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Case report

Pulmonary arterial hypertension associated with pulmonary arteriovenous malformations and pulmonary veno-occlusive disease: A devastating combination

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ABSTRACT

We describe a case of an adolescent male with the rare combination of pulmonary arterial hypertension (PAH) and pulmonary arteriovenous malformations (PAVM's) without confirmed hereditary hemorrhagic telangiectasia (HHT). The patient showed clinical deterioration on standard vasodilator therapy, leading us to question our initial diagnosis. Post-mortem evaluation confirmed the presence of pulmonary veno-occlusive disease of which no conclusive signs were recognized at diagnostic work-up. This case demonstrates the heterogeneity in the diseases causing PAH and shows that an unexpected treatment response should alert the physician to question the original diagnosis.

Abbreviations

AVM	arteriovenous malformation
ECLS	extra corporal life support
HHT	hereditary hemorrhagic telangiectasia
PAH	pulmonary arterial hypertension
PAVM	pulmonary arteriovenous malformation
ppm	parts per million
RV	right ventricle
WHO-FC	World Health Organization – Functional Class
WU	Woods Units

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1. Introduction

Pulmonary arterial hypertension (PAH) is a severe progressive vascular disease eventually leading to right ventricular failure and death. Although PAH-targeted drugs, including endothelin-receptor-antagonists, 5-Phosphodiesterase-inhibitors and prostacyclin analogs, may slow disease progression, there is currently no cure for PAH apart from lung transplantation. Current guidelines propose to treat PAH patients following treatment algorithms based on risk stratifications.

We describe a 16-year old patient diagnosed with PAH who had macroscopic pulmonary arteriovenous malformations (shown by angiography and CT scans) and a suspected diagnosis of hereditary hemorrhagic telangiectasia. Based on current treatment algorithms, we chose to initiate oral dual combination therapy. Two attempts were made to introduce sildenafil to a background therapy of bosentan. Both times the boy rapidly deteriorated, which was characterized by deep and progressive cyanosis. Unfortunately, the patient deceased while listed for lung transplantation. Post-mortem pathology examination provided an explanation for his extreme and rapid deterioration on vasodilator therapies.

2. Case presentation

A sixteen-year-old male was referred to the Dutch national referral center for pediatric pulmonary hypertension because of exercise-induced dyspnea and cyanosis that had gradually progressed over the previous two and a half years. The previously healthy boy had experienced two episodes of syncope during exercise and several episodes of (non-massive) hemoptysis. So far, the patient's complaints had been attributed to dysfunctional breathing and recurrent airway infections. There was no family history of pulmonary arterial hypertension (PAH), hereditary hemorrhagic telangiectasia (HHT) or congenital heart disease. The patient's history and physical examination revealed dyspnea at rest, WHO-FC III, weight loss, transcutaneous oxygen saturation of 91% in rest that decreased to 85% during walking, clubbed fingers and acrocyanosis, a loud second heart sound without a murmur, normal respiratory auscultation and no enlarged liver or spleen. The differential diagnosis included pulmonary hypertension, cardiomyopathy and (interstitial) pulmonary diseases.

2.1. Diagnostic work-up

An electrocardiography showed right ventricular hypertrophy with strain pattern. An echocardiography showed signs of increased right ventricular pressure (tricuspid regurgitation v_{max} of 3.4 m/s, septal flattening, decreased pulmonary arterial acceleration time), right ventricular hypertrophy and right ventricular dilatation with a poor systolic right ventricular function, in the absence of structural cardiac anomalies. Laboratory results showed increased NT-proBNP and Troponin T.

A full diagnostic work-up for pulmonary hypertension was performed. Right heart catheterization confirmed the diagnosis of PAH (mean pulmonary arterial pressure 63 mmHg, pulmonary vascular resistance index of 8 WU.m² and normal wedge pressures). There was no acute response to vasodilator testing. There was no intra-cardiac shunting. Angiography showed signs of multiple macroscopic arteriovenous malformations. An echocardiographic bubble study confirmed intrapulmonary right-to-left shunting.

Further work up revealed no signs of connective tissue disease, coagulation disorders, liver diseases or portal hypertension. Lung function test were normal, including a normal diffusion capacity of carbon monoxide. Thorax computed tomography scan (CT-scan) showed multiple pulmonary arteriovenous malformations (PAVM's), neovascularization, an inhomogeneous perfusion pattern, signs of pulmonary bleeding, diffuse ground-glass opacities, and thickened interlobar septal lines (Fig. 1). No additional cutaneous, mucous, visceral (including brain and liver) telangiectasia or arteriovenous malformations were found. Genetic analyses revealed no mutations associated with PAH, nor with HHT. Furthermore, there was no mutation in the EIF2AK4 gene, which is associated with pulmonary veno-occlusive disease.

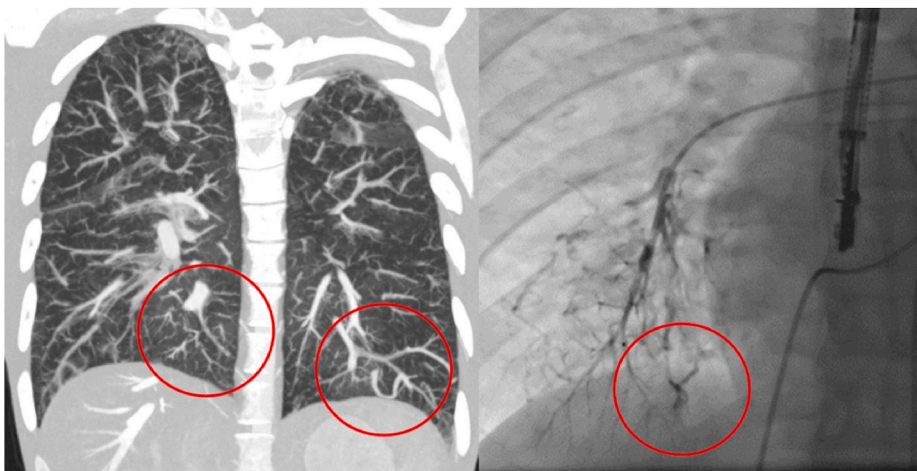


Fig. 1. Oblique-coronal maximum intensity projection (left), and angiography (right) demonstrate AVM's (circles).

Based on these investigations the patient was diagnosed with PAH with PAVM's. A diagnosis of HHT could not be confirmed genetically, nor clinically according to the diagnostic Curaçao criteria.

2.2. Management and follow-up

Continuous oxygen therapy and PAH-targeted dual therapy (bosentan and sildenafil) was initiated. At this stage, intravenous epoprostenol therapy was considered not desirable because of increased risks of systemic emboli associated with indwelling catheter in the presence of intrapulmonary right to left shunting. Coiling of the PAVM's was considered not feasible due to the large number and small size of the diffuse PAVM's.

In the first month of dual therapy, the patient deteriorated with increased shortness of breath, more profound desaturation and a decline in exercise capacity (timeline shown in Fig. 2). Echocardiography did not show signs of deterioration of PAH or RV function, while NT-proBNP remained unchanged. There were no signs of pulmonary edema, intercurrent pneumonia or infection. The timing of deterioration matched the timing of an expected sildenafil effect, leading to the speculation that the deterioration might be due to increased right to left shunting due to a vasodilator effect of sildenafil in the PAVM's. In order to test this hypothesis we decided to perform a withdrawal and reintroduction trial of sildenafil. Withdrawal of sildenafil led to clinical improvement, reintroduction (4.5 months later) again led to clinical deterioration. At that moment sildenafil was stopped and not re-introduced (Fig. 2).

After these attempts to introduce sildenafil, the patient showed rapidly progressive disease, including progressive and profound hypoxemia, that did not respond to targeted therapy. He was therefore listed for urgent lung transplantation. While he was on the transplant list he was admitted at our pediatric intensive care unit, because of respiratory deterioration and profound hypoxemia. As rescue therapy, he was mechanically ventilated with nitric oxide 20 ppm. and continuous epoprostenol infusion was started. Treatment resistant hypoxemia with tcSO₂ down to 60% led to the acute installment of veno-arterial extra corporal life support (ECLS). After 11 days of ECLS, he died of massive pulmonary hemorrhage, 5 months after listing for lung transplantation.

Histopathologic evaluation of lung tissue, obtained at autopsy, showed both macroscopic and microscopic arteriovenous malformations. Furthermore, microscopic evaluation of lung tissue samples showed segmental capillary hyperproliferation, iron accumulation and segmental pulmonary venous obstruction, which are signs of pulmonary veno-occlusive disease (PVOD) including pulmonary capillary hemangiomatosis (PCH) (Figs. 3 and 4).

3. Discussion

PAH is a progressive disease, associated with a variety of conditions. In children, the majority of patients are diagnosed with idiopathic or heritable PAH, or PAH associated with congenital heart diseases [1]. Although there is still no cure for PAH, currently available PAH-targeted therapies are able to improve quality of life and survival. The here reported patient, however, showed an accelerated deterioration of clinical condition that co-occurred in time with the introduction of standard PAH-targeted therapy, leading us to question the initial diagnosis.

Our patient had a combination of PAH with PAVM's. PAH and PAVM's is a well-recognized combination in patients with HHT (Osler-Weber-Rendu disease). PAH associated with HHT is very rare in children (< 1% of pediatric PAH cases) [1]. HHT, is an autosomal dominant disease. Mutations in three different genes have been associated with HHT and PAH: ACVLR1 (or ALK1), ENG, and SMAD4 [2]. HHT is characterized by vascular abnormalities, such as mucocutaneous telangiectasia and visceral arteriovenous malformations (AVM's) mostly located in the lung, liver and brain [3]. PAVM's lead to direct blood flow from the pulmonary arteries to

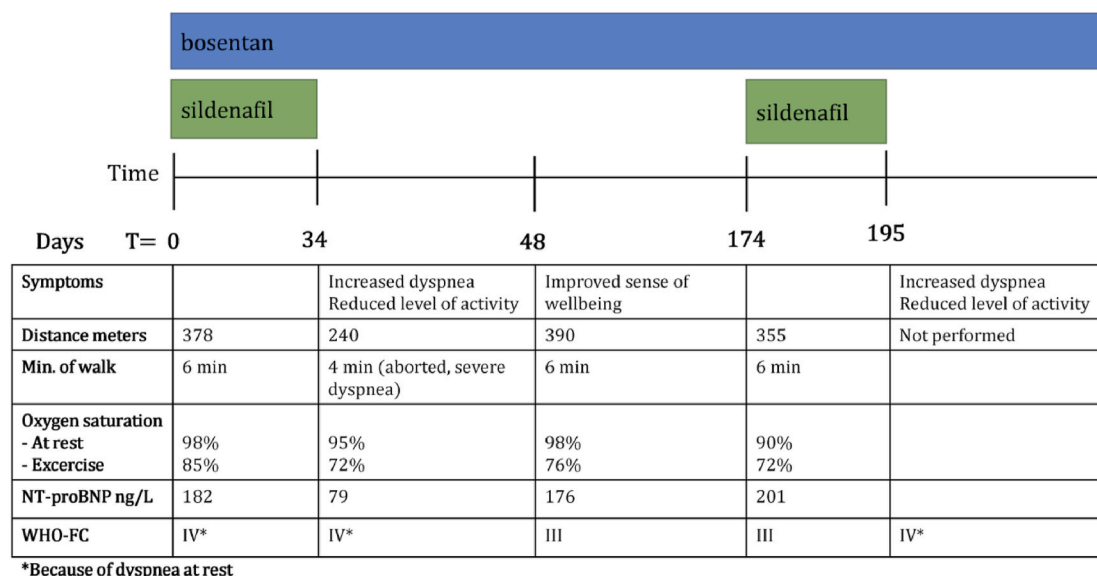


Fig. 2. Timeline. Course spanning 195 days.

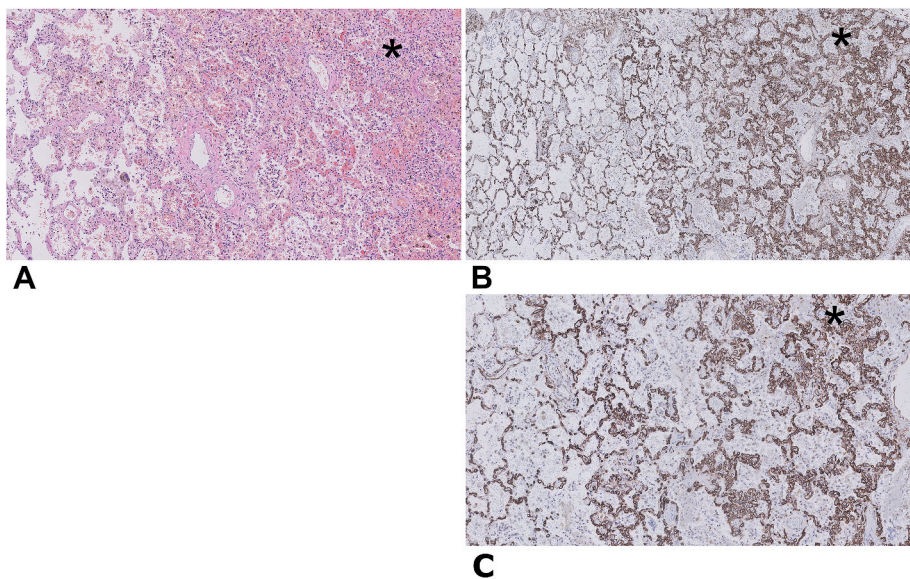


Fig. 3. Lung tissue showing segmental capillary hyperproliferation at the right side of the slides (asterisk), bordering more normal parenchyma at the left side of the slides (hematoxylin-eosin staining magnification 100x (A) and CD34 positive staining magnification 50x (B) and 100x (C)).

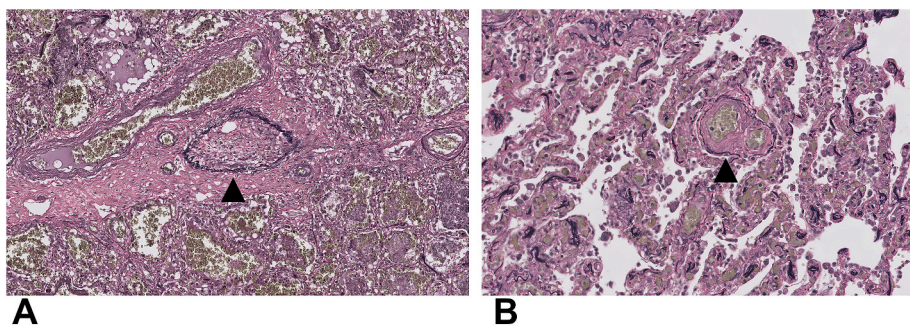


Fig. 4. Lung tissue showing pulmonary venous obstruction (arrowheads) within an interlobar septum (A, magnification 200x) and in parenchyma (B, magnification 200x).

the pulmonary veins, resulting in intrapulmonary right to left shunting [2]. Typical symptoms for PAVM's are dyspnea, cyanosis, clubbing, polycythemia and hemoptysis. In adults with PAH, the presence of PAVM's has been suggested to have a positive effect on survival, by reducing right ventricular afterload via chronic intrapulmonary right-to-left shunting [4]. However, the arteriovenous malformations in HHT can also lead to increased morbidity and mortality in PAH through rupture and hemorrhage, progressive cyanosis or embolisms causing strokes by right to left shunting [2,5]. HHT diagnosis is based on genetic testing or clinical diagnosis by the Curaçao criteria (presence of at least 3 of the following 4 criteria: (1) nosebleeds, (2) telangiectasia, (3) visceral telangiectasia or arteriovenous malformations, (4) first degree relative with HHT) [6]. In children, clinical diagnosis of HHT is difficult, since clinical criteria emerge and progress over the course of time and usually do not manifest before adulthood. In our patient only 1 Curaçao criterium was present (visceral arteriovenous malformations) without genetic mutations associated with HHT. As such HHT could not be confirmed in our patient.

Although systematic data on treatment of PAH with HHT is lacking [2], current treatment guidelines for PAH recommend similar treatment in these patients as in idiopathic PAH. In previously published case reports, positive effects of sildenafil and bosentan therapy in patients with PAH and HHT have been described, including a report on sildenafil therapy in a patient with PAH and hepatic AVM's and a report on bosentan in a patient with PAH and AVM's in the liver, pancreas and lungs as part of HHT. Both treatment regimens led to improved exercise capacity and hemodynamic parameters [7,8]. A third report described a patient with PAH and PAVM's on bosentan and sildenafil that eventually received a lung transplantation [4].

Our patient deteriorated on dual PAH-targeted therapy. We could not find support for our initial hypothesis that patients with PAH and PAVM's may respond adversely to pulmonary vasodilator therapy due to preferential dilatation and increased shunting of the PAVM's. Adverse response to pulmonary vasodilator therapy is well known in patients with PAH due to PCH/PVOD who develop pulmonary edema due to pulmonary vasodilatation [9]. Our patient however did not present with present with conclusive signs of PCH/PVOD and did not have relevant pulmonary edema to explain his clinical deterioration. His deterioration was characterized by

profound hypoxemia without signs of pulmonary edema, at which we considered PCH/PVOD to be unlikely. We were, at that time, not aware of the reported combined occurrence of PAVM's and PCH/PVOD.

PVOD is a rapidly progressive disease in which lung transplantation is often the only treatment option. In our patient the diagnosis of PCH/PVOD was confirmed not earlier than post-mortem, which is not unusual for PVOD. Presenting signs and symptoms of the disease are similar to those in patients with other forms of PAH. Specific results of lung function tests (disproportionately decreased carbon monoxide diffusion) or CT-imaging (subpleural thickened septal lines, centrilobular ground-glass opacities, and mediastinal lymphadenopathy) may direct to a clinical suspicion of PVOD, but is not always conclusive [10–12]. Histopathologic evaluation is often required to confirm the diagnosis. Since lung biopsies in patients with PAH are not advised due to high associated risks, this confirmation is mostly post-mortem or in explant lungs in case of lung transplantation for PAH. Current understanding is that PCH and PVOD both are entities of the same disease spectrum [13]. In our case, diagnostic work up, including lung function tests and CTA, did not direct us towards a diagnosis of PCH/PVOD. Furthermore our patient lacked pulmonary edema at clinical deterioration, which is typically present in PVOD. A literature search revealed that the coexistence of PCH/PVOD and PAVM's (either or not in the context of HHT) has been described in incidental case reports only. Two adults have been reported with macroscopic PAVM's and PCH/PVOD [13,14]. Of these 2 cases, one had confirmed HHT, the other did not. We report the first patient with a combination of macroscopic PAVM and PCH/PVOD presenting in childhood.

This rare case of PAH with PAVM and PCH/PVOD underscores the heterogeneity in underlying diseases causing PAH. It also illustrates that not all PAH patients may respond well to standard PAH-targeted therapy and an unexpected treatment response should alert the physician to question the original diagnosis and consider other rare (or unexpected combination of) diagnoses. In our case the presence of PAVM's modified the clinical picture in such a way that it was characterized by profound and progressive hypoxemia and not pulmonary edema, leading us away from the diagnosis of PCH/PVOD.

4. Conclusion

- Although scarcely described, in children PAH can present in the co-existence of PAVM's and PCH/PVOD.
- PAH with PAVM's and PCH/PVOD has a rapidly progressive and devastating disease course.
- In PAH associated with PAVM's and PCH/PVOD clinical deterioration and adverse response to pulmonary vasodilating treatment is characterized by profound and progressive hypoxemia without signs of pulmonary edema, the latter may cause PCH/PVOD to remain clinically unrecognized.

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Prior presentation

None.

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