Pulmonary Hypertension in a Patient with Hereditary Hemorrhagic Telangiectasia

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ABSTRACT

Hereditary Hemorrhagic Telangiectasia (HHT), also known as Osler-Weber-Rendu Disease, is an autosomal dominant genetic disorder that is characterized by the abnormal development of blood vessels. While the pathophysiology underlying the development of pulmonary hypertension (PH) in patients with HHT is not fully understood, it is believed to occur by one of two mechanisms: increases in pulmonary vascular resistance or cardiac output. In the following report, we describe an interesting case of a 26-year-old woman with HHT whose right heart catheterization initially demonstrated PH with elements of both pre- and post-capillary PH. Once the pre-capillary PH component was treated, however, an underlying high-normal cardiac-output state was unmasked.

KEYWORDS: arteriovenous malformation, pre-capillary pulmonary hypertension, post-capillary pulmonary hypertension

INTRODUCTION

Hereditary Hemorrhagic Telangiectasia (HHT) is a genetic disorder characterized by the development of telangiectasias in the skin, mucosa, and gastrointestinal tract.[1,2] Arteriovenous malformations (AVMs) may also develop in the central nervous system, liver, and lungs. Pulmonary hypertension (PH) develops in 1% of patients.[3–5]suggesting that alveolar capillary NO production is increased. We speculated that alveolar capillary NO overproduction might have a similar mechanistic role in the development of shunting vessels, arteriovenous malformations, in hereditary hemorrhagic telangiectasia (HHT). In the following case report, we describe a patient with HHT who presented with PH of unusual etiology.

CASE DESCRIPTION

A 26-year-old female with two months of progressive dyspnea presented with a six-day history of acutely worsening dyspnea on exertion, palpitations, and chest discomfort consistent with New York Heart Association Functional Class (NYHA FC) Three. Past medical history was notable for asthma and HHT with associated epistaxis, pulmonary AVMs status post embolization in 2012 to alleviate symptoms of exercise intolerance, and hepatic AVMs (**Figure 1**). There was no family history of HHT and the patient had not undergone any genetic testing. Hemoglobin level was 14.7 g/dL and thyroid function tests were within normal limits. Electrocardiogram demonstrated sinus rhythm with right-axis deviation, ST depressions in leads III and aVF, and diffuse T-wave inversions. CT angiography demonstrated pulmonary artery (PA) enlargement, an increase in cardiac size since February 2013, and previously noted pulmonary AVMs in the left upper and right lower lobes. No other AVMs were visualized. Mucosal telangiectasias were noted, but were believed to be insignificant clinically. Due to constraints on equipment availability at the

Figure Legend

The patient's hepatic AVM can be seen circled in the accompanying figure. Hepatic AVMs can reduce systemic vascular resistance, leading to increased cardiac output and blood flow through the pulmonary vessels. Over time, these changes can lead to high-output heart failure and remodeling of the pulmonary vasculature.

time of evaluation, the patient and staff mutually agreed to admit the patient overnight for evaluation of PH.

Transthoracic echocardiogram demonstrated moderate enlargement of the right ventricle (RV) associated with moderately decreased systolic function, interventricular septal flattening, right atrium enlargement, and dilation of the proximal PA with normal left ventricular function. The estimated PA diastolic pressure was elevated to at least 16 mm Hg, and the PA systolic pressure was elevated at an estimated 45.8 mm Hg. No prior echocardiography testing was available for comparison. Right heart catheterization (RHC) showed elevated mean PA pressure (PAP_{mean}) of 50 mm Hg and pulmonary vascular resistance (PVR) of 1160 dynes·s/cm^5 in the context of decreased cardiac index of 1.63 L/min/m^2 calculated via the Fick method (**Table 1**) and normal pulmonary artery wedge pressure (PAWP) of 8 mm Hg. Venous oximetry demonstrated an oxygen saturation "step-up" from the superior vena cava (56%) to the right atrium (74%), determined to be secondary to a left-right shunt through hepatic AVMs. The PA oxygen saturation was approximately 78-79%. The patient was started on tadalafil 40 mg daily. Repeat RHC performed five months later showed continued PVR elevation at 608 dynes·s/cm^5 and cardiac index of 3.11 L/min/m^2 calculated via the Fick method. The PA oxygen saturation at this time was 79.4%. Macitentan 10 mg daily was added, improving symptoms to NYHA FC One. Hemoglobin level was found to be 15.2 g/dL and thyroid function tests were within normal limits. Repeat transthoracic echocardiogram eight months after initial presentation showed reduced RV size, new RV hypertrophy, and reduced RV function consistent with the prior study. RV systolic pressure was estimated to be at least 54 mm Hg. PA systolic pressure can be equated with this value as there is no evidence of a RV outflow obstruction. PA diastolic pressure was not reported. There was insufficient tricuspid regurgitation to calculate RV systolic pressure at the patient's most recent transthoracic echocardiogram, which was conducted 20 months after initial presentation.

DISCUSSION

The pathophysiology underlying the development of PH in patients with HHT is believed to occur by increases in either PVR or CO, as demonstrated by the equation PAP_{mean} = (PVR*CO) + PAWP. RHC is the gold standard for the diagnosis of PH and yields information that is necessary to distinguish between etiologies.

In patients with hepatic AVMs, a reduction in systemic vascular resistance leads to increased CO and blood flow through the pulmonary vessels. Over time, progression of the intrahepatic shunt leads to elevated left-sided pressures, high-output cardiac failure, and remodeling of the pulmonary vasculature due to sheer stress.[5–7] Ultimately, these changes lead to what is known as post-capillary PH because of the increase in PAWP.[5,8] On RHC, these patients have elevated PAWP and CO with normal PVR. Management of these patients is aimed at limiting complications of high-output cardiac failure with diuretics and beta-blockers, but liver transplantation is the only definitive treatment.[6] While angiogenesis inhibitors, including bevacizumab and thalidomide, have emerged as potential alternatives to liver transplantation, data regarding their long-term efficacy and safety is lacking.[9] In contrast, the second mechanism underlying the development of PH occurs in patients with Type II HHT. A mutation in the gene *ACVRL1* causes the intima and media to proliferate throughout the pulmonary vasculature, leading to pre-capillary PH. These patients tend to be women in their 20s and 30s and have a poor prognosis.[10] RHC shows normal PAWP and low-to-normal CO with elevated PVR.[5,11]

Table 1. The patient's right heart catheterization hemodynamic parameters.

Parameter	Normal Values[17]	Test Result (RHC April 2015)	Test Result (RHC September 2015)
Hemoglobin	12-16 g/dL	14.7 g/dL	15.2 g/dL
Mean Right Atrial Pressure	0-8 mmHg	7 mmHg	8 mmHg
Right Ventricle Pressure	15-25/0-8 mmHg	75/5 mmHg	84/8 mmHg
Pulmonary Artery Pressure (Mean)	15-25/8-12 (16) mmHg	75/31 (50) mmHg	92/38 (59) mmHg
Mean Pulmonary Capillary Wedge Pressure	9 mmHg	8 mmHg	17 mmHg
Cardiac Output	5 L/min	2.90 L/min (via Fick method)	5.53 L/min (via Fick method)
Cardiac Index	2.8-4.2 L/min/m^2	1.63 L/min/m^2	3.11 L/min/m^2
Pulmonary Vascular Resistance	20-120 dynes·s/cm^5	1160 dynes·s/cm^5	608 dynes·s/cm^5
Superior Vena Cava Oxygen Saturation	70-80%	56%	Data not available
Right Atrium Oxygen Saturation		74%	Data not available
Pulmonary Artery Oxygen Saturation		78-79%	79.4%

The patient in this case exhibited features of both pre- and post-capillary PH. The initial RHC data revealed elevated PVR and low CI, which are suggestive of pre-capillary PH. Tadalafil therapy initiated shortly thereafter moderately improved systolic function and ameliorated the degree of RV enlargement.

Interestingly, however, after the pre-capillary PH component was treated, the patient was found to have an underlying high-normal CO and high PCWP. This feature is more suggestive of post-capillary PH and may be explained by the presence of hepatic AVMs.

It is not clear what led to this patient's features of both pre- and post-capillary PH. The large difference in the initial oxygen saturation between the SVC and right atrium suggest significant left-to-right shunting. Over time, as the amount of blood traveling through the shunt grew, and the patient's PVR rose, the patient's heart may not have been able to maintain its output, leading to decreases in CI and PCWP. By the time the patient presented, in fact, the disease was quite advanced.

In studies of sildenafil therapy in patients with pre-capillary PH, cardiopulmonary hemodynamics improved with treatment.[12] The exact mechanism of this is unknown.[13] It has been hypothesized that sildenafil may have similar effects as prostenoids and endothelin-1 receptor antagonists, which are believed to reverse the remodeling of the pulmonary vasculature.[14,15] On that basis, it is plausible that tadalafil may also exert these effects. Additionally, macitentan, an endothelin-1 receptor antagonist, has been shown to reduce morbidity and mortality in patients with pre-capillary PH. Macitentan was thus prescribed to optimize her treatment regimen.[16] Managing PH in patients with HHT is challenging. PH in these patients is clinically categorized as heritable (part of group 1 pulmonary arterial hypertension or PAH) and is treated with prostacyclins, endothelin receptor antagonists, and phosphodiesterase type 5-inhibitors. In patients who inadequately respond to monotherapy, combination therapy may be employed.[12] For patients with severe PAH intractable to medical management, lung transplantation is a last therapeutic option.

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