ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Pulmonary Hypertension Due to High-Output Heart Failure: Hereditary Hemorrhagic Telangiectasia

Yüksek Debili Kalp Yetersizliğine Bağlı Pulmoner Hipertansiyon: Herediter Hemorajik Telenjiektazi

ABSTRACT

Pulmonary hypertension (PH) is a complex disorder that should be managed with a multidisciplinary approach. Although most of the underlying causes of left heart disease can be easily diagnosed with cardiac imaging, some pathologies might necessitate careful investigation to go beyond the obvious. High-output heart failure (HF) due to arteriovenous malformation (AVMs) is an unnoticeable cause for HF and PH. Patients with hepatic AVMs should always be carefully evaluated with regard to hereditary hemorrhagic telangiectasia (HHT) since they can have multiple signs related to the other systems without any symptoms. In this case report, we discussed a patient who was initially diagnosed as PH associated with HF with preserved ejection fraction but eventually was found to have PH associated with high-output HF due to hereditary hemorrhagic telangiectasia (HHT, or Osler Weber Rendu syndrome) after detailed evaluation.

Keywords: Bevacizumab, hereditary hemorrhagic telangiectasia, high-output heart failure, Osler Weber Rendu, pulmonary hypertension

ÖZET

Pulmoner hipertansiyon (PH), multidisipliner bir yaklaşımla yönetilmesi gereken kompleks bir hastalıktır. Sol kalp hastalığının altında yatan nedenlerin çoğu kardiyak görüntüleme ile kolayca teşhis edilebilse de, bazı patolojiler bariz olanın ötesine geçmek için dikkatli araştırmayı gerektirebilir. Arteriovenöz malformasyonlara (AVM) bağlı yüksek debili kalp yetersizliği (KY), KY ve PH için fark edilmeyen bir nedendir. Hepatik AVM'leri olan hastalar, herhangi bir semptom olmaksızın diğer sistemlerle ilgili birden fazla bulguya sahip olabileceğinden, Herediter Hemorajik Telenjiektazi (HHT) açısından her zaman dikkatli değerlendirilmelidir. Bu vakada, yüksek debili KY ve bununla ilişkili olarak ortaya çıkan PH'ye sahip hastada ayrıntılı değerlendirme sonucunda HHT saptandı.

Anahtar Kelimeler: Bevacizumab, herediter hemorajik telenjiektazi, yüksek debili kalp yetersizliği, Osler weber rendu, pulmoner hipertansiyon

CASE REPORT
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Received: May 15, 2023
Accepted: July 8, 2023

Cite this article as: Kılıçkıran Avcı B, Soysal AU, Cerme E, et al. Pulmonary hypertension due to high-output heart failure: Hereditary hemorrhagic telangiectasia. *Turk Kardiyol Dern Ars.* 2023;51(7):493-497.

DOI:10.5543/tkda.2023.13614

Pulmonary hypertension (PH) is a complex disorder that requires a multidisciplinary approach for management. While most underlying causes of left heart disease can be readily diagnosed with cardiac imaging, some pathologies may necessitate thorough investigation to uncover less apparent issues. High-output heart failure (HF) due to arteriovenous malformation (AVMs) is a subtle but significant contributor to HF and PH. Patients with hepatic AVMs should always undergo careful evaluation for hereditary hemorrhagic telangiectasia (HHT), as they may exhibit multiple signs related to other systems without experiencing any symptoms themselves. In this case report, we discuss a patient who was initially diagnosed with PH associated with HF with preserved ejection fraction but was eventually found to have PH associated with high-output HF due to hereditary hemorrhagic telangiectasia (HHT, also known as Osler Weber Rendu syndrome) following a comprehensive evaluation.

Case Report

A 51-year-old woman with no history of chronic disease was referred to our cardiology clinic with the preliminary diagnosis of HFpEF-associated PH for further evaluation. Over the past 2 years, she had developed progressive dyspnea World Health Organization (WHO functional capacity-III), accompanied by palpitation and chest discomfort with exertion. Physical examination demonstrated the following: Tachycardia (110 beats/min), distended jugular veins, increased intensity of S2 heart sound, hepatomegaly,

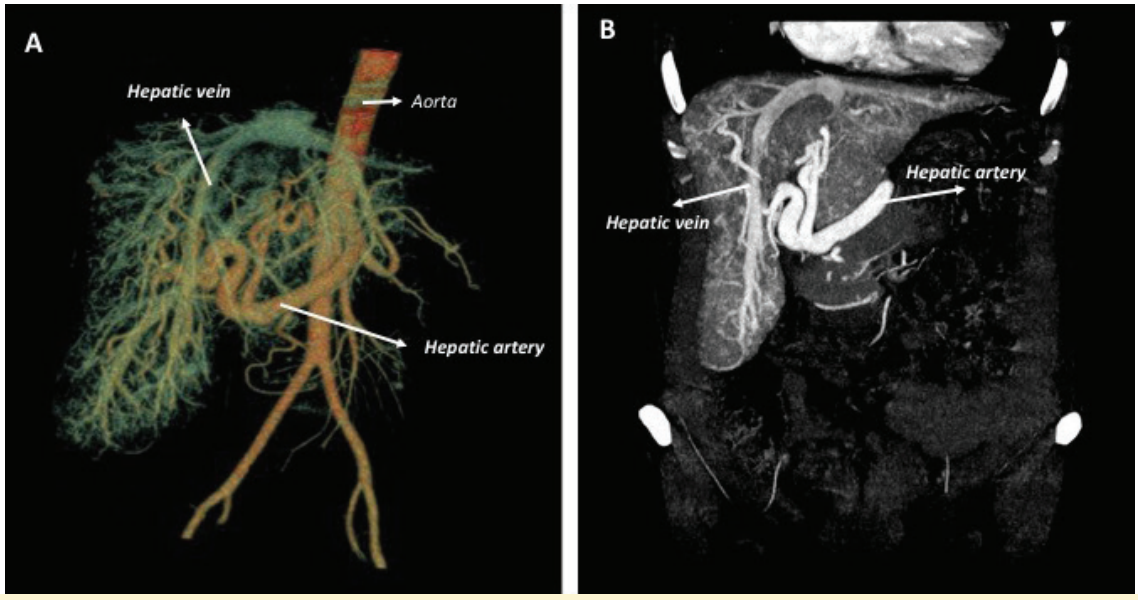

Figure 1. Hepatic arteriovenous malformations. Coronal oblique maximum intensity projection (A) and volume-rendered reconstruction (B) computed tomography images demonstrate dilated hepatic artery and branches with early enhancement of a hepatic vein in the arterial phase.

a continuous murmur on the epigastric area, and mild edema. There was neither cyanosis nor clubbing. She had never smoked or drank alcohol. Blood tests indicated mild iron deficiency anemia and elevated NT-proBNP levels (284 pg/mL). Renal, hepatic, thyroid functions, and viral serology were normal. ECG showed sinus tachycardia. Transthoracic echocardiography revealed preserved left and right ventricular systolic functions, Grade-2 left ventricular diastolic dysfunction, slightly enlarged left atrium, and right ventricle, and increased right ventricular systolic pressure of 45 mmHg. There was a mild mitral and tricuspid regurgitation. Pulmonary function test and ventilation-perfusion lung scan results were normal.

A pre-existing thorax computed tomography (CT) had revealed enlarged main pulmonary arteries with normal lung parenchyma. The hepatic artery and its intrahepatic branches were dilated.

ABBREVIATIONS

AVM	Arteriovenous malformation
CO	Cardiac output
CT	Computed tomography
ECG	Electrocardiography
FC	Functional capacity
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HHT	Hereditary hemorrhagic telangiectasia
LT	Liver transplantation
LV	Left ventricle
mPAP	Mean pulmonary artery pressure
PCWP	Pulmonary capillary wedge pressure
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
Qp	Pulmonary blood flow
Qs	Systemic blood flow
VEGF	Vascular endothelial growth factor
VM	Vascular malformation
WHO	World Health Organization

She underwent contrast-enhanced abdominal CT for further evaluation of possible arteriovenous fistula or other etiologies. It revealed a widely dilated celiac trunk and the subsequent hepatic arteries with an increased diameter of the hepatic vein (Figure 1). The liver was enlarged. There were no signs of portal hypertension.

Invasive angiography showed multiple arteriovenous malformations (AVMs) arising from renal arteries and celiac trunk to hepatic veins (Figure 2). A heart catheterization revealed left-to-right shunt (pulmonary to systemic flow ratio, pulmonary blood flow [Qp]/systemic blood flow [Qs]: 2.2) and increased cardiac output (CO) (9.6 l/min) with post-capillary PH findings (mean pulmonary artery pressure [mPAP]: 28 mmHg, pulmonary capillary wedge pressure [PCWP]: 22 mmHg, pulmonary vascular resistance [PVR]: 0.8 WU). Beta-blocker, mineralocorticoid receptor antagonist, and loop-diuretic treatment were started. A thorough examination of the skin revealed mucosal (lips) and facial telangiectasias (Figure 3). When asked, she gave a history of spontaneous episodes of epistaxis since her early childhood and reported having a sibling with a similar bleeding phenotype. Her further evaluation resulted in severe fibrosis in the liver (12.7 kPa) being detected through transient elastography (FibroScan). Upper gastrointestinal endoscopy demonstrated telangiectasias in the duodenal region. No varices were detected in the esophagus or fundus. Cranial magnetic resonance imaging did not show any cerebral AVMs. Contrast echocardiography was negative for pulmonary AVMs.

At the multidisciplinary meeting, she was considered to suffer from HHT based on having three out of the four Curaçao criteria (spontaneous, recurrent epistaxis, mucocutaneous telangiectasias, and hepatic AVMs) (Figure 4).[1,2] Although her sibling had similar episodes of recurrent epistaxis, the fourth criterion could not be met with certainty due to a lack of sufficient clinical details. It was stated that the fistulas in the patient could not be treated with percutaneous or surgical methods, and liver transplantation (LT) should be considered. Therefore, it was

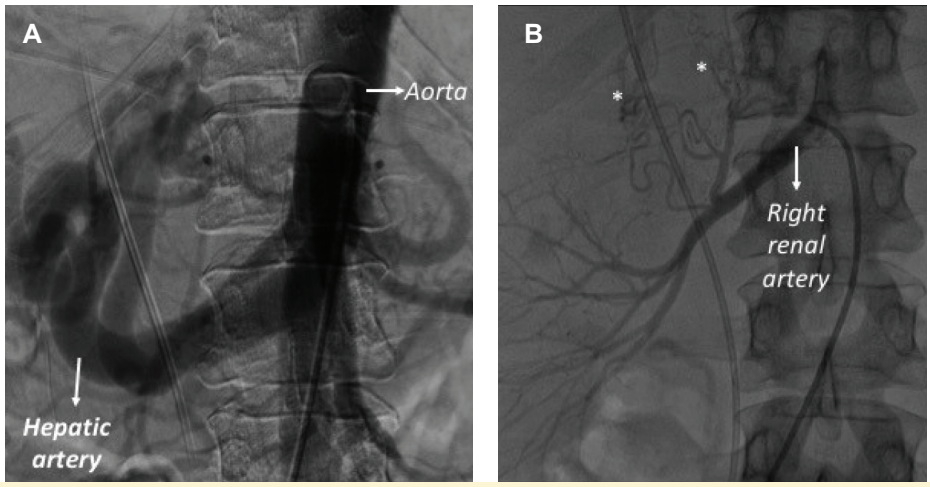

Figure 2. Invasive angiography shows tortuous, dilated hepatic artery (A) and right renal artery (B) to hepatic AVMs (*).

Figure 3. Flat red marks (black arrows) indicate telangiectasias on lips (A) and face and neck (B).

decided to start the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab, as a possible option before LT.

Following a period of time on bevacizumab (5 mg/kg, every 14 days for a total of 15 injections and then every 3–4 weeks as maintenance therapy), the patient showed a significant clinical improvement (WHO FC improved from III to I, palpitation, and chest discomfort subsided). The NT-proBNP level had decreased to normal (26 pg/mL). The need for diuretic treatment (40 mg/3 days in a week) was markedly reduced. At the 8th month of bevacizumab treatment, repeat right heart catheterization showed significant improvement in Qp/Qs to 1.6, mPAP to 18 mmHg, and PCWP to 11 mmHg. Repeat FibroScan revealed a decline in fibrosis grade (8.3 kPa).

CURAÇAO CRITERIA
I. Spontaneous, recurrent epistaxis
II. Telangiectasia at characteristic sites (mucocutaneous, face, lips, fingers, nose)
III. Visceral AVMs (pulmonary, hepatic, cerebral, spinal, gastrointestinal)
IV. A first degree relative with HHT
Three of the four criteria provide a definitive diagnosis of HHT, whereas two of the four criteria are considered as possible HHT (1,2)

Figure 4. Curaçao criteria.

Discussion

We presented here a patient with PH associated with high-output HF secondary to hepatic AVMs due to HHT.

High-output HF is an uncommon type of HF. These patients demonstrate hyper-dynamic states characterized by natriuretic peptide activation, increased plasma volume, elevated cardiac

filling pressures, and PH. The most common causes of high-output HF are cirrhosis, obesity, liver disease, and arteriovenous shunts.[3] Hyperthyroidism, beriberi, and severe anemia can also cause a high-output state that can easily be differentiated from other causes through chemical blood analysis.

A diagnosis of high-output HF may be missed in a person with no obvious diseases known to cause high output. This is especially true for AVMs. Without thorough history and physical examination, these patients are often considered to have HFpEF, as in the case of our patient. Indeed, in our patient, the lack of detailed examination caused the continuous murmur heard in the abdomen to be missed, and thus the diagnosis was overlooked on the first presentation. Given the patient's symptoms, increased NT-pro-BNP level, and signs of LV diastolic dysfunction on echocardiography, a diagnosis of HFpEF could easily be made and would provide an explanation for PH in this patient.[4] However, detecting a murmur in the epigastric area has been an important step on the path to diagnosis of complex intra-abdominal AVMs and, consequently, the diagnosis of PH due to high-output HF.

Diagnosis of diseases with multiorgan involvement often requires a multidisciplinary approach, as in this patient, which led to a definitive diagnosis of HHT. HHT is an autosomal dominant vascular disorder characterized by recurrent epistaxis, telangiectasias involving the skin and mucus membranes, and vascular abnormalities including AVMs that affect liver, lungs, and central nervous system.[1-3] All patients with HHT should be screened for pulmonary, hepatic, and cerebral AVMs.

HHT-associated liver vascular malformations (VMs) may appear in three different types of vascular shunting: Hepatic artery to hepatic vein, hepatic artery to portal vein, or portal vein to hepatic vein. The most common presentation of the hepatic artery to hepatic vein shunting is high output HF with secondary PH. Other VMs include arterioportal or venoportal shunt, which leads to portal hypertension and biliary or mesenteric ischemia.[1,2,5,6] HHT-related high-output HF could be worsened by anemia, which is also common in HHT patients.

PH is a less frequent complication of HHT and reported mainly as post-capillary PH in the context of a high-output state due to hepatic AVMs with the increase in PCWP and less frequently as pre-capillary PH with increased PVR with low to normal CO and normal PCWP related to mutations in endoglin or ALK-1 gene.[7,8] Heart catheterization is the diagnostic tool to differentiate these two types of PH. Treatment options differ regarding the type of PH in HHT. Our patient exhibited features of post-capillary PH.

Management of symptomatic hepatic AVMs involves limiting complications of high-output HF with diuretics, beta-blockers, and correction of anemia. Embolization of liver VMs is not recommended as it is associated with biliary ischemic necrosis and high mortality.[9]

LT is considered the only definitive curative treatment of HHT with symptomatic complications of liver VMs refractory high-output HF, complicated portal hypertension, or biliary ischemia.[2] Although LT reverses high-output state, perioperative and post-operative complications and the necessity of life-long immunosuppressive drugs limit its utilization as the standard therapy. VEGF, a proangiogenic cytokine, is significantly elevated in HHT. Systemic anti-angiogenic therapy with VEGF-inhibitor, bevacizumab, was found to have beneficial effects in reversing high-output state and reducing epistaxis frequency in HHT.[2,10-12] Nevertheless, there is no consensus on the duration of induction therapy and maintenance dosing. Our patient benefited significantly from bevacizumab treatment both clinically and hemodynamically. We could also show some improvement in the extent of fibrosis on FibroScan, which could most possibly be related to the decrease in liver congestion as a beneficial effect of bevacizumab.

Conclusions

High-output HF due to AVMs is an unnoticeable cause for HF and PH. Patients with hepatic AVMs should always be carefully evaluated with regard to HHT since they can have multiple signs related to the other systems (skin, cavities, gastrointestinal, pulmonary, or cerebral) without any symptoms. Multidisciplinary evaluation in experienced tertiary care centers is required for early diagnosis and proper treatment. Systemic bevacizumab seems to be a plausible treatment option in the case of high-output HF associated with HHT-induced hepatic shunting.

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.K.A.; Design – B.K.A., A.U.S., E.C.; Supervision – A.İ.H., M.C.A., Z.Ö.; Funding – None; Materials – B.K.A., E.C., O.A.K.; Data Collection and/or Processing – A.U.S., E.C., O.A.K., B.K.A.; Literature Review – B.K.A., E.C., A.İ.H., M.C.A., Z.Ö.; Writing – B.K.A., A.İ.H., M.C.A.; Critical Review – B.K.A., A.U.S.

Conflicts of Interest: No conflict of interest disclosure has been received from the authors.

Funding: The authors declared that this study received no financial support.

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