# Complex Intrahepatic Vascular Shunts in Hereditary Hemorrhagic Telangiectasia: From Portal Hypertension to High-Output Cardiac Failure

## Shunts Vasculares Intra-hepáticos Complexos na Telangiectasia Hemorrágica Hereditária: Da Hipertensão Portal à Insuficiência Cardíaca de Alto Débito

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## Abstract:

Hereditary haemorrhagic telangiectasia (HHT) is a rare autosomal dominant vascular disorder that may involve the liver through complex intrahepatic vascular malformations. We report the case of a 64-year-old man with genetically confirmed HHT type 2 who developed symptomatic hepatic vascular shunts, complicated by clinically significant portal hypertension, recurrent gastrointestinal bleeding, and high-output cardiac failure. The patient was treated with supportive measures and antiangiogenic therapy with bevacizumab, resulting in transient clinical and hemodynamic improvement. However, disease progression was marked by refractory ascites, variceal bleeding, severe malnutrition, sarcopenia, and progressive frailty, ultimately limiting therapeutic options, including liver transplantation. This case illustrates the heterogeneous clinical expression of hepatic involvement in HHT, the potential benefits and limitations of bevacizumab therapy, and highlights the impact of frailty and nutritional deterioration on clinical decision-making and prognosis.

**Keywords:** Hypertension, Portal; Liver Diseases; Telangiectasia, Hereditary Hemorrhagic.

## Resumo:

A telangiectasia hemorrágica hereditária (THH) é uma doença vascular rara, de transmissão autossómica dominante, que pode envolver o fígado através de malformações vasculares intra-hepáticas complexas. Apresentamos o caso de um homem de 64 anos, com THH tipo 2 geneticamente confirmada, que desenvolveu *shunts* vasculares hepáticos sintomáticos, complicados por hipertensão portal clinicamente significativa, hemorragia digestiva recorrente e insuficiência cardíaca de alto débito. O doente foi submetido a terapêutica de suporte e a tratamento antiangiogénico com bevacizumab, com melhoria clínica e hemodinâmica transitória. A evolução foi, contudo, marcada por ascite refratária, hemorragia varicosa, desnutrição grave, sarcopenia e fragilidade progressiva, condicionando as opções terapêuticas, incluindo o transplante hepático. Este caso ilustra a complexidade do envolvimento hepático na THH e o impacto da fragilidade no prognóstico.

**Palavras-chave:** Doenças do Fígado; Hipertensão Portal; Telangiectasia Hemorrágica Hereditária.

### Learning points

1. Hepatic involvement in hereditary haemorrhagic telangiectasia may manifest through complex intrahepatic arterioportal and arteriovenous shunts, leading simultaneously to clinically significant portal hypertension and high-output cardiac failure.
2. Bevacizumab may provide transient clinical and hemodynamic improvement in selected patients with symptomatic hepatic vascular malformations, particularly in the setting of high-output cardiac failure, although long-term efficacy remains uncertain.
3. Frailty and sarcopenia are critical but often underrecognized determinants of prognosis and therapeutic eligibility in advanced hepatic involvement of hereditary haemorrhagic telangiectasia, significantly influencing candidacy for liver transplantation.
4. Optimal management of hepatic HHT requires early multidisciplinary assessment and careful timing of advanced therapies, as progressive nutritional deterioration and clinical decline may ultimately limit curative options such as liver transplantation.

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## Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber disease, is a rare autosomal dominant vascular disorder characterized by the presence of widespread mucocutaneous and visceral telangiectasias, resulting from abnormal vascular development.[1] The diagnosis is primarily clinical, based on the Curaçao criteria - recurrent epistaxis, mucocutaneous telangiectasias, visceral arteriovenous malformations, and a positive family history, or can be established through the identification of a pathogenic genetic variant.[2] Mutations in endoglin (*ENG*) and activin A receptor type II-like 1 (*ACVRL1*) genes account for most cases.[1] Although HHT is a multisystem disease, visceral involvement, including pulmonary, cerebral, and hepatic vascular malformations, represents a major determinant of morbidity and prognosis.[1]

Hepatic vascular malformations (HVMs) are among the most frequent visceral manifestations of HHT, being detected in up to almost 85% of patients on imaging studies, although the majority remain asymptomatic.[3] These malformations consist of intrahepatic arteriovenous, arterioportal, and portovenous shunts, which may coexist and evolve over time. HVMs are significantly more prevalent and more frequently symptomatic in patients with HHT type 2 (ACVRL1-related disease) compared with HHT type 1.[4] When clinically relevant, hepatic involvement can lead to severe complications, including high-output cardiac failure, portal hypertension, biliary ischemia, and gastrointestinal bleeding, reflecting the hemodynamic consequences of abnormal intrahepatic shunting.[5]

The management of hepatic involvement in HHT is complex and requires a multidisciplinary approach, tailored to the dominant clinical manifestations. While asymptomatic HVMs do not require specific treatment, symptomatic disease often necessitates intensive supportive care and targeted interventions. Antiangiogenic therapy with bevacizumab has emerged as a therapeutic option in selected patients, particularly those with high-output cardiac failure, although long-term efficacy and optimal treatment strategies remain incompletely defined.[6,7] Liver transplantation remains the only definitive curative treatment for severe hepatic involvement but is associated with significant perioperative risk, highlighting the importance of appropriate patient selection and timing.[8] In this context, we report a case of HHT with complex intrahepatic vascular shunts, illustrating the natural history, therapeutic challenges, and clinical impact of hepatic involvement in this rare disease.

## Case Report

In 2022, at the age of 64, a man with a family history of HHT involving his mother, maternal aunt, and cousin was evaluated in private practice because of recurrent epistaxis, gastrointestinal telangiectasias, visceral involvement with multiple hepatic arteriovenous malformations, and a positive family history. Although these manifestations had been present for at least 10 years, thus fulfilling all four Curaçao criteria for HHT during that period, genetic testing was performed only at that time. This identified a heterozygous pathogenic variant in *ACVRL1*, thereby confirming the diagnosis of HHT type 2. No specific treatment had been initiated until then.

In November 2022 he was admitted to an intermediate care unit due to recurrent upper gastrointestinal bleeding (fourth episode within four months), secondary to gastric and duodenal telangiectasias, requiring endoscopic haemostasis with clip placement, and blood transfusion. No hypovolemic or circulatory shock was observed at any time. No oesophageal varices were documented. In view of recurrent bleeding, he had been treated with long-acting octreotide and tranexamic acid for the preceding 4 months. Ascites was identified, with a serum–ascites albumin gradient >1.1 g/dL, consistent with portal hypertension. Thoracic computed tomography excluded pulmonary arteriovenous malformations but revealed dilation of the pulmonary artery trunk (21 mm), right pulmonary artery (29 mm), and left pulmonary artery (28 mm), raising suspicion of pulmonary hypertension, confirmed by transthoracic echocardiography, which showed mild tricuspid regurgitation allowing estimation of pulmonary artery systolic pressure at approximately 47 mmHg, severe dilation of the left cardiac chambers, mild right chamber dilation, and a dilated inferior vena cava (25 mm) with <50% respiratory collapse. Global biventricular systolic function was preserved.

The presence of arterioportal and portovenous shunts explained both the clinically significant portal hypertension and the high-output cardiac failure (Fig. 1).

The patient was started on diuretic therapy with furosemide and spironolactone and was proposed for treatment with bevacizumab, administered at a dose of 10 mg/kg every two weeks, started in December 2022. At treatment initiation, he weighed 63 kg, with a height of 1.88 m (BMI 17.8 kg/m$^2$). During this time, he required only one further hospitalization for rectal bleeding, and was able to resume daily activities, reporting subjective clinical improvement. Bevacizumab was maintained for one year, until December 2023. During this period, only one transfusion of 2 units of packed red blood cells was required. He also initiated a physical rehabilitation program with muscle-strengthening exercises and increased protein intake.

At the time bevacizumab was discontinued, the haemoglobin level was 13.7 g/dL, ferritin 589 ng/mL, transferrin saturation 22%, and serum iron 48 µg/dL. One month after discontinuation of bevacizumab, he developed progressive clinical deterioration, with reduced oral intake and recurrence of ascites requiring escalation of diuretic therapy. A decrease in BMI and progressive development of sarcopenia were documented. Despite this worsening, follow-up echocardiography performed four months after treatment discontinuation, demonstrated improvement in pulmonary haemodynamics, with normalization of pulmonary flow and no evidence of significant pulmonary hypertension. Mild aortic and mitral regurgitation were noted.

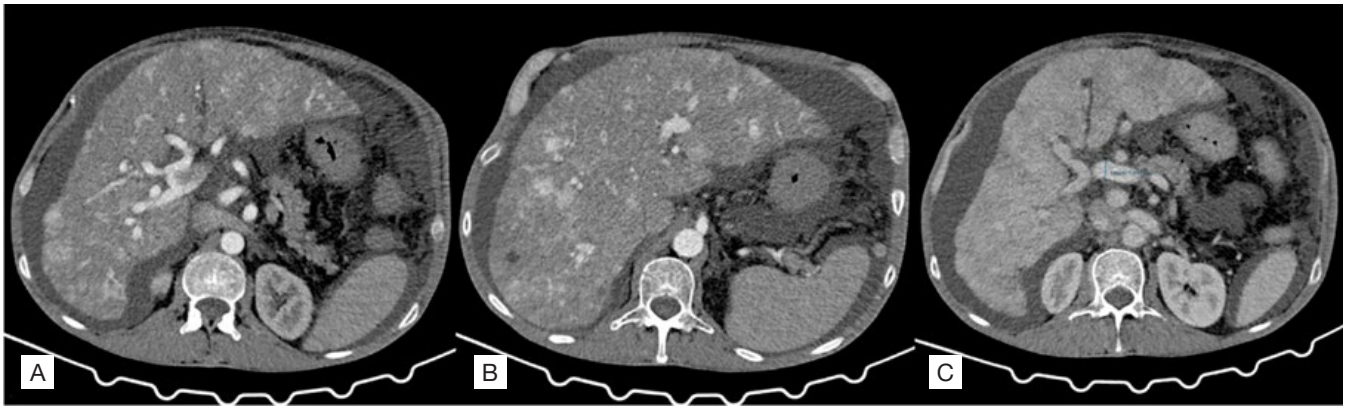


**Figure 1**: Contrast-enhanced triphasic abdominal computed tomography demonstrating hepatic vascular malformations in hereditary haemorrhagic telangiectasia. [**A, B**] Arterial phase images show marked enlargement of the hepatic arterial branches with extensive arterioportal shunting, resulting in early and heterogeneous hepatic parenchymal enhancement. Multiple intrahepatic vascular malformations are identified, with abnormal early opacification of portal venous branches. [**C**] Late venous phase image demonstrates persistent heterogeneous enhancement consistent with complex intrahepatic vascular malformations, including communications between the hepatic artery and hepatic veins, as well as dilation of the portal vein trunk, explaining the coexistence of portal hypertension and high-output cardiac failure.

Ascites became increasingly refractory, necessitating repeated large-volume paracenteses and albumin infusions. He subsequently developed recurrent upper gastrointestinal bleeding caused by oesophageal varices in the context of significant portal hypertension. This finally culminated in May 2024 in yet another hospital admission for portal hypertensive bleeding, requiring endoscopic variceal ligation and terlipressin, complicated by acute kidney injury (KDIGO stage 2). His haemoglobin level was 7.4 g/dL. Following intravenous iron administration, haemoglobin levels subsequently stabilized at approximately 9-10 g/dL. The clinical course was further complicated by severe oral bleeding from palatal telangiectasia, haematochezia and by severe malnutrition, which required both enteral and parenteral nutritional support, as well as transfusion of 2 units of packed red blood cells. Bevacizumab was reintroduced on a biweekly schedule, and the patient received three additional doses. However, despite these interventions, his condition progressively deteriorated, culminating in severe consumptive syndrome and death 3 months later.

## Discussion

Hepatic involvement in hereditary haemorrhagic telangiectasia (HHT) is reported to be 2-4 times more frequent in HHT type 2 (ACVRL1-related disease) than in HHT type 1, as observed in the present case, and may affect up to 85% of patients.[3,4] Clinical manifestations depend on the type and predominance of intrahepatic vascular malformations and the resulting shunt patterns.

Arterioportal shunts, resulting from abnormal communications between branches of the hepatic artery and the portal vein, may lead to the development of clinically significant portal hypertension and its associated complications. In our patient, this initially manifested as ascites and later progressed to the development of oesophageal varices, ultimately complicated by variceal bleeding. The management of portal hypertension in this context follows the same principles recommended for portal hypertension of other aetiologies, as outlined in the Baveno VII consensus.[9] However, particularly in the earlier stages of hepatic involvement in HHT, gastrointestinal bleeding more commonly originates from gastric or intestinal angioectasias, as was initially observed in this patient. Although octreotide is not routinely recommended, it was used in this case given its reported benefit in preventing recurrent bleeding from gastrointestinal angiodysplasias.[10] Hepatic artery embolization may appear theoretically attractive, as it could reduce portal hypertension by decreasing blood flow from a high-pressure to a low-pressure system, and in quite selected patients it may be considered.[11] Nevertheless, despite having been attempted in selected symptomatic patients, this intervention carries a substantial risk of ischemic liver injury, acute liver failure, need for urgent liver transplantation, and death, and is therefore not recommended in current guidelines.[1,8]

Arteriovenous shunts between the hepatic artery and hepatic veins are responsible for the development of high-output cardiac failure, a well-recognized and potentially life-threatening complication of hepatic HHT.[1] In the present case, before initiation of bevacizumab therapy, the patient exhibited inferior vena cava dilation and echocardiographic signs suggestive of pulmonary hypertension. Follow-up echocardiography one year after completing bevacizumab treatment demonstrated normalization of pulmonary artery pressures and improvement in cardiac hemodynamics, strongly suggesting a therapeutic effect of the drug. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), has shown particular benefit in

patients with HHT-related high-output cardiac failure. Prospective studies, although limited by small sample sizes, have demonstrated improvements in dyspnoea, cardiac output, pulmonary pressures, and epistaxis severity.[7,12] Despite these encouraging results, data on long-term efficacy and tolerability remain limited. Consequently, current international recommendations support the use of bevacizumab in patients with high-output cardiac failure due to hepatic vascular malformations who have not responded adequately to first-line therapies, while emphasizing the need for careful patient selection and monitoring.[1] At present, no formal guideline defines a fixed total duration for systemic bevacizumab in HHT. Treatment is generally individualized, with induction followed by maintenance or retreatment according to clinical response, recurrence of bleeding/anaemia, and tolerability, as was the case of our patient.[1] In our case, bevacizumab was likely reintroduced too late, after clinical decompensation had already become established. Earlier and more aggressive reinstitution of therapy might have resulted in a better outcome, despite the severity of the clinical presentation.

Although not commonly emphasized in the literature, frailty and sarcopenia represented major clinical determinants in this patient, as has been sporadically reported in advanced cases of hereditary haemorrhagic telangiectasia with severe hepatic involvement.[13] In the setting of chronic disease characterized by high-output cardiac failure, clinically significant portal hypertension, recurrent gastrointestinal bleeding, and chronic anaemia, a progressive decline in muscle mass and functional reserve substantially limited therapeutic options. Sarcopenia and frailty are increasingly recognized as independent predictors of poor outcomes in patients with portal hypertension and advanced liver disease, including reduced tolerance to invasive therapies and impaired eligibility for liver transplantation.[14-16] In this patient, these factors ultimately contributed to exclusion from liver transplantation candidacy and led to discontinuation of bevacizumab, particularly after reintroduction during the second treatment cycle.

Liver transplantation remains the only definitive curative therapy for patients with HHT and severe hepatic involvement. While transplantation is associated with significant perioperative morbidity, it has been shown to provide substantial survival benefit and marked improvement in cardiac function.[17,18] Nevertheless, the optimal timing of transplantation during the disease course remains insufficiently defined, particularly in patients with progressive frailty and nutritional deterioration, underscoring the need for earlier identification of patients at risk and multidisciplinary assessment. ■

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FN – Conceptualization of the study, clinical management, data interpretation, manuscript drafting, and critical review
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