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Case Report

Early Signs of Cardiovascular Senescence in a Patient with Hereditary Hemorrhagic Telangiectasia

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SUMMARY

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant genetic disease with manifestations of epistaxis, mucocutaneous telangiectasias, and arteriovenous malformations of multiple organs, including the lungs, liver, and brain. It can also lead to fatal events such as high-output cardiac failure, respiratory failure, stroke, sepsis, and other hemodynamic complications. Therefore, early awareness of HHT is essential. We describe a 55-year-old man highly suspected of HHT with a rare initial presentation of atrial fibrillation (AF) and remarkable varicose veins at an unusually young age. AF occurring at a young age and refractory varicose veins caused by high-output heart failure might be a whistleblower for HHT, and early awareness may help diagnosis and appropriate management.

1. Introduction

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant genetic disease with key symptoms of arteriovenous malformations (AVMs), arteriovenous shunts, and telangiectasia. The prevalence, which is higher than previously thought, has revealed a wide geographic distribution of 1 in 5,000–8,000 in well-studied populations.[1] Multiple organs including the lungs, liver, gastrointestinal tract, brain, skin, and mucosa can be involved. Besides, among the deceased HHT patients, 26% died from heart failure.[2] HHT is diagnosed clinically based on the Curaçao criteria.[3] The management of HHT is symptomatic, but only pulmonary AVMs are worth actively treating.[3] Affecting 15 to 30% of HHT patients, pulmonary AVMs can lead to right-to-left shunts and cause hypoxemia and paradoxical emboli.[4] Embolization, which is recommended if amenable before symptoms present, requires early detection and long-term follow-up.[5]

With aging, the function of cardiovascular structure and protective systems decline. These predisposing factors contribute to the development of heart failure (HF) in which 50% of diagnoses and 90% of all death occur in the part of the population over age 70.[6] Cardiovascular aging also causes the commonest cardiac arrhythmia, atrial fibrillation (AF) and AF is related to a 5-fold increase in the stroke risk resulting in significant public health burden.[7] Besides, varicose veins are associated with aging and is reported to be a risk factor for HF.[8,9]

We describe a case of a patient with a rare initial presentation of young-onset AF, varicose veins, and high-output heart failure, which was finally diagnosed as HHT.

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2. Case report

A 55-year-old man presented with 2-week history of paroxysmal nocturnal dyspnea, orthopnea, and chest tightness. The patient has had recurrent epistaxis since childhood and atrial fibrillation with slow ventricular response since his late thirties, followed by hypertension, mild pulmonary hypertension (PH), and early-stage cirrhosis noticed several years later. His bradycardia soon became symptomatic and was well-managed with a pacemaker implantation. There was also a surgical history of sclerotherapy with conventional high ligation and ablation for refractory varicose veins (Figure 1A) related to cramping pain two years before this admission.

Physical examination findings were as follows: height, 163 cm; weight, 67.2 kg; body mass index, 25.2; body temperature, 36.7 °C; pulse rate, 60 beats/min; respiratory rate, 18 breaths/min; peripheral capillary oxygen saturation (SpO_2), 80%; blood pressure, 116/62 mmHg; clubbing fingers; bilateral leg edema; and diffuse crackles in both lungs. Laboratory findings showed a B-type natriuretic peptide level of 493 pg/mL, hemoglobin of 8.8 g/dL, and total bilirubin level of 4.1 mg/dL. Chest radiography revealed cardiomegaly, bilateral pulmonary congestion, and a right pleural effusion (Figure 1B). Gastric telangiectases were identified using esophagogastroduodenoscopy (Figure 1C). Several skin telangiectasia were observed in the chest wall and abdomen (Figure 1D). Hepatic venography and abdominal sonography revealed dilated hepatic veins (Figure 1E) and cystic lesions in the right lobe, which had been misdiagnosed as hepatic AVMs on color Doppler ultrasonography (Figure 1F). Echocardiography showed four dilated chambers, diastolic paradoxical septal wall motion, left ventricular ejection fraction of 40.5%, and systolic pulmonary artery pressure of 65 mmHg. The patient was intubated with mechanical ventilator support because of respiratory distress and severe hypoxia. Diuretics and vaso-

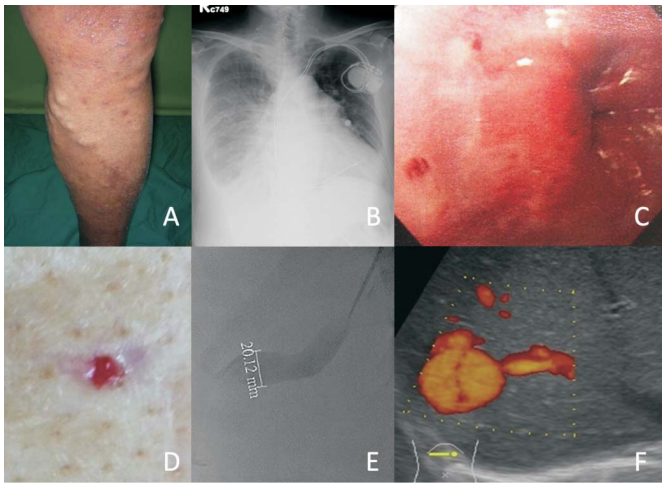

Figure 1. Clinical presentation. (A) Varicose veins in the lower limbs. (B) Chest radiography revealed cardiomegaly, pleural effusion, and a pacemaker. (C) Esophagogastroduodenoscopy showed gastric telangiectasias. (D) Skin telangiectasia. (E) An extremely engorged hepatic vein, measuring 20.12 mm in diameter. (F) A hepatic AVM with a dilated feeding vessel. AVM, arteriovenous malformation.

dilators were administered to treat acute decompensated HF with pleural effusion. Thoracocentesis confirmed a transudative pleural effusion.

High-resolution computed tomography showed dilated tortuous vessels in the peripheral lung field (Figure 2A). Albumin microbubble contrast echocardiography showed a grade 3 intrapulmonary shunt (Figure 2B).[10] Selective pulmonary angiography revealed prominent pulmonary AVMs in the bilateral lung fields (Figures 2C and D). Therapeutic embolization was performed by a radiologist. However, hypoxemia did not improve substantially after the procedure. Right heart catheterization was performed for hypoxemia, HF, and PH. The results were as follows: cardiac index, 6.46 L/min/m^2; pulmonary vascular resistance, 103 dynes.sec.cm^{-5} (1.29 Wood units); systemic vascular resistance, 294 dynes.sec.cm^{-5}; mean pulmonary arterial pressure, 39 mmHg; pulmonary artery wedge pressure, 25 mmHg; left ventricular end diastolic pressure, 24 mmHg; hepatic vein wedge pressure, 25 mmHg; and right atrium-hepatic wedge pressure gradient, 1 mmHg. The results excluded the existence of portal hypertension. The oxygen saturation was as follows: left ventricle 83%, inferior vena cava 66%, superior vena cava 65%, right iliac vein 70%, right atrium 60%, and right ventricle 56%. Based on the relatively high oxygen saturation in the right iliac venous blood, extremely low systemic vascular resistance, and refractory varicose veins, we concluded that the patient had extensive systemic (including lower limb) AVMs, which led to high cardiac output status.

HHT was confirmed based on the Curaçao criteria, although the patient's genetic background was unrelated to the mutations (such as *ENG*, *ACVRL1*, or *SMAD4*) known for HHT development. One month after admission, he died of septic shock.

3. Discussion

To the best of our knowledge, this is the first case report demonstrating varicose veins and AF at a young age as potential early signs of HHT. HHT is diagnosed based on the presence of at least three of the following four criteria: recurrent epistaxis, mucocutaneous telangiectasis, visceral telangiectasias or AVMs, and first-degree family history of HHT.[3] Our patient was confirmed to have HHT because of a history of recurrent epistaxis, cutaneous telangiectasis, as well as AVMs and telangiectasis of diffuse visceral involvement. Although related mutations were not found in our case, this did not preclude the diagnosis of HHT. Mutations that lead to HHT are under investigation, and some remain undiscovered.[3]

AF, the most common sustained arrhythmia, affects 1–2% of the people in the world, but only 0.5% of the affected population is under the age of 40 years. Studies on young-onset AF (under the age of 60 years) have suggested the subsequence of congenital heart disease and lone AF, which depict structural and electrophysiological abnormalities in the atrial substrate.[11] Several risk factors are associated with young-onset AF, including hypertension, smoking, obesity, and alcohol consumption, but our patient did not have these issues at the time.[11] The AF started in his late thirties and coexisted with structural heart disease, and the cause-and-consequence relationship created a pathophysiological cycle.[12] HHT-related insidious but growing AVMs, which gradually increase atrial wall stress, may have initiated and later perpetuated AF, which was followed by progressive heart dilatation. However, to the best of our knowledge, young-onset AF has not yet been reported as the initial presentation of an HHT patient.

PH was confirmed by right heart catheterization. Two types of PH have been found to relate to HHT in previous studies. Post-capillary PH is most commonly induced by high pulmonary blood flow that accompanies a high cardiac output, and precapillary PH is less frequently observed. In line with this fact, it's been reported that 26% of deceased HHT patients died from heart failure.[2] HHT-related gene mutations in *ENG* or *ACVRL1* seemed to be responsible for the development of precapillary PH.[13] Moreover, the expression of S-endoglin, an alternative isoform of the ENG gene, is associated with endothelial senescence and cardiovascular pathology related to age,[14,15] implying that early cardiovascular senescent presentation may be a potential sign of HHT, just like the case we reported. The present case is of post-capillary PH (pulmonary artery wedge pressure > 15 mmHg) caused mainly by a peripheral AVM-related hyperdynamic state and high cardiac output, which led to both right HF and left HF. Another factor that may further aggravate post-capillary

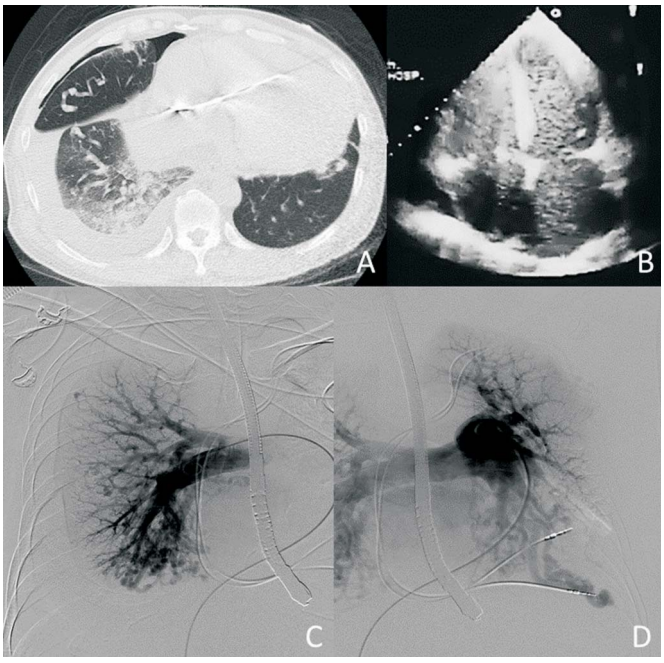

Figure 2. Intrapulmonary shunts. (A) Chest computed tomography revealing dilated tortuous vessels in the right peripheral lung field. (B) Albumin microbubble transthoracic contrast echocardiography showing intrapulmonary shunts. (C) Angiography of the right pulmonary artery and (D) left pulmonary artery illustrating multiple pulmonary arteriovenous malformations.

PH is longstanding AF and right ventricular pacing, which may result in left ventricular remodeling and diastolic dysfunction. HHT with pre-capillary PH can be easily stratified according to currently available risk-assessment tools,[16] followed by appropriate goal-oriented therapy; whereas there has been no good risk assessment tool in HHT with post-capillary PH. Therefore, early awareness of potential sequalae of HHT with post-capillary PH is probably the best strategy.

Varicose veins cause discomfort to our patient with unbearable swelling and cramping pain. This was an unusual event, especially in the absence of established risk factors, such as sex, older age, obesity, pregnancy and family history of varicose veins.[17] Elastin defects have been discovered among patients of HHT with specific mutations. However, little attention has been paid to varicose veins in the legs in patients with HHT, and further study is required. The first skin manifestation in our patient was refractory varicose veins, which was initially thought to be a consequence of increased right heart pressure and volume. Besides, we also found the skin telangiectasia in the trunk, which were not characteristic of the predominant HHT1 or HHT2 types but of the HHT5 variant, suggesting the involvement of growth differentiation factor 2 (GDF2) mutations.[18,19] After the eradication of varicose veins, hepatic AVMs and dyspnea progressed within one year. In fact, varicose veins may be a consequence of increased lower-limb AVMs, reflected by a relatively higher oxygen saturation in the iliac vein. It may be prudent to postpone surgery if peripheral AVMs can be detected early. Although the exact mechanism and treatment strategy for varicose veins in HHT have not yet been clarified, we may learn from studies on hepatic AVMs, showing that hepatic artery ligation or transcatheter therapeutic embolization is associated with high morbidity and mortality.[3,5] Prescription of bevacizumab, a vascular endothelial growth factor inhibitor, can reduce cardiac output and improve symptoms of dyspnea.[20]

4. Conclusion

Early awareness of the sequelae of HHT is important for avoiding substantial risks and mismanagement. This is the first reported case to demonstrate varicose veins and AF at a young age as potential early manifestations of HHT. Attention should be paid to patients who are susceptible to HHT, as an initial subtle presentation can have potentially poor outcomes.

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