ESC European Society of Cardiology

European Heart Journal - Case Reports (2023) **7**, 1–5
https://doi.org/10.1093/ehjcr/ytad533

CASE REPORT
Adult congential heart disease

Percutaneous embolization of pulmonary arteriovenous malformations in adult patient with Rendu–Osler–Weber: a case report

Wouter Schutyser [1]*, Werner Budts[1], and Peter Verhamme[2]

[1]Department of Cardiovascular Diseases, University Hospitals Leuven, Belgium; and [2]Department of Cardiovascular Sciences, University Hospitals Leuven, Belgium

Received 1 July 2023; revised 15 October 2023; accepted 25 October 2023; online publish-ahead-of-print 3 November 2023

Background Hereditary haemorrhagic telangiectasia (HHT), or Rendu–Osler–Weber syndrome, is a rare genetic disorder characterized by the development of telangiectasias and arteriovenous malformations (AVMs) throughout the body. We present a case of percutaneous embolization of pulmonary AVMs in an adult patient.

Case summary A 26-year-old male patient with polycythaemia of unknown origin and a family history of secundum atrial septal defect underwent cardiac evaluation which revealed clubbing as a sign of peripheral cyanosis. Transthoracic echocardiography showed no intracardiac shunting, but further imaging revealed pulmonary AVMs in the lower lobe of the left lung. Magnetic resonance imaging of the brain detected vascular-ischaemic lesions, likely due to embolization through the pulmonary malformations. Right heart catheterization and pulmonary angiography confirmed the presence of large AVMs in the left lower pulmonary lobe. Percutaneous closure using Amplatzer devices was performed, followed by temporary anticoagulation therapy. Oxygen saturation improved and follow-up imaging confirmed successful closure of the AVMs. Genetic testing using whole exome sequencing identified a mutation in the ENG gene, confirming the diagnosis of HHT.

Discussion Our case highlights the importance of investigating both intra- and extracardiac shunting in patients with clinical features of right-to-left shunting. Arteriovenous malformations can serve as a pathway for paradoxical emboli, potentially leading to ischaemic brain events, and might cause pulmonary arterial hypertension. Screening for arteriovenous malformations in various organs and embolization of significant shunts are essential aspects of managing HHT. Genetic testing aids in confirming the diagnosis and guides family testing.

Keywords Case report • Adult congenital heart disease • Interventional cardiology • Genetics

ESC curriculum 9.7 Adult congenital heart disease • 9.4 Thromboembolic venous disease

Learning points

- When assessing patients with possible right-to-left shunting, it is crucial to explore both intracardiac and extracardiac factors; while not employed in this case, contrast bubble echocardiography can be valuable for suspected extracardiac shunting, with computed tomography angiography as a valid alternative.
- Screening HHT patients for AVMs in multiple organs, such as the liver, brain, and lungs, is vital, and early detection and proper management of pulmonary AVMs are essential for improving oxygenation, alleviating symptoms, and preventing complications in HHT patients.

* Corresponding author. Tel: +016 34 8656, Email: wouter.schutyser@uzleuven.be
Handling Editor: Filippo Puricelli
Peer-reviewers: Cristiano Spadaccio; Jamol Uzokov
Compliance Editor: Emmanouil Mantzouranis

Introduction

Rendu–Osler–Weber, also known as hereditary haemorrhagic telangiectasia (HHT), is a rare genetic disorder that affects blood vessels. It is caused by a mutation in genes associated with angiogenesis and is typically inherited in an autosomal dominant pattern.[1]

The disorder is characterized by the development of abnormal blood vessels, known as telangiectasias, which are fragile and prone to bleeding. These blood vessels can occur in various parts of the body, but are most found in the nose, mouth, fingers, and gastrointestinal tract.[1] In addition to telangiectasias, HHT can also cause arteriovenous malformations (AVMs), which occur mostly in the lungs and brain.

Symptoms of HHT can vary widely depending on the location and severity of the telangiectasias and AVMs. Common symptoms include nosebleeds, shortness of breath, chest pain, and gastrointestinal bleeding.[2] While there is currently no cure for HHT, treatments are available to manage symptoms and prevent complications.

Summary Figure

Day	Events
1	Patient referred due to polycythaemia (Hb 20.7 g/dL). Physical exam shows clubbing and low resting saturation (87%) is found. Echocardiography shows no structural heart disease. Chest radiography reveals multiple nodular opacities
4	CT scan shows multiple AVMs connecting pulmonary arteries and veins, no AVMs found in the liver
12	Ambulatory follow-up to discuss results with patient, blood sampling for genetic testing. Brain magnetic resonance imaging reveals multiple vasculo-ischaemic lesions in frontal and cerebellar lobes, no intracranial AVMs detected
89	Percutaneous closure of four pulmonary AVMs
193	Follow-up angiography CT shows no remaining shunting, and the patient's resting oxygen saturation improved to 95%, while his haemoglobin level lowered to 17.7 g/dL. Whole exome sequencing identified a specific mutation (c.1411C > T, p.Gln471*) in the ENG gene, confirming the definite diagnosis of HHT

Case presentation

A 26-year-old male patient was referred to our cardiology department by his general practitioner to exclude a cardiac origin of polycythaemia. The patient visited his general practitioner due to recurrent infections in the upper respiratory tract. He also reported a progressive increase in fatigue compared to individuals of similar age, particularly evident during physical activities with friends. Blood tests revealed polycythaemia with elevated levels of haemoglobin (20.7 g/dL) and increased haematocrit (60.4%), with no other abnormalities detected. The patient had a positive family history of secundum atrial septal defect (ASD) in his father. Physical examination revealed clubbing of the fingers (*Figure 1*). No audible heart murmurs were detected, and examination of the lips yielded no evidence of telangiectasis. The patient's resting oxygen saturation was found to be 86%, indicating hypoxia, and arterial blood tests showed low oxygen levels (pO_2 57 mmHg). A transthoracic echocardiogram did not show any signs of intracardiac right-to-left shunting. Despite its potential usefulness in further investigating the right-to-left shunting, contrast echocardiography was not feasible in this case as the necessary resources were not available in the clinic.

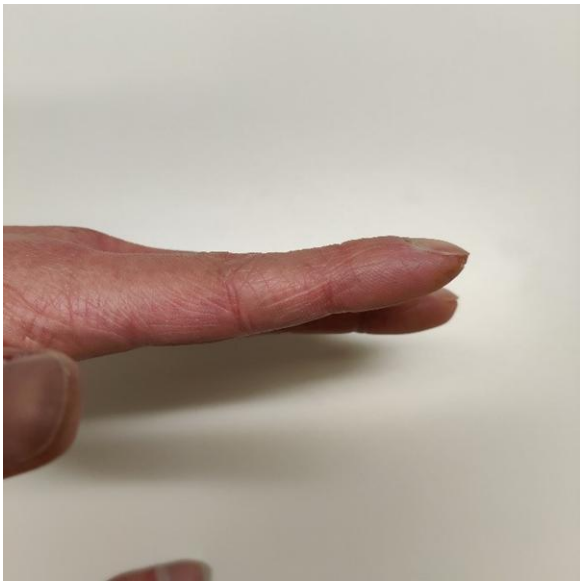

Figure 1 Digital clubbing as seen in the index finger of the patient, with the typical enlarged, rounded, and bulbous fingertip deformity.

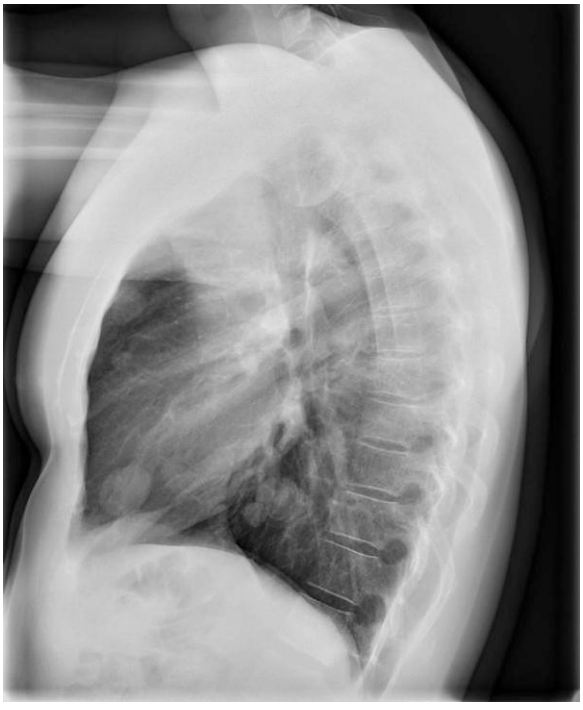

Figure 2 Chest X-ray reveals a large, rounded opacity in the lower region of the lung.

Subsequent chest X-ray revealed multiple nodular opacities, particularly in the lower lobe of the left lung (*Figure 2*). Further evaluation using

chest computed tomography (CT) confirmed that these findings correlated with pulmonary arteriovenous malformations (pulmonary AVMs) (*Figure 3*). No hepatic AVMs were found. Magnetic resonance imaging (MRI) of the brain showed several old ischaemic lesions in the frontal and cerebellar lobes, likely caused by embolization of blood clots through the pulmonary AVMs (*Figure 4*). Neurological examination did not reveal any abnormalities, and no AVMs were found within the brain on MRI.

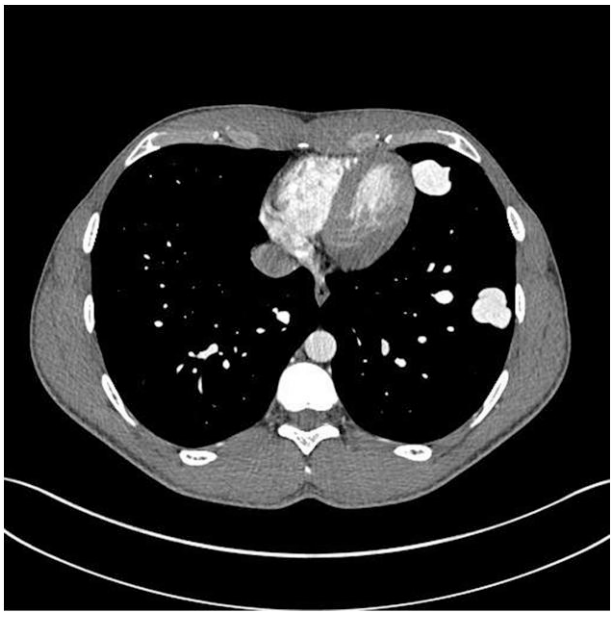

Figure 3 CT angiography shows several large pulmonary arteriovenous malformations.

To investigate further, a right heart catheterization was performed by femoral access. Angiography revealed four large pulmonary AVMs in the lower lobe of the left lung (*Figure 5*). Each AVM was successfully closed percutaneously using Amplatzer devices. The correct placement of the devices was confirmed using angiography. The patient was started on anticoagulant therapy with vitamin K antagonists (VKA) to prevent thrombus formation distally from the devices. In accordance with ESC guidelines, we also recommended the patient to initiate endocarditis prophylaxis when undergoing invasive dental procedures.

Follow-up evaluation 3 months after the closure of the AVMs, CT angiography showed no residual shunting. The patient's resting oxygen saturation improved to 95%, while his blood work indicated a decrease in haemoglobin level to 17.7 g/dL. Genetic testing through whole exome sequencing revealed that the patient had a specific genetic mutation (c.1411C > T, p.Gln471*) in the ENG gene. Based on these findings, the definitive diagnosis of HHT was made.

Discussion

Upon evaluation, the patient's presentation raised concerns about the possibility of right-to-left shunting due to observed low resting oxygen saturation, clubbing, and secondary polycythaemia. The patient did not experience any symptoms of epistaxis or gastrointestinal bleeding. Given the patient's family history of ASD in his father, our initial focus was to investigate any intracardiac factors contributing to the shunting. It is known that first-degree relatives of individuals with ASD have an increased likelihood of having an ASD themselves.[3] Atrial septal defect is a congenital abnormality that initially causes left-to-right shunting, leading to increased volume load on the right atrium, right ventricle, and pulmonary vasculature, eventually resulting in pulmonary hypertension. In some cases, significant pulmonary hypertension can lead to the occurrence of right-to-left shunting later in life through shunt lesions.

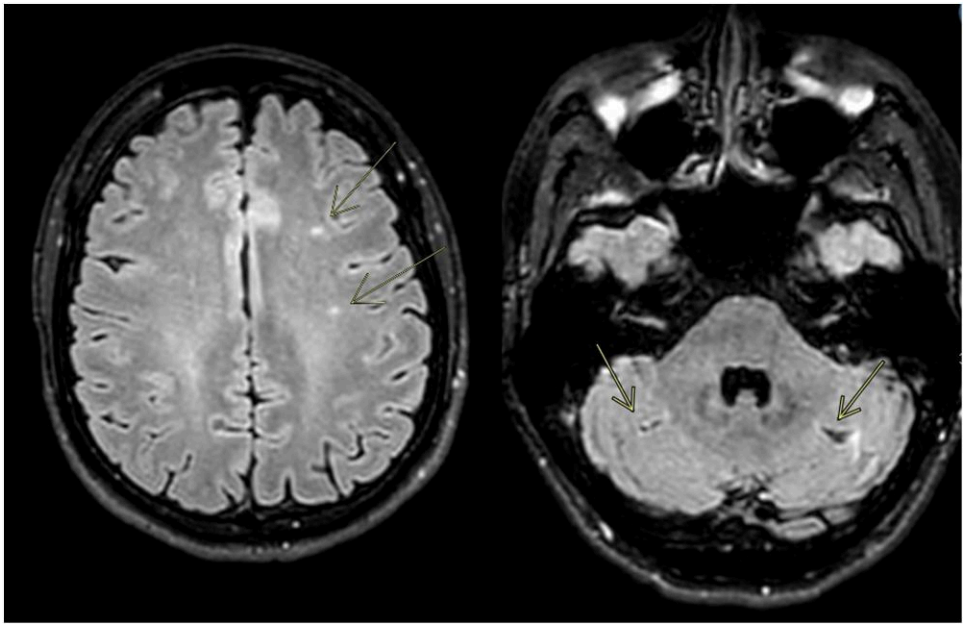

Figure 4 Two frontal white matter lesions (left), accompanied by bilateral sequalae of splinter infarctions.

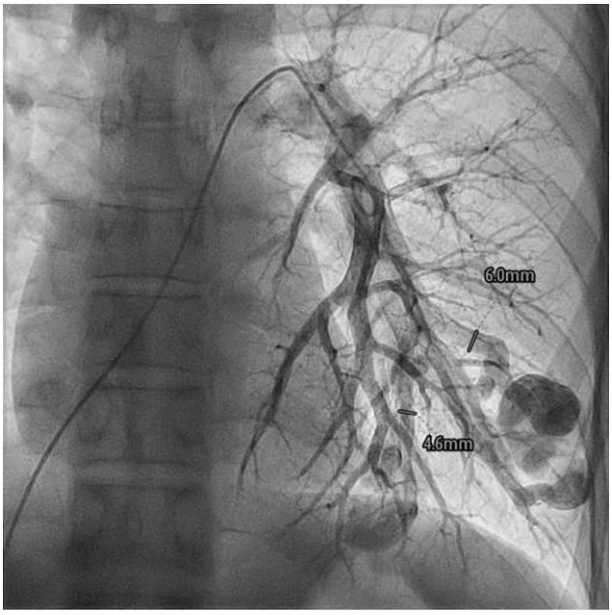

Figure 5 Selective angiography of the left pulmonary artery demonstrating visualization of multiple pulmonary arteriovenous malformations, of which diameter measurements were obtained.

If investigations regarding an intracardiac shunt yield no significant findings (i.e. transthoracic and transoesophageal echocardiography), it is important to explore the possibility of an extracardiac shunt, often found within the pulmonary circulation. Notably absent in this case were epistaxis occurrences or evident clinical telangiectasis which, if present, would have prompted an immediate suspicion of HHT. Contrast 'bubble' echocardiography is recognized for its high efficacy in detecting both intra- and extracardiac shunts.[4] This assessment can raise suspicion for intracardiac or intrapulmonary shunts, with current guidelines suggesting an intracardiac shunt determination within three to six cardiac cycles after right atrial opacification, albeit the derivation of this criterion from case literature rather than rigorous pathophysiological analysis. In this case, a CT scan was undertaken as the necessary resources for contrast 'bubble' echocardiography were not available. This scan revealed the presence of large pulmonary AVMs. These AVMs can facilitate the shunting of both blood and other substances such as air, thrombi, and vasoactive agents, and pathogens. Several documented cases have shown that paradoxical emboli resulting in transient ischaemic attacks (TIA) or cerebrovascular accidents can arise from such pulmonary AVMs.[5] Some reports suggest that embolization of pulmonary arteriovenous malformations in HHT patients may lead to a decrease in migraine prevalence, indicating that the presence of a right-to-left shunt, rather than its location, plays a role in the development of migraines.[6] Furthermore, it is worth noting that pulmonary arterial hypertension has been reported in patients with HHT and pulmonary AVMs, even in the absence of significant shunting through the pulmonary AVMs,[7] as well as high-output heart failure in case of high-flow pulmonary or liver AVMs.[8]

Management of patients with HHT includes screening for AVMs and prevention/treatment of bleeding. International guidelines emphasize the need for AVM screening in suspected or confirmed HHT.[9] This includes screening for liver AVMs (Doppler ultrasound or MRI), brain AVMs (MRI), and pulmonary AVMs (contrast transthoracic echocardiography or CT angiography).

In this case, the patient had several pulmonary AVMs of haemodynamic importance. AVMs in other organs were not found on screening. Guidelines state the importance of treatment of pulmonary AVMs.[10] Embolization in patients with pulmonary AVMs is recommended, even if they are asymptomatic. The aim is to reduce the risks of paradoxical emboli, improve oxygenation, alleviate symptoms associated with right-to-left shunting, and prevent haemorrhage.[11,12] The presence of radiologically visible pulmonary AVMs, regardless of size, thus warrants closure. While complete obliteration of all pulmonary AVMs is not always achievable, at least reducing the shunting should be a common goal.

If AVMs are found in patients, it is crucial to perform genetic testing to exclude or confirm HHT. According to the Curaçao Criteria, HHT can be diagnosed if a patient presents with spontaneous and recurrent nosebleeds, multiple mucocutaneous telangiectasia, visceral involvement (such as gastrointestinal telangiectasia or AVM), and/or having a first-degree relative with HHT.[9] Genetic testing can confirm the diagnosis by identifying pathogenic variants in specific HHT genes (ENG, ACVRL1, SMAD4, or GDF2).[13] While diverse genetic anomalies contributing to HHT have been documented, it is noteworthy that all these anomalies result in some form of disruption to protein coding. These proteins are integral to vascular development processes. Ultimately, the disruption of these processes culminates in the vulnerability of blood vessels, giving rise to vascular lesions characterized clinically as telangiectasis/epistaxis and AVM. Whole genome sequencing showed a c.1411C > T (p.Gln471*) mutation in the ENG gene in our patient, which has been described as a likely pathogenic mutation in individuals of Asian heritage.[14] Remarkably, our patient's background is Western European in origin, signifying a notable difference from the previously established pattern.

The robustness of this case report resides in its unconventional diagnostic approach to HHT. Conventionally, the detection of pulmonary AVMs is indicated via contrast echocardiography. Yet, due to the unavailability of requisite equipment for this procedure in our outpatient setting, we opted to proceed differently. Another significant determinant influencing the chosen diagnostic path is the patient's clinical presentation. As seen in other cases, younger patients with distinct clinical issues, like ischaemic stroke, are more promptly considered for a diagnosis of paradoxical ischaemic stroke.[15] Following the exclusion of an intracardiac shunt through conventional transthoracic echocardiography, we therefore opted for CT angiography of the lungs. Our findings underscore the feasibility of reliably identifying pulmonary AVMs through this diagnostic pathway.

Lead author biography

Wouter Schutyser is a cardiology resident at the University Hospitals Leuven in Leuven, Belgium. His primary clinical focus lies in percutaneous interventions for coronary and vascular disease, with a particular interest in congenital heart disease.

Acknowledgements

The authors hereby confirm that there are no other contributors to this article, other than those already listed as authors.

Consent: The patient hereby affirms being well informed and acknowledges receiving a document providing information about their inclusion in this case report. After careful consideration, he voluntarily

consents to be included in this report. The authors confirm that written informed consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE (Committee on Publication Ethics) guidance.

Conflict of interest: None declared.

Funding: None.

Data availability

The data are subject to restrictions due to patient confidentiality and privacy considerations, although the data will be shared on reasonable request to the corresponding author.

References

1. McDonald J, Bayrak-Toydemir P, Pyeritz R. Hereditary hemorrhagic telangiectasia: an overview of diagnosis, management, and pathogenesis. *Genet Med* 2011;**13**:607–616.
2. Begbie ME, Wallace GMF, Shovlin CL. Hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu syndrome): a view from the 21st century. *Postgrad Med J* 2003;**79**: 18–24.
3. Posch MG, Perrot A, Berger F, Özcelik C. Molecular genetics of congenital atrial septal defects. *Clin Res Cardiol* 2010;**99**:137–147.
4. Bernard S, Churchill TW, Namasivayam M, Bertrand PB. Agitated saline contrast echocardiography in the identification of intra- and extracardiac shunts: connecting the dots. *Echo Res Pract* 2021;**34**:1–12.
5. Das A, Greisman JD, Vazquez S, Feldstein E, Spirollari E, Lui A, et al. Acute ischemic stroke in patients with pulmonary arteriovenous malformations: paradoxical embolism or epiphenomenon? *Stroke Vascu Interven Neurol* 2023;**3**:e000571.
6. Post MC, Thijs V, Schonewille WJ, Budts W, Snijder RJ, Plokker HWM, et al. Embolization of pulmonary arteriovenous malformations and decrease in prevalence of migraine. *Neurology* 2006;**66**:202–205.
7. Soubrier F, Chung WK, Machado R, Grünig E, Aldred M, Geraci M, et al. Genetics and genomics of pulmonary arterial hypertension. *J Am Coll Cardiol* 2013;**62**:D13–D21.
8. Faughnan ME, Granton JT, Young LH. The pulmonary vascular complications of hereditary haemorrhagic telangiectasia. *Eur Respir J* 2009;**33**:1186–1194.
9. Faughnan ME, Mager JJ, Hetts SW, Palda VA, Lang-Robertson K, Buscarini E, et al. Second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. *Ann Intern Med* 2020;**173**:989–1001.
10. Shovlin CL, Condliffe R, Donaldson JW, Kiely DG, Wort S, Kiely DG, et al. Pulmonary arteriovenous malformations emerge from the shadows. *Thorax* 2017;**72**:1071–1073.
11. Shovlin CL, Jackson JE, Bamford KB, Jenkins IH, Benjamin AR, Ramadan H, et al. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. *Thorax* 2008;**63**:259–266.
12. Hsu CC, Kwan GN, Evans-Barns H, van Driel ML. Embolisation for pulmonary arteriovenous malformation. *Cochrane Database Syst Rev* 2018;**1**:CD008017.
13. Shovlin CL, Simeoni I, Downes K, Frazer ZC, Megy K, Bernabeu-Herrero ME, et al. Mutational and phenotypic characterization of hereditary hemorrhagic telangiectasia. *Blood* 2020;**136**:1907–1918.
14. Komiyama M, Ishiguro T, Yamada O, Morisaki H, Morisaki T. Hereditary hemorrhagic telangiectasia in Japanese patients. *J Hum Genet* 2014;**59**:37–41.
15. Lu X, Hu WT, Li YD, Cheng YZ. PAVM and paradoxical ischemic stroke in hereditary hemorrhagic telangiectasia. *JACC Cardiovasc Interven* 2020;**13**:e127–e129.