

Pulmonary arteriovenous malformation with unexplained cyanosis as the first presentation of hereditary haemorrhagic telangiectasia, case report, and literature review

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Background

Pulmonary arteriovenous malformations (PAVMs) are rare pulmonary vascular anomalies. They can result in right-to-left shunt and, if significant, low systemic saturation, cyanosis, polycythaemia, and paradoxical systemic embolization.

Case summary

Eighteen months old female child was referred to our centre due to unexplained central and peripheral cyanosis. Based on the agitated saline contrast echocardiography study, computed tomography scan confirmed the presence of abnormal vasculature at the left lower lobe. Percutaneous closure of the PAVM was performed using Amplatzer Duct Occluder type 1 device. The genetic study revealed a pathogenic mutation in the endoglin gene, which is a known cause of hereditary haemorrhagic telangiectasia (HHT) inherited in an autosomal dominance pattern.

Discussion

PAVM could be the first manifestation of HHT. Closing the malformation percutaneously is feasible, which can eliminate the right to left shunt and improves the saturation. Genetic study is warranted in these cases, as well as long-term follow-up.

Keywords

Pulmonary arteriovenous malformations • Hereditary haemorrhagic telangiectasia • Cardiac catheterization • Case report

Learning points

- Cyanosis of unrevealed cause might be related to extracardiac right to left shunt (e.g. intrapulmonary shunt), which can be diagnosed by agitated saline contrast echocardiography.
- Pulmonary arteriovenous malformation (PAVM) could be related to hereditary haemorrhagic telangiectasia (HHT).
- The arteriovenous malformation can be closed percutaneously using the available devices.
- Long-term follow-up is mandatory for patients with PAVM to look for recurrence as well as for other features of HHT.

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Introduction

Pulmonary arteriovenous malformations (PAVMs) are rare pulmonary vascular anomalies resulting in right-to-left shunt and low systemic saturation, cyanosis, polycythaemia, and paradoxical systemic embolization.¹ PAVM might be sporadic, autosomal dominant, or associated with hereditary haemorrhagic telangiectasia (HHT).

We are reporting an 18 months old female child referred to us because of unexplained central and peripheral cyanosis. After diagnosis and intervention, the genetic study revealed a *de novo* pathogenic mutation in the endoglin (ENG) gene, which is a known cause of HHT. This genetic abnormality is inherited as an autosomal dominance condition.²

Timeline

Date	Case progression
20 July 2018	Diagnosis
24 July 2018	Echocardiography contrast study
26 July 2018	Cardiac catheterization
26 July 2018	Arterial saturation improved from 85% to 95%
27 July 2018	Discharged
After 1, 3, 6, and 12 months of intervention	Follow-up
3 months later	Genetic consultation
17 December 2020	On follow-up. Asymptomatic, saturation 95% at room air

Ao, aorta; LA, left atrium; MVO₂, mixed venous saturation; PA, pulmonary artery; RA, right atrium.

Case presentation

Eighteen months old female referred to our clinic because of chronic cyanosis of unrevealed cause. There were no respiratory or gastrointestinal symptoms with normal growth and development. No family history of the same illness, or history suggesting HHT. All family members were examined and screened by pulse oxymetry. Clinically, apart from the presence of central and peripheral cyanosis with first-degree clubbing, her general and systemic examinations were normal with no skin or eye lesions. Her saturation was 85% in room air and her haemoglobin level was 17.3 g/dL (normal value 11–13 g/dL). Electrocardiogram was normal. Chest X-ray revealed a circumscribed opacity in the left lower lung field with no cardiomegaly (Figure 1). Echocardiography revealed normal intracardiac anatomy with intact interatrial and interventricular septums. An echocardiographic contrast study using agitated normal saline revealed the appearance of significant air bubbles (contrast) in the left atrium after 3–5 beats. The contrast came mainly from the left lower pulmonary vein (Figure 2) (Supplementary material online, File S1). Chest and cardiac computed tomography (CT) angio confirmed the diagnosis of pulmonary arteriovenous malformation.

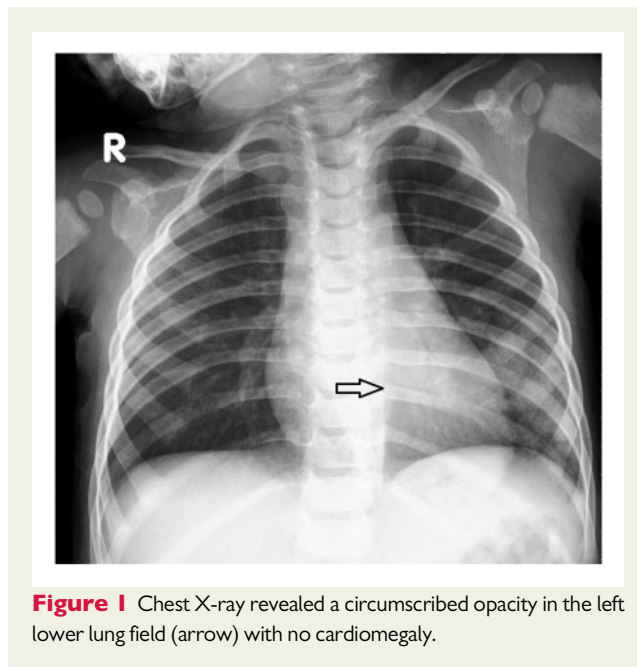


Figure 1 Chest X-ray revealed a circumscribed opacity in the left lower lung field (arrow) with no cardiomegaly.

CT scan revealed the presence of abnormal vasculature at the left lower lobe (Figure 3). After discussion, she was admitted electively for diagnostic catheterization and closure of PAVM.

Cardiac catheterization was performed and the PAVM was closed using an 8/6 Amplatzer Duct Occluder Type I device (ADO1) (St. Jude Medical, St. Paul, MN, USA). The (Figure 4, Video 2) patient saturation improved immediately after balloon occlusion of the arteriovenous malformation as well as after device closure. Haemodynamics are presented in Tables 1 and 2.

After PAVM closure, the systemic saturation improved to 95%, with an increase in the Qp: Qs to 0.8, and a reduction of the right to left shunt to 0.6 L/min/m². She was discharged on the second post-intervention day with a stable general condition. The saturation on discharge was 95% in room air. Currently, she is asymptomatic with normal oxygen saturation and exercise capacity.

Whole-genome sequencing identified a novel heterozygous pathogenic variant (c.774 c>a, p.Tyr 258*). This is a *de novo* mutation that is not present in the parents (both parents' genetic study was negative for this mutation).

Discussion

PAVM is a rare anomaly with a reported incidence of 2–3 per 100 000 population.¹ The latest estimates suggest a prevalence of ~1 in 2600. PAVMs with a male to female ratio vary from 1:1.5 to 1.8.³

PAVMs can be either congenital or acquired and could be single or multiple.⁴ Microscopic PAVM can be present and could be the cause of unexplained cyanosis. More than 80% of PAVMs are congenital, and of these 47–80% are associated with Osler–Weber–Rendu disease or HHT.²

PAVM can present with dyspnoea on exertion, hypoxemia, cyanosis, and clubbing. Paradoxical embolization with central nervous



Figure 2 Four-chamber view during transthoracic echocardiographic contrast study using agitated normal saline. Significant air bubbles (contrast) seen in the left atrium after 3–5 beats (Supplementary material online, File S1). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

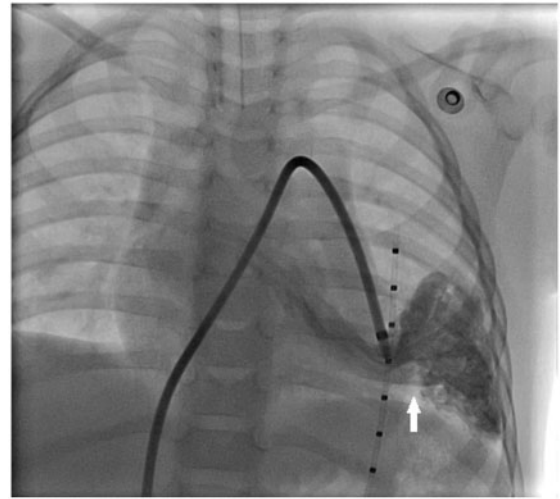
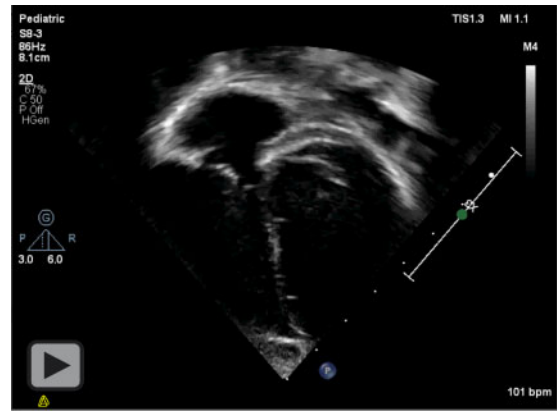


Figure 4 Left pulmonary artery angiogram through the delivery sheath, showing a large fistula at the left lower lobe supplying the left lower segment (arrow).



Figure 3 Chest computed tomography scan, coronal section, showing the abnormal vasculature at the left lower lobe (arrow).



Video 1 Four chamber echocardiographic view during bubble contrast study. The agitated normal saline was injected from the upper limb vein and bubbles appear in the right atrium. Significant air bubbles appear in the left atrium after 3 to 5 beats indicating significant intrapulmonary right to left shunt.

system affection and brain abscess might be the first presentation. Epistaxis, melaena, and neurological symptoms should alert the clinician to the possibility of coexisting HHT.⁵

Stigmata of Osler–Weber–Rendu disease or HHT, an autosomal dominant disorder with wide variation in the clinical presentation, should alert the clinician to the possibility that both may coexist.⁶

In our case, there were no dermatologic or ophthalmologic findings. The genetic study revealed a likely pathogenic mutation in the ENG gene which is a known cause of HHT.

PAVM could be the first presentation of HHT. There might be a risk for the development of recurrent arteriovenous malformations and the appearance of other clinical features of HHT.

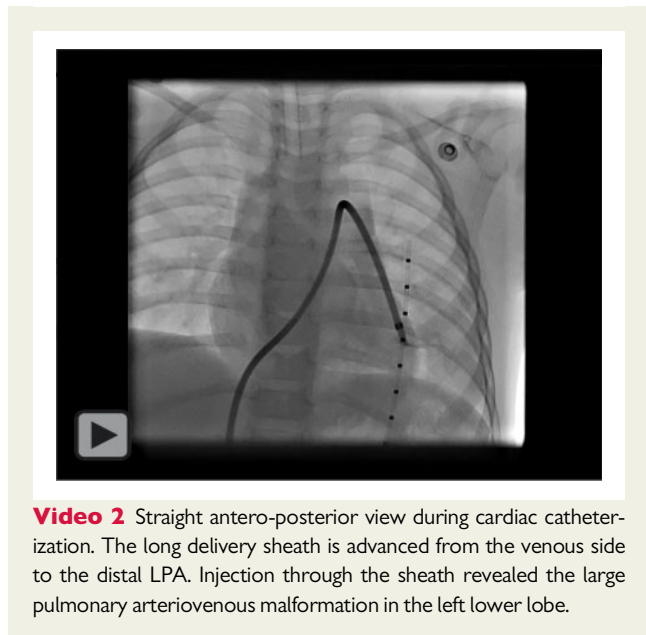
In contrast to systemic arteriovenous malformation, PAVMs does not affect cardiac haemodynamics.⁷ Electrocardiographic and

haemodynamic findings are usually within normal limits. The fundamental defect is a right-to-left shunt from the pulmonary artery to the pulmonary vein and the degree of the shunt determines the clinical effects on the patient.⁷

If shunting is minimal, the symptoms are usually subacute or even absent. If the right-to-left shunt is greater than 20% of the systemic cardiac output or there is a reduced haemoglobin of more than 5 g/dL, the patient will have obvious cyanosis, clubbing, and polycythaemia. The peripheral oxygen saturation is low and as expected does not normalize with 100% oxygen. Asymptomatic patients are common and account for between 13% and 55% of patients in different series.⁸

In a significant number of patients (43–67%), a history of neurological symptoms (headache, vertigo, paresis, numbness, paraesthesia, syncope, or confusion) can be found.⁸ The most common physical findings are cyanosis, clubbing, and pulmonary vascular bruit.⁸ The most commonly reported complications related to the central nervous system (migraine, transient ischaemic attack, stroke, abscess, and seizure) and the incidence varies in different series from 19% to 59%.⁹

The classic chest X-ray features of PAVM are a round or oval sharply defined mass of uniform density, frequently lobulated, and ranging in size from 1 to 5 cm in diameter; two-thirds are located in the lower lobes.⁷ Chest tomography, although not used commonly, is more accurate in identifying connecting vessels and PAVM.



Video 2 Straight antero-posterior view during cardiac catheterization. The long delivery sheath is advanced from the venous side to the distal LPA. Injection through the sheath revealed the large pulmonary arteriovenous malformation in the left lower lobe.

Contrast echocardiography is extremely sensitive in detecting left-to-right shunt.¹⁰ Besides, contrast echocardiography allows assessment of efficiency of embolotherapy and is useful to exclude the presence of PAVM in family members of patients with HHT.¹¹

With intrapulmonary shunts, as seen in PAVMs, microbubbles in the left heart usually appear three to four cardiac cycles after the contrast cloud appears in the right heart.¹⁰ Contrast-enhanced CT is a valuable tool in the diagnosis and defining of the vascular anatomy of PAVM.¹²

Pulmonary angiography remains the gold standard in the diagnosis of PAVM.^{4,7} Despite limited information about the natural history of PAVM, available data suggest treatment should be offered to all symptomatic patients and asymptomatic patients with lesions with 2 cm or more in diameter on chest radiography.⁹

The current preferred treatment for the majority of patients with PAVM is percutaneous embolization. Different materials are used for PAVM embolization depending upon the size of the malformation, including coils, detachable balloons, or devices with a very good success rate.¹³

Complications following PAVM embolization are rare and might include: transient pleuritic chest pain, air embolism, pulmonary infarction, device migration, myocardial rupture, cerebrovascular accident, vascular injury, deep vein thrombosis, and pulmonary hypertension.¹⁴ Surgical resection of PAVMs is indicated in patients who fail embolotherapy, develop serious bleeding complications despite embolotherapy, have intrapleural rupture of the PAVM, or have untreatable contrast allergy and lesions not amenable to embolotherapy.

Our patient had successful PAVM closure using 8/6 Amplatzer duct Occluder type 1. Her genetic study using whole-genome sequencing identified a novel heterozygous pathogenic variant (c.774 c>A, p.Tyr 258*).

Table 1 Haemodynamics, condition 1: pre-fistula device closure (calculations in room air), oxygen consumption (VO_2) 180 mL/min/m², Hb 17.3 g/dL

Pressures	Mean (mmHg)	Site	Sat %	Qp (L/min/m ²)	2.9	L-R	0.1
RA	7	MVO ₂	71%	Qs (L/min/m ²)	4.8	R-L	1.9
PA	17	PA	72%	Q eff (L/min/m ²)	2.8		
Ao	45	Systemic	87%	Rp (Wood U)	3.1	Rs	7.9
Wedge or LA	8	PulmVen	98%	Qp/Qs Ratio	0.6	Rp/Rs	0.4

Ao, aorta; LA, left atrium; MVO₂, mixed venous saturation; PA, pulmonary artery; RA, right atrium.

Table 2 Haemodynamics, condition 2: post-fistula device closure (calculations in room air), oxygen consumption (VO_2) 180 mL/min/m², Hb 17.3 g/dL

Pressures	Mean (mmHg)	Site	Sat %	Qp (L/min/m ²)	Qp	3.5	L-R
RA	7	MVO ₂	77%	Qs (L/min/m ²)	Qs	4.3	R-L
PA	17	PA	76%	Q eff (L/min/m ²)	Q eff	3.6	
Ao	45	Systemic	95%	Rp (Wood U)	Rp	2.6	Rs
Wedge or LA	8	PulmVen	98%	Qp/Qs ratio	Qp/Qs	0.8	Rp/Rs

Mutations in two genes (ENG and ACVRL1 genes) in the transforming growth factor-beta signalling pathway have been reported to cause up to 85% of HHT.² Recently, two additional genes in the same pathway, SMAD4, and GDF2, have been identified in a smaller number of patients with a similar or overlapping phenotype to HHT. Approximately 15% of individuals suspected to have HHT have no mutation in ENG, ACVRL1, or SMAD4 genes. The availability of whole-exome sequence and genome testing helps explain clinical variability and the spectrum of hereditary telangiectasia disorders. *De novo* mutations and mosaicism for genes causing HHT are rare but have both been reported. These reported cases have no family history of HHT.¹⁵ McDonald *et al.*² proposed an algorithm for genetic testing for patients with clinical manifestations suggestive of HHT.

Conclusion

PAVM is an uncommon disorder and could be the first presentation of HHT. A contrast echocardiography study should be performed for any patient with unexplained cyanosis and/or systemic embolization. Long-term follow-up is warranted to look for other clinical features of HHT. Genetic consultation and screening are warranted.

Lead author biography



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Supplementary material

[Supplementary material](#) is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated

text has been obtained from the patient's family in line with COPE guidance.

Conflict of interest: All authors declare that they don't have any conflict of interest related to the production of this manuscript.

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Ethical statement

All procedures performed for the patient were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's family.

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