A Case of High-Output Heart Failure

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CASE PRESENTATION: A 55-year-old woman with a medical history of hereditary hemorrhagic telangiectasia (HHT) complicated by recurrent nosebleeds, severe blood loss anemia, hepatic arterial-venous malformation (AVM), pulmonary hypertension, and severe tricuspid regurgitation presented to the HHT specialty clinic with acute hypoxic respiratory failure (new 3-L O₂ requirement), weight gain, and volume overload. She was directly admitted to the pulmonary hypertension unit of our hospital. She had two recent admissions for similar symptoms thought to be due to worsening pulmonary arterial hypertension. In prior admissions, she had undergone right heart catheterization demonstrating mild pulmonary hypertension (pulmonary arterial pressure, 29 mm Hg, cardiac output by Fick 5.76, and cardiac index 3.22, mildly elevated pulmonary vascular resistance to 5.5 woods units). She would undergo diuresis with symptomatic improvement; however, after discharge she would rapidly develop recurrent heart failure symptoms. She reported compliance with guideline-directed medications, diuretics, and dietary restrictions and was still suffering severe symptoms. Notably she had previously elevated liver enzymes concerning for cirrhosis and had begun a workup to evaluate for causes of cirrhosis; she had a history of mild alcohol use, negative hepatitis viral serology, and no known history of liver disease.

Physical Examination Findings
Vital signs were significant for hypoxia (oxygen saturation 84% on room air) on admission, which required 3L oxygen, heart rate of 79 beats/min, and stable BP of 90/50 mm Hg. Examination was remarkable for small facial hemangiomas and no epistaxis. The patient had a significant amount of telangiectasias in oropharynx, around lips, and on ears. She had warm extremities, with an elevated jugular vein distention to the mandible, loud systolic 6/6 murmur at the third sternal border, diffuse crackles, and bilateral +2 pitting lower extremity edema. She appeared well but with some increased work of breathing with limited exertion. There was no known history of prior large or complicating AVMs, no history of recurrent hemoptysis, and no history of stroke.

Diagnostic Evaluation
Laboratory results on admission were remarkable for hyponatremia, with sodium 125 mg/dL, an acute kidney injury, with creatinine elevated to 1.34 mg/dL from baseline 1.1 mg/dL, hemoglobin 10.2 g/dL, and hematocrit of 32.2 g/dL stable from baseline; liver function normal, and an elevated NT-pro-B-naturetic peptide to 1,729 pg/dL. Chest imaging showed cardiomegaly, mild interstitial edema, and small pleural effusions (Fig 1). Cardiac echocardiography was remarkable for left ventricular ejection fraction 72% with a flattened septum consistent with right ventricular volume and pressure overload; the right ventricle was enlarged with right ventricular hypertrophy yet normal right ventricular function. There was severe, torrential tricuspid regurgitation with poor leaflet coaptation.
Given these findings, right ventricular systolic pressure was elevated and likely underestimated at 51 mm Hg. The inferior vena cava was dilated without respiratory collapse, and right atrial pressure was estimated at 15 mm Hg. Agitated saline showed a small right-to-left inter-atrial shunt consistent with small patent foramen ovale. Cardiac MRI showed similar findings, with normal left ventricular function and enlarged right chambers with septal straightening, severe tricuspid regurgitation, and an enlarged pulmonary artery consistent with pulmonary hypertension. No evidence of amyloidosis or local delayed enhancement was seen on MRI. Liver ultrasound was remarkable for hepatomegaly, dilated hepatic veins, dilated inferior vena cava, and dilated hepatic arteries with arteriovenous shunting physiology—all consistent with portal hypertension (Fig 3). She had not undergone genetic testing but had confirmed HHT based on meeting four out of four Curaçao criteria.

After several days of diuresis and attempted medical optimization, right heart cardiac catheterization showed elevated right-sided filling pressures (mean right atrial pressure, 24 mm Hg; right ventricular pressure, 63 mm Hg/10 mm Hg, with right ventricular end-diastolic pressure 24 mm Hg), severe pulmonary hypertension (pulmonary artery pressure mean = 40 mm Hg), pulmonary capillary wedge pressure 20 mm Hg, cardiac output by Fick (output 12 L/min; index 6.63), pulmonary vascular resistant 1.6 woods units, and also equalization of filling pressures with right atrial pressure, right ventricular end-diastolic pressure, and left ventricular end-diastolic pressure all 24 mm Hg. Initially there was concern for cardiac constriction or restriction given equalization of filling pressures on cardiac catheterization. She underwent repeat right heart catheterizations, each showing consistently elevated right-sided filling pressures and pulmonary hypertension.
Figure 3 – Grayscale, color doppler, and spectral doppler images pre-embolization. Large hepatic arteriovenous malformation, arterialized portal venous waveform.

What is the diagnosis?
**Diagnosis:** High-output heart failure in the setting of liver arterial venous malformations attributable to hereditary hemorrhagic telangiectasia

**Discussion**

Hereditary hemorrhagic telangiectasia is an autosomal dominant disease with prevalence of 1 in 5,000. Clinical manifestations are defined by vascular malformations (VMs) of skin and mucous membranes of the nose, GI tract, and within the brain, lungs, and liver; also associated is iron deficiency anemia due to bleeding malformations. Diagnosis is made by meeting three of four Curaçao criteria; thee Curaçao criteria are (1) epistaxis (with an epistaxis score of > 2), (2) multiple telangiectasias (>7 on examination); (3) internal lesions—GI, pulmonary, cerebral, or spinal AVMs; (4) family history. If not all Curaçao criteria are met, genetic testing can be obtained to confirm the diagnosis.

Genetic testing has become important in the care and management of patients with HHT and can be diagnostic in some instances. The most common genetic mutations are ENG, encoding endoglin associated with HHT-1, and ACRLV1 (ALK-1) associated with HHT-2. These genes encode endothelial cell trans-membrane proteins that are associated with receptor complexes for transforming growth factor-beta and cellular growth. The ALK-1 mutations are most commonly associated with hepatic complications. Recognition of common genetic mutations has allowed for the development of more targeted therapies directed toward the treatment of HHT.

Pulmonary arterial hypertension is a rare complication of HHT, with the most likely cause being high-output heart failure. High-output heart failure in HHT is due to hepatic AVMs; AVMs are created between the hepatic artery and portal vein, causing liver dysfunction. The mechanism of the development of high-output heart failure involves the shunting of blood from the hepatic artery to the hepatic vein, bypassing the liver and decreasing liver perfusion; this results in increased systemic oxygen demand as well as reactive decreased systemic vascular resistance. The decreased systemic vascular resistance as in classic cirrhotic portal hypertension causes sympathetic activation and activation of the renin-angiotensin-aldosterone system; resulting in increased cardiac output. Over time, increased venous return causes elevated right-sided pressures, increased pulmonary artery pressure, and ultimately elevated left-ventricular end-diastolic pressure and volume overload, causing heart failure and pulmonary hypertension. The high-output heart failure is due to peripheral hypoxemia rather than intrinsic cardiac pathology.

Hepatic vascular malformations occur in up to two thirds (40%-70%) of patients diagnosed with HHT and are most commonly associated with mutations in the ALK-1 gene. Diagnosis of these vascular malformations can be made by abdominal ultrasound with Doppler; CT scan and MRI also can be useful in characterizing AVMs. Although the presence of hepatic AVMs is relatively common in patients with HHT, these liver vascular malformations cause symptoms in 5% to 8% of patients. Complications of liver involvement of HHT include high-output heart failure, portal hypertension, and cirrhosis. The presence of large AVMs between hepatic artery and vein can cause left-to-right shunting, which results in increased cardiac output that can be worsened by iron-deficiency anemia, common in patients with HHT. Complications also can include portal hypertension due to shunting between the hepatic artery and portal vein and increased sinusoidal blood flow, which can lead to deposition of fibrous tissue and pseudo-cirrhosis; this can result in clinically significant portal hypertension with GI bleeding and hepatic encephalopathy. Typical features of hepatic involvement include hepatomegaly, liver bruise, and abnormal liver function. Patients with known HHT with any of these manifestations consistent with hepatic involvement should undergo diagnostic studies such as CT, MRI, Doppler ultrasound, or angiography to diagnose liver involvement.

Little research exists on the subject and history of liver involvement in HHT; it is known that the presence of liver AVMs is associated with increased morbidity and mortality. It has been shown that amongst patients with HHT and hepatic AVMs, 25% had a major vascular complication, and 5% died of a vascular complication. Complications included the development of high-output heart failure as well as atrial fibrillation due to atrial stretch.

Treatments for hepatic involvement in HHT had historically involved the symptomatic management of cirrhosis, portal hypertension, and hepatic encephalopathy and monitoring for symptoms and progression. This includes salt restriction, diuretics, catheter embolization of AVMs, vascular endothelial growth factor (VEGF) inhibitors, and ultimately liver
transplant. Catheter embolization, while used, is not generally recommended and can lead to an increase in mortality. However, in certain circumstances it can be used as a bridge to more definitive therapy.

Vascular endothelin growth factor inhibitors (VEGF-i) are targeted therapies that inhibit the progression of vascular malformations in HHT. As discussed, genetic mutations in HHT are found in genes encoding endothelial cell transmembrane proteins that are associated with receptor complexes for transforming growth factor-beta and cellular growth. Because of the mechanism of VEGF-i and HHT both involve cellular growth signaling, it has been proposed that VEGFs could help to prevent and slow vascular malformations in HHT. Previous therapies had been solely symptomatic based rather than preventative or curative. Treatment with VEGF-i therapy found that 80% of patients showed reduced cardiac output with bevacizumab therapy alone; this level of benefit had only been shown in patients undergoing liver transplantation. Patients also described symptomatic improvement and improvements in quality of life.

The role of bevacizumab and targeted therapies are to stabilize patients and reduce the extent, severity, and symptoms of AVMs to clinically stabilize patients as a bridge to definitive therapy of liver transplantation.

Clinical Course
Her hospital course was incredibly complicated after the diagnosis of high-output heart failure was made based on her cardiac index of 11 L/min/m² (greater than 4 L/min/m²), compared with her prior cardiac index of 3.22 L/min/m² several months before presentation.

She underwent a complete workup, including evaluation of common vitamin deficiencies and hematologic and endocrine causes of high-output heart failure. As above, she was noted to have mild right-to-left cardiac shunting on agitated saline study. She had a known history of cirrhosis and liver dysfunction. Liver ultrasound was remarkable for large AVMs and shunting physiology. Given these findings, high-output heart failure and symptomatic decompensation was thought to be caused by liver AVMs.

During her course, she became vasopressor dependent and was placed on inotropes because of worsening cardiac dysfunction. A multidisciplinary team of providers including specialists in pulmonology, gastroenterology, interventional radiology, and hematology was involved in the care of this complex patient to develop both short- and long-term care plans.

She underwent guided angiography of her common femoral system and superior mesenteric artery, and then embolization of several segments of her hepatic arteriogram and hepatic artery. Hepatic embolization is not typically recommended and can increase mortality, but in certain acute circumstances it is appropriate to improve symptoms and bridge to definitive treatment. The role of embolization was to temporize her largest hepatic AVMs to clinically stabilize her, improve her cardiac output, and allow discontinuation of vasopressor support. Several days after the procedure, she was clinically stable and all vasopressors and inotropes were discontinued. She underwent repeat cardiac angiography demonstrating similar findings as before, but she had clinically and symptomatically improved greatly.

During her hospitalization, she was also started on VEGF-I therapy, bevacizumab, to reduce proliferation of AVMs. She was clinically stabilized and discharged on bevacizumab infusions every 2 weeks, diuretics, and macitentan.

Her follow-up after finishing six doses of bevacizumab revealed clinical improvement. At that time, she underwent repeat right heart catheterization, which showed reduced cardiac index and reduced right-sided filling pressures.

Her severe tricuspid regurgitation was thought to be in the setting of pulmonary hypertension and high-output heart failure. For further medical optimization of her pulmonary hypertension and tricuspid regurgitation, she was evaluated by a multidisciplinary valve clinic for consideration for transvenous valve replacement; intervention was deferred so she was started on tadalafil in addition to her macitentan. She reported significant symptomatic improvement and was functional class I.

Clinical Pearls
1. Hereditary hemorrhagic telangiectasia is a rare autosomal dominant disease. Clinical manifestations include multi-organ vascular malformations (VMs) causing associated iron-deficiency anemia
2. Diagnosis of HHT is clinical, based on meeting at least three out of four Curaçao criteria. Genetic testing can be confirmatory and evaluate for mutations in endothelin and ALK-1.
3. **Pulmonary hypertension from high-output heart failure** occurs because of changes in systemic vascular resistance and hepatic remodeling, causing right ventricular overload.

4. **Hepatic involvement in HHT** is made by clinical signs and symptoms of liver dysfunction and then confirmed by Doppler ultrasound with evidence of shunting physiology.

5. **In patients with HHT and severe hepatic involvement**, infusion with bevacizumab has been shown to decrease cardiac output.

6. **Definitive management of hepatic involvement in HHT** is liver transplantation.

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**Suggested Readings**


