PULMONARY HYPERTENSION IN A GERIATRIC PATIENT WITH ANEMIA FROM HEREDITARY HEMORRHAGIC TELANGIECTASIA: CASE REPORT

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Abstract

Introduction: Hereditary Hemorrhagic Telangiectasia (HHT) is a rare autosomal dominant disorder causing mucocutaneous telangiectasia and arterial-venous malformations (AVMs) in various organs. Pulmonary AVMs cause right-to-left shunting, causing hypoxemia, paradoxical embolisms, and other complications. In contrast, hepatic AVMs can result in high-output heart failure due to the left-to-right shunting. About 10% of HHT patients develop pulmonary arterial hypertension (PAH), caused by small artery remodeling leading to elevated vascular resistance. This case report describes a 74-year-old woman with HHT as the cause of pulmonary hypertension, right heart failure, and anemia.

Case presentation: A 74-year-old female hospitalized at Internal Medicine due to a two-week history of dyspnea, edema of the inferior sides, and recurrent spontaneous epistaxis. On physical examination, we found telangiectasias on her hands and ears. The patient previous medical history included HHT, diabetes mellitus type 2, arterial hypertension, and chronic atrial fibrillation untreated for the last 10 days due to epistaxis. Laboratory results revealed anemia with hemoglobin at 7 g/dL, altered liver tests, elevated D-Dimer and NT-proBNP. Echocardiography showed a normal left ventricular function (FE 61%), dilated right heart chambers, tricuspid regurgitation, and PAP of 60 mmHg, abdominal ultrasound revealed dilated hepatic veins and portal vein measuring 16mm (7-13mm). These findings raise the suspicion of pulmonary thromboembolism, which was ruled out. Pulmonary arterial hypertension and signs of right heart failure resulted from HHT, which improved under diuretic therapy, and topical treatment for epistaxis.

Conclusion: This case highlights the complex and intricate multiorgan complications of HHT, such as anemia from recurrent nosebleeds and right heart failure brought on by elevated pulmonary artery pressures. Management in geriatric patients with HHT requires careful consideration of comorbidities such as atrial fibrillation and pulmonary embolism, particularly concerning anticoagulation strategies and bleeding risks associated with the respective treatments.

Keywords: hereditary hemorrhagic teleangioectasia, pulmonary hypertension, hepatic arteriovenous malformation.

HIPERTENSIONI PULMONAR NË NJË PACIENT GERIATRIK ME ANEMI NGA TELEANGIOEKTAZIA HEMORAGJIKE HEREDITARE

Abstrakt

Hyrje: Teleangioektazia Hemoragjike Hereditare (THH) është një çrregullim gjenetik autosomal dominant që shkakton teleangioektazi mukokutane dhe malformacione arterovenoze (MAV) në organe të shumta. MAV pulmonare shkaktojnë shunte gjaku djathtas-majtas, duke sjellë hipoksemi, emboli paradoksale dhe ndërlikime të tjera. Nga ana tjetër, MAV hepatike mund të prodhojnë insuficiencë kardiake me debit të lartë për shkak të shunteve të gjakut majtas-djathtas. Rreth 10% e pacientëve me THH zhvillojnë hipertension arterial pulmonar (HAP), për shkak të rimodelimit të arterieve të vogla duke çuar në rritje të rezistencave vaskulare. Ky rast klinik përshkruan një grua 74 vjeçare me THH, si shkaktare e hipertensionit pulmonar, insuficiencës kardiake të djathtë dhe anemisë.

Prezantimi i rastit: Pacientja 74 vjeçare shtrohet në shërbimin e Mjekësisë Interne, për shkak të historisë dy javore me dispne, edema të anësive inferiore dhe episodeve rekurrente te epistaksis spontan. Në ekzaminimin fizik u gjendën teleangioektazi në pëllëmbët e duarve dhe në veshë. Në historikun mjekësor të pacientes përfshihej THH, diabeti mellitus tip 2, hipertensioni arterial, si dhe fibrilacioni atrial kronik i pa trajtuar në 10 ditët e fundit për shkak të epistaksisit. Analizat laboratorike treguan anemi me hemoglobinë 7g/dL, testet e funksionit hepatik të alteruara, D-Dimer dhe NT-proBNP të rritura. Ekokardiografia tregoi funksion sistolik ventrikular në normë (FE 61%), dhomat e djathta të zemrës të dilatuara, regurgitim trikuspidal, dhe PsAP=60 mmHg. Ekografia abdominale tregoi vena hepatike të dilatuara dhe vena porta me madhësi 16mm (7-13mm). Këto gjetje ngritën dyshimin për tromboemboli pulmonare që u përjashtua. THH rezulton të jetë shkaku i hipertensionit arterial pulmonar dhe insuficiencës kardiake të djathtë, që u përmirësuan me terapinë me diuretike. U aplikua edhe terapia topike për epistaksisin, terapia për diabetin dhe aneminë.

Konkluzione: Ky rast vë në dukje komplikacionet e ndërsjella dhe komplekse të THH, si anemia prej epistaksisit rekurrent dhe insuficienca kardiake e djathtë e shkaktuar nga rritja e presioneve në arteriet pulmonare. Menaxhimi i pacientëve geriatrikë me THH ka nevojë për marrjen në konsideratë të bashkësëmundshmërive si fibrilacioni atrial dhe embolitë pulmonare, veçanërisht për sa i përket antikoagulimit dhe rrezikut për gjakrrjedhje të shoqëruar me trajtimet përkatëse.

Fjalë kyçe: teleangioktazi hemoragjike hereditare, hipertension pulmonar, malformacion arteriovenoz hepatik.

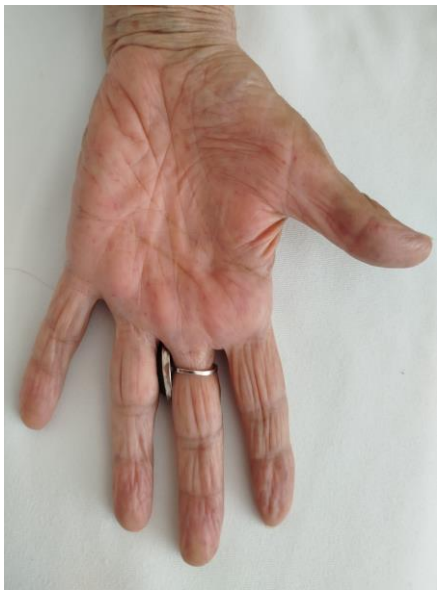
Introduction

Hereditary hemorrhagic telangiectasia (HHT) and pulmonary hypertension (PH) are apparently very different diseases that both affect the pulmonary vascular system. HHT, also known as Rendu-Osler-Webber syndrome, is a rare autosomal dominant disorder causing mucocutaneous telangiectasias and arteriovenous malformations (AVMs) in various organs, which are direct deviations between arteries and veins that lack a capillary bed (1). Pulmonary AVMs cause right-to-left shunting, causing hypoxemia, paradoxical embolisms,

and other complications (2). In contrast hepatic AVMs can result in high-output heart failure due to the left-to-right shunting (1). PH, a typical high-resistance vascular condition that can lead to heart failure, is defined as an increase in mean pulmonary arterial pressure greater than 25 mmHg. About 10% of HHT patients develop pulmonary arterial hypertension (PAH), caused by small artery remodeling leading to elevated vascular resistance (3). In the context of pulmonary vascular diseases, HHT presents an interesting paradoxical situation, where lung involvement can be characterized by pulmonary AVM and PH, which are low-resistance and high-resistance vascular states, respectively.

Case presentation

A 74-year-old female hospitalized at internal medicine department due to a two-week history of dyspnea, edema of the inferior sides, and recurrent spontaneous epistaxis. On physical examination, we found telangiectasias on her hands and ears (Fig. 1,2).



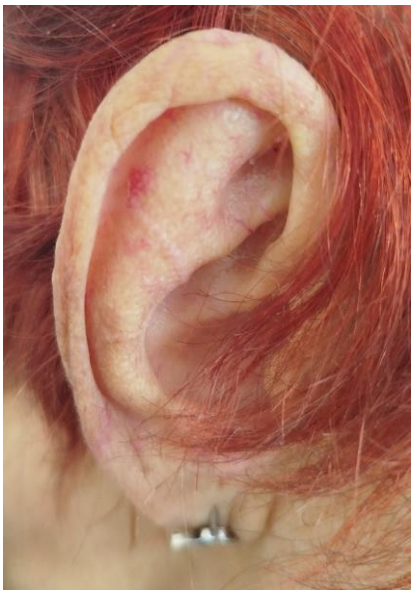


Figure 1. Telangiectasia of the hand

Figure 2. Telangiectasia of the ear

The patient previous medical history included HHT, diabetes mellitus type 2, arterial hypertension, and chronic atrial fibrillation untreated for the last 10 days due to epistaxis.

The laboratory tests performed during hospitalization are summarized in Table 1.

Table 1. Laboratory tests

Laboratory tests	Values	Reference range
RBC (mln / uL)	2.50	4-5.6
Hgb* (g/dL)	7.0	12.1-15
HTC (%)	22.3	37-46
Reticulocytes (<20)	15	
Ferritine (ng/mL)	15.65	5-204
TSH (mU/L)	3.898	0.35-4.94
FT4 (ng/dL)	0.85	0.7-1.48
Uric Acid (mg/dL)	10.5	1.6-6
Blood nitrogen (mg/dL)	46.1	21-43
Total bilirubin (mg/dL)	1.92	0.3-1.2
Direct bilirubin (mg/dL)	1.11	0.1-0.5
AST / SGOT (U/L)	37	5-34
NTproBNP (< 125 pg/mL)	3567.70 pg/mL	< 125
D-dimer (< 0.5 ug/mL)	2.37 ug/mL	< 0.5
* *During hospitalization the patient was given 3 blood transfusions. On discharge Hgb = 9.9 g/Dl*		

Echocardiographic examination showed a severely dilated (basal diameter 50 mm) and hypokinetic right ventricle (TAPSE 10 mm) with severe pulmonary hypertension (PAP >60 mmHg), dilated left atria and a nondilated left ventricle with preserved systolic ejection fraction.

Abdominal ultrasound (not shown) revealed blunt liver edge and dilated hepatic veins and dilated portal vein measuring 16 mm (normal range of 7-13 mm) with blood flow velocity of 9.7 cm/sec (normal value: 19.3 cm/s), suggestive of hypertension portal and it was found the presence of a vascularized lesion which showed multiple dilated peripheral vascular channels, with a flow pattern similar to portal venous flow. No abdominal fluid (ascites) was present, and other abdominal organs were without pathological alterations.

In order to determine the nature of the vascularized hepatic lesion, a contrast-enhanced CT scan of the liver and bile ducts was performed, which revealed a well-defined lobulated isodense lesion with a hypodense center surrounded by multiple dilated tortuous vascular channels in the periphery of the lesion which follow similar contrast enhancement pattern as that of the portal vein in all the phases, with contrast opacification of the portal vein and its branches in the arterial phase, due to arterio-portal shunting (Fig. 3).

Cardiac echo, high d-dimer and atrial fibrillation not regularly treated due to repeated hemorrhagic phenomena, raise the suspicion of pulmonary thromboembolism, which was ruled out with angio-CT. Pulmonary hypertension and signs of right heart failure resulted from HHT, which improved under diuretic therapy. After the hemorrhage was stopped with supportive treatment including pressure, packing without necessity of cauterization in our patient, and anemia was corrected with hemotransfusions and iron supplements were started, it was decided to start anticoagulation with a reduced dose due to the high hemorrhagic risk presented by the patient.

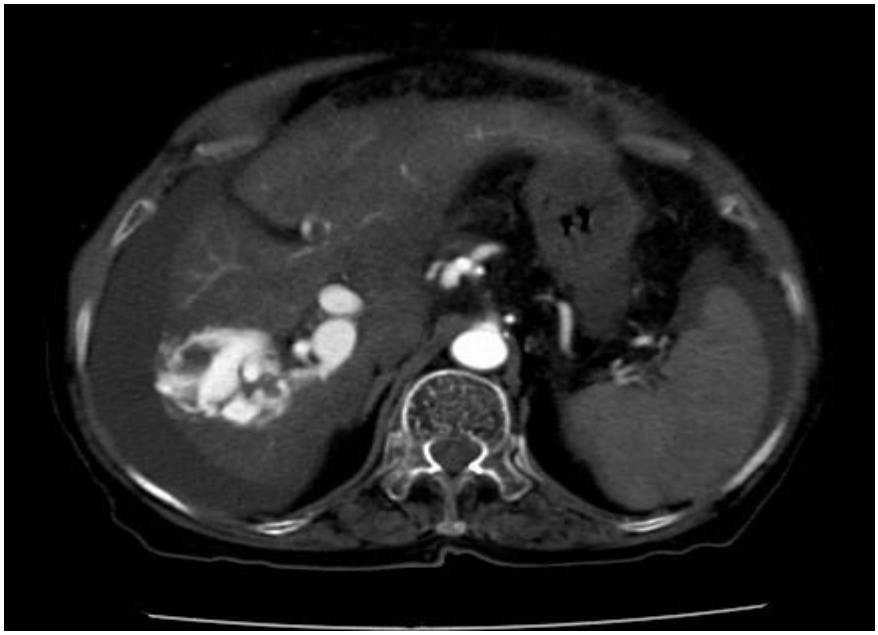


Figure 3. CT Scan in arterial phase

Discussion

HHT is a genetically heterogenous disorder that presents with a series of vascular defects throughout the body. On the molecular level HHT is caused by mutations that affect the TGF-β signaling pathway, which plays a crucial role in vascular development. There are two main mutations, comprising up to 96% of "classic HHT" cases, producing two main forms of the disease. Heterozygous mutations in endoglin (ENG; HHT1) or Activin A receptor type 1-like (ACVRL 1, encoding ALK1; HHT2), which encode transmembrane receptors that, in cooperation with an additional receptor such as BMPR2, bind to soluble bone morphogenetic protein (BMP) ligands to activate transcriptional responses within endothelial cells (4,5). The cellular response to this signal may include both effects on endothelial cell migration, but also the proliferation and recruitment of smooth muscle cells that prevent AVMs (5). HHT predominantly affects the Caucasian population, with a wide geographic distribution, which can also be found in Asiatic, African and Arabic populations. The worldwide prevalence of HHT ranges from 1:5000 to 1:10000 individuals (6). The clinical diagnosis of HHT is based on the Curacao criteria, which include epistaxis, telangiectasia, visceral lesions, and family history. Visceral lesions may occur in the gastrointestinal, pulmonary, hepatic, spinal, or cerebral organs (1). Our patient, in addition to cutaneous hemorrhagic phenomena and epistaxis, she also had a positive and significant family history for HHT (father, daughter, uncle, and cousin).

PH is part of a heterogeneous group of chronic, progressive hemodynamic disorders with different etiologies, characterized by an increase in arterial pressure in the pulmonary artery, which over time can lead to dysfunction of the right side of the heart. The most accurate way of determining PH is between the catheterization of the right side of the heart with an average pulmonary arterial pressure > 20 mmHg at rest (7). PH, in contrast to HHT, has multiple underlying causes. According to the latest ESC/ERS guidelines, pulmonary hypertension is divided into 5 groups distinguished by hemodynamics and the location and type of

pulmonary vascular lesions that cause elevated pressure: Group 1-pulmonary arterial hypertension; Group 2-PH due to left heart disease; Group 3-PH due to lung disease or hypoxia; Group 4-chronic thromboembolic PH); and Group 5-PH due to unclear multifactorial mechanisms (8).

In patients with HHT, PH has been considered primarily to be group 1 (pulmonary arterial hypertension), which is characterized by increased dilatation and vasoconstriction in the pulmonary vascular bed leading to a state of high resistance, low cardiac output, and right heart failure (9). According to genetic concepts, the presence of PAH in patients with HHT is explained by heterozygous mutations in BMPR2, which acts in the same pathway as ACVRL1 and ENG, which account for more than 70% of inherited PAH and 20% of idiopathic PAH (10).

It remains unclear how disruption of the same signaling pathway leads to different phenotypes of dilated pulmonary AVMs (HHT) and proliferative obliterative vasculopathy (PAH).

In patients with HHT, systemic AVMs, particularly in the liver, may cause a state of increased cardiac output leading to increased flow through the pulmonary circuit, elevated pressures, and group 2 PH, or pulmonary venous hypertension (PVH) (11). Liver AVMs can be present in up to 75% of patients with HHT but manifest with clinical signs and symptoms in less than 10% of patients. These AVMs can vary in type depending on the combination of vessels involved in the shunts. Hepatic AVMs can result in three patterns of shunting: hepatic arteries to hepatic veins, hepatic arteries to portal veins, and portal veins to hepatic veins (12). Hepato-portal AVMs can result in portal hypertension and potentially hepatic encephalopathy, although this is extremely rare. Common manifestations of hepatic AVMs include hepatomegaly, auscultatory sounds such as bruits due to the turbulent blood flow in the shunts, and altered liver function tests (11, 12).

HHT appears to be the root cause of the pulmonary hypertension and right heart failure. HHT patients even at relatively young ages have an increased risk of thromboembolic events, in the form of deep vein thrombosis and pulmonary embolisms, despite inflammation not being a prominent disease feature (13, 14). It is believed this result from increased levels of coagulation factor VIII, probably caused by the low levels of iron (15). The findings of the cardiac echo, together with elevated d-dimer levels and atrial fibrillation (untreated due to hemorrhagic phenomena) raised concern for a pulmonary embolism, which in our patient was ruled out through an angio-CT scan. At our patient was excluded the presence of underlying hyperthyroidism, because it should be taken into consideration in patients with pulmonary hypertension, especially in those with high cardiac output, as hyperthyroidism causes systemic vasodilation and increases metabolic demands (16). In our case, since there is a lack of detailed hemodynamic information and relevant genotype data necessary to determine genotype/phenotype correlations to generate mechanistic hypotheses regarding the underlying causes of PH and HHT, based also on hepatic AVMs present in abdominal CT angiography, it was considered PH group 2. The presence of PH, regardless of etiology, is a poor prognostic indicator of disease, including HHT (17). Given the multifactorial etiology of PH in HHT and the distinct prognostic and therapeutic implications of different PH groups, it is important to consider a complete hemodynamic profile in HHT patients with PH. Another discussion during the treatment of our patient was the necessity of using anticoagulation due to atrial fibrillation and active hemorrhagic phenomena (epistaxis). While guidelines do not

contraindicate the use of anticoagulants in HHT patients, there is a fine balance to be found between anticoagulation strategies and bleeding risks associated with the respective treatments and prevention of thromboembolic events. Hence, despite guidelines non contraindicating anticoagulation, decisions must be personalized to fit each patient's unique medical circumstances in a case-by-case basis (1). Thus, after the hemorrhage was stopped with supportive treatment including pressure, packing without necessity of cauterization (18) in our patient, and anemia was corrected with hemotransfusions and iron supplements were started, it was decided to start anticoagulation with a reduced dose due to the high hemorrhagic risk presented by the patient.

Conclusion

This case highlights the complex and intricate multiorgan complications of HHT, such as pulmonary hypertension with different mechanisms and right heart failure brought on by elevated pulmonary artery pressures, or anemia from recurrent nosebleeds. Other potential complications include: strokes, cerebral abscesses, and VTEs. Management in geriatric patients with HHT requires careful consideration of comorbidities such as atrial fibrillation and pulmonary embolism, particularly concerning anticoagulation strategies and bleeding risks associated with the respective treatments. HHT is a quintessential internal medicine condition, requiring a holistic and multidisciplinary understanding and approach, which places the internal medicine specialist in the ideal position for its management.

Conflict of interest: None

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