Huge Pulmonary Arteriovenous Malformation, Venous Thromboembolism and Anticoagulation Treatment in a Patient with Hereditary Hemorrhagic Telangiectasia

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Abstract

Hereditary hemorrhagic telangiectasia (HHT) usually presents in association with pulmonary arteriovenous malformations (PA VMs). In addition, the incidence of venous thromboembolism tends to be increased in these patients. A 74-year-old female with HHT presented with cyanosis and hypoxemia. Contrast-enhanced multislice computed tomography (MSCT) revealed two left PA VMs and one in the right upper lobe. Both left PA VMs were treated with embolotherapy. Follow-up MSCT revealed an incidental pulmonary embolism in the right pulmonary branches. Deep venous thrombosis was confirmed and anticoagulation was initiated. Follow-up MSCT revealed the resolution of thromboembolism. Finally, embolotherapy was performed. This case illustrates the chronic adaptation to hypoxemia and adds further evidence to the relative safety of anticoagulation treatment in these patients.

Key words: hereditary hemorrhagic telangiectasia, pulmonary arteriovenous malformation, pulmonary embolism, anticoagulation, deep vein thrombosis, Osler Weber-Rendu disease


Introduction

Hereditary hemorrhagic telangiectasia (HHT, former Rendu-Osler-Weber syndrome) is an autosomal dominant disease affecting vascular regions. Its main clinical characteristics are epistaxis, mucocutaneous telangiectases and arteriovenous malformations (AVMs) in organs such as the lung, liver and brain. The clinical diagnosis was established based on the Curaçao Criteria (1). Genetically, HHT is characterized by mutations in Endoglin (ENG), ACVRL (Activin receptor like kinase type 1 -ALK-1-) and MADH 4 (SMAD 4). These genes codify for proteins involved in the transforming growth factor (TGF)-β receptor-signaling pathway which regulates angiogenesis (2).

Pulmonary arteriovenous malformations (PA VMs) are abnormal communications between the pulmonary veins and arteries, and are present in nearly half of all HHT patients (3). Approximately 80-90% of PA VMs are due to HHT and up to one third of such patients have clinical symptoms such as dyspnea, hemoptysis and platypnea. Right to left shunts explain most of the distal complications of PA VMs, such as paradoxical emboli presenting as transient ischemic attacks, stroke, brain abscess or migraine (4).

PAVMs can be simple, with one or more feeding arteries arising from the same segmental artery, or complex, with multiple feeders from different segmental arteries (5). Embolization is regarded as the treatment of choice and it is generally indicated when the diameter of the feeding artery is 3 mm or larger. In this scenario, the occurrence of brain
The incidence of thromboembolic disease is known to increase in HHT patients and can be associated with thrombus formation inside the AVMs or deep veins. The underlying mechanism of this association appears to be an augmented activity of factor VIII due to iron deficiency anemia (7, 8). Moreover, polycythemia due to hypoxemia might also increase the aforementioned risk. In this clinical setting, the decision regarding whether to start anticoagulation treatment or not is a clinical dilemma which requires careful judgment (8-10). Even though hemorrhagic complications of HHT can be life-threatening, anticoagulation is not usually contraindicated (8-10).

**Case Report**

A 74-year-old female who was diagnosed to have HHT after fulfilling the four Curaçao criteria was admitted to our hospital for evaluation. The diagnosis was based on her family history, mild epistaxis (Sadick Scale 1) (11), mucocutaneous telangiectases, and the presence of hepatic and pulmonary AVMs. A huge PAVM within the left upper lobe had been diagnosed 15 years before this presentation, but treatment had been discouraged at that time due to the risk of complications. Physical evaluation revealed telangiectases present in face, lips, tongue and fingers, distal cyanosis, tachycardia, a systo-diastolic murmur on left hemithorax and hypoxemia at rest [saturation level of oxygen in hemoglobin (SaO2) 74%]. Laboratory studies revealed polycythemia (hematocrit 47%) and iron deficiency. Magnetic resonance imaging (MRI) of the central nervous system revealed old silent ischemic images, but no AVMs.

Contrast-enhanced multislice computed tomography (MSCT) showed the presence of a huge PAVM within the left upper lobe, a smaller PAVM close to the latter and a third complex PAVM within the apical segment of the right lobe with two feeding arteries with a diameter of 6, 5 mm (Fig. 1). The main left PAVM had a single feeding artery measuring at 12 mm in diameter and a huge aneurysm that measured 90×88×74 mm with a thrombus inside. Successful embolotherapy using 10 and 18 mm Amplatzer vascular plugs of both left PAVMs was performed and thereafter pulse oximetry improved significantly (SaO2 94% at rest).

Three months later the patient was admitted for reevaluation. A new MSCT scan showed complete occlusion of the aneurysm sac and the adjacent PAVM. Surprisingly, the study revealed segmental and subsegmental pulmonary embolism (PE) in the right lung. A thrombus was present in the feeding artery of the upper right lobe (Fig. 2). The patient did not complain of any shortness of breath. Lower limb ultrasound revealed deep vein thrombosis (DVT) and the serum factor VIII levels were increased. Treatment with low molecular weight heparin was started and the factor anti-Xa levels were monitored. She remained in-hospital for a week so as to monitor any bleeding and/or embolic complications. After seven days of treatment, a new MSCT scan revealed the complete resolution of PE. Embolotherapy of the remaining right PAVM was then successfully performed. The patient was discharged thereafter was administered oral anticoagulation for six months. During this period she only presented with mild episodes of epistaxis that were treated with YAG laser cauterization. After six months, she underwent the last part of the required embolotherapy procedure. At that time, the upper lobe PAVM was adequately closed and the anticoagulation medication was stopped.

**Discussion**

This case highlights some interesting features regarding the pathophysiology of HHT and the clinical decision-making process in the management of these patients. Our patient presented with severe hypoxemia without any evident dyspnea, thus reflecting the chronic adaptation to hypoxemia in HHT subjects (12). Moreover, after successfully treating the left PAVM, she suffered a PE, which was fortunately asymptomatic. Paradoxically, HHT patients can sometimes demonstrate an improved oxygenation and exercise tolerance after the auto-embolization of PAVM (13). This interesting mechanism could partially explain why the patient...
Figure 2. A control CT scan after embolization of the bulky PAVM with a type II amplatzer. a) Sagittal MIP reconstruction. b) Axial MIP reconstruction. c) Sagittal Volume Rendering color reconstruction shows the complete occlusion of the large feeding artery and total thrombosis of the sac. d) Coronal MIP reconstruction of the same CT exam shows pulmonary embolism in the feeding artery of the PAVM in the right superior pulmonary lobe as an incidental finding.

This case also exhibits the complexity of thromboembolic events that these patients may suffer. It is unclear whether DVT and PE after embolotherapy might have been triggered by the intervention itself, but the patient did have increased levels of Factor VIII due to iron deficiency, which is a well-recognized thromboembolic factor in HHT. As PE was an asymptomatic finding after MSCT screening, we therefore could not be certain that it was the patient’s first episode. Moreover, even though the patient had no history of neurologic symptoms, the MRI findings suggested the possible presence of old silent strokes. The latter, if arising from previous DVT or PAVM, can possibly be further evidence of a probable hypercoagulable state.

Finally, this case also reflects a frequent scenario that clinicians often face while attending HHT patients. The presence of a thrombus in a PAVM exhibits the therapeutic dilemma of choosing between primary embolotherapy or anticoagulation. In the present case, the presence of PE and DVT motivated our preference for anticoagulation. Even though we could have performed embolotherapy of the right-upper lobe fistula to prevent a stroke before anticoagulation, this was precluded by the fact that such a procedure could have potentially induced thrombus migration. Although anticoagulation is not contraindicated in patients with HHT, it must be managed very carefully. Since this patient had only mild epistaxis, we were therefore encouraged to start anticoagulation. Furthermore, we decided to perform laser photocoagulation in order to increase the safety and comfort of our patient.

In summary, valuable information regarding the chronic adaptation to hypoxemia, diverse thromboembolic pathways and evidence of anticoagulation safety among HHT patients was obtained by the case presented herein. HHT patients with severe complications should therefore be managed after expert consultation.

The authors state that they have no Conflict of Interest (COI).

References
4. Angriman F, Ferreyro BL, Wainstein EJ, Serra MM. Pulmonary arteriovenous malformations and embolic complications in patients...


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