evidence that endovascular treatment is safe and effective when appropriately indicated, even in anticoagulated patients [12–14]. The coexistence of HHT and primary antiphospholipid syndrome presents a significant therapeutic challenge. While long-term anticoagulation is essential to prevent thrombotic events in high-risk APS, it may exacerbate bleeding manifestations intrinsic to HHT, including epistaxis and gastrointestinal bleeding [15]. This delicate balance requires individualized, multidisciplinary decision-making and close clinical monitoring. Long-term surveillance following embolization is essential, as recanalization or development of new PAVMs may occur, particularly in patients with HHT type 1 [13,14]. Finally, this case underscores the importance of family screening and genetic counseling, as first-degree relatives have a 50% risk of inheriting the disease, and early identification allows timely screening and prevention of severe complications [2,9].

6. Conclusion

This case highlights the diagnostic and therapeutic complexity of hereditary hemorrhagic telangiectasia, particularly in the context of concomitant high-risk thrombotic disease requiring long-term anticoagulation. Recognition of characteristic clinical features and appropriate use of contrast echocardiography and chest computed tomography were essential for identifying pulmonary arteriovenous malformations and establishing the diagnosis, later confirmed by genetic testing [2,6,9]. Endovascular embolization proved to be a safe and effective therapeutic option, leading to symptomatic improvement despite ongoing anticoagulation therapy [12–14]. Multidisciplinary management and systematic family screening remain fundamental to optimizing outcomes and preventing potentially life-threatening complications associated with HHT [9].

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