Case Report

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Improvement of ischemic cholangiopathy in three patients with hereditary hemorrhagic telangiectasia following treatment with bevacizumab

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Abstract

The ischemic biliary phenotype of hereditary hemorrhagic telangiectasia (HHT) is rare but distinct, with progressive biliary tree ischemia usually resulting in an irreversible secondary sclerosing cholangiopathy. When clinically severe, liver transplant is often indicated. We report three patients with marked HHT associated biliary disease, in whom prolonged anti-vascular endothelial growth factor therapy (bevacizumab) notably reversed imaging evidence of biliary disease and clinically obviated need for liver transplantation during the first year of follow-up.

Introduction

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder, characterized by mucocutaneous telangiectasias and visceral arteriovenous malformations [1]. Although radiological signs of liver involvement occur in more than 70% of patients, less than 10% of these patients develop symptoms [2]. Symptomatic liver HHT from intrahepatic shunting can lead to patients presenting with high-output cardiac failure (HOCF), portal hypertension or ischemic biliary disease [3,4]. A recent Italian prospective cohort study found that over prolonged follow-up, substantial morbidity and mortality were associated with liver vascular malformations in HHT patients [5]. The biliary tree is notably susceptible to ischemia given its dependence on blood flow from the hepatic artery; ischemic biliary damage is also a feature of cholangiopathies post-liver transplant (hepatic artery thrombosis and ischemia-reperfusion injury).

Medical treatments for HHT-related hepatic complications have been limited [6]. With dysregulated angiogenesis, elevated plasma concentrations of vascular endothelial growth factor (VEGF) and transforming growth factor beta [1,7] are seen in HHT. Bevacizumab, an anti-VEGF antibody, improves anemia from chronic HHT-related bleeding [8] and high cardiac output secondary to hepatic vascular malformations (VMs) [9]. We report three patients with hepatic HHT based on the Curaçao criteria [10], complicated by ischemic cholangiopathy, whose clinical (Table 1) and radiological (Fig. 1) response to bevacizumab obviated liver transplantation in the first year of follow-up.

Case report

Patient 1

A 43-year-old woman with newly diagnosed HHT, based on Curaçao clinical diagnostic criteria (recurrent spontaneous epistaxis since childhood, multiple typical mucocutaneous telangiectasias, liver and lung VMs) presented with a 3-month history of right upper quadrant pain, weight loss, worsening epistaxis, and melena. The patient's family history was not immediately

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Abbreviations: HHT, hereditary hemorrhagic telangiectasia; HOCF, high-output cardiac failure; VEGF, vascular endothelial growth factor; VMs, vascular malformations; CI, cardiac index; MRI, magnetic resonance imaging; INR, international normalized ratio; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; ALT, alanine transaminase; AST, aspartate transaminase; Hb, hemoglobin; CRP, C-reactive protein.

Table 1. Laboratory findings before and after therapy.

	Patient 1			Patient 2			Patient 3		
Parameter	Pre	Start	Post	Pre	Start	Post	Pre	Start	Post
Total bilirubin (<23 μmol/L)	23	100	17	9	17	10	48	73	36
INR (<1.2)	1.4	1.5	1.1	1.1	1.6	1.1	1	1.6	1
Platelets (<400 x 10^9/L)	418	359	228	221	240	144	148	120	252
ALP (<125 IU/L)	170	320	609	36	85	46	105	486	357
GGT (<78 IU/L)	83	75	167	33	-	71	18	218	328
ALT (<45 IU/L)	19	16	64	19	25	40	34	356	74
AST (<40 IU/L)	21	32	58	26	24	33	52	444	70
Hb (<155 g/L)	68	90	133	106	61	132	151	132	135
CRP (<5 mg/L)	-	40	11	4.7	101	3	-	140	5

Pre-treatment values are from 6 months prior, except for patient 2 (two months); post-treatment values are 12 months post initiation of bevacizumab therapy.
INR, international normalized ratio; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; ALT, alanine transaminase; AST, aspartate transaminase; Hb, hemoglobin; CRP, C-reactive protein.

suggestive of HHT but the family did not come for formal clinical assessment of HHT. The patient's genetic testing revealed a variant in the *ACVRL1* gene.

Physical examination revealed cutaneous telangiectasias, a hyperdynamic heart and hepatic bruit. Laboratory tests demonstrated anemia (hemoglobin (Hb) 93 g/L, normal range 110–155 g/L; INR 1.5) and cholestasis. Echocardiography revealed normal left ventricular function and a cardiac index (CI) of 6.5 L/min/m^2 (normal range in women 2.8–3.6 L/min/m^2). Magnetic resonance imaging (MRI) of the liver demonstrated hepatomegaly (21 cm), markedly dilated arterial vasculature, typical hepatic telangiectasias, early opacification of the hepatic and portal veins suggestive of arteriosystemic and arterioportal shunting, and multiple regions of biliary stenosis and dilatation, attributable to ischemic cholangiopathy. The patient was placed on a polymeric diet (a liquid diet similar to an elemental diet, apart from containing intact proteins and complex carbohydrates) empirically with the goal of reducing mesenteric steal post-prandially, as well as ursodeoxycholic acid in conjunction with regular narcotics due to ongoing, intractable abdominal pain. Despite an initial improvement, she was readmitted five months later with abdominal pain, symptoms of HOCF and severe anemia. She was febrile with a worsening cholestatic picture and found to have *Enterobacter cloacae* bacteremia. Repeat MRI revealed progression of the intrahepatic biliary strictures, persistent hepatic vascular shunting, and development of large bilomas. Gastroenterology identified and treated two bleeding duodenal telangiectatic vessels with argon plasma coagulation, and the patient was transfused three units of packed red blood cells within the first week of admission. The patient was treated with intravenous piperacillin-tazobactam for 30 days and then subsequently oral levofloxacin and metronidazole for 30 days. The fever was intermittent for three weeks and then resolved. She was also placed on furosemide to treat her HOCF. In the context of the patient's complex and worsening HHT manifestations, she was referred for liver transplantation and concurrently started on bevacizumab (5 mg/kg administered as an intravenous infusion) at two-week intervals for a total of six doses, the first two doses given during her admission (at weeks three and five). She required two more units of packed red blood cells between the first and second dose of bevacizumab, and then none further. Her symptoms gradually improved and she was discharged in stable condition after six weeks in hospital.

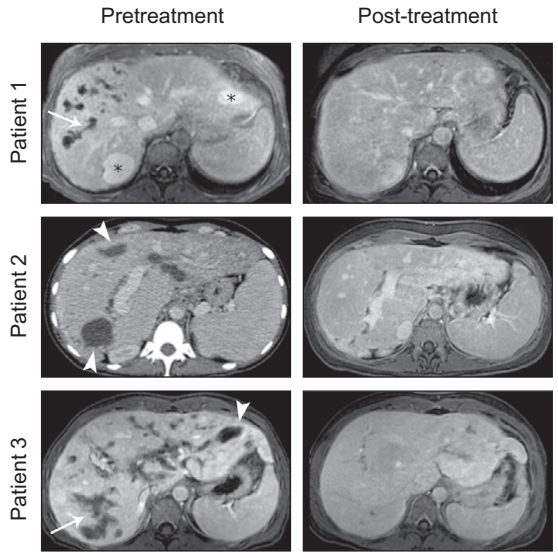

Fig. 1. Radiologic improvement in biliary disease after treatment with intravenous anti-vascular endothelial growth factor in patients with hereditary hemorrhagic telangiectasia. Contrast-enhanced T1-weighted MRI images and contrast-enhanced CT image (Patient 2, left column) obtained during the portal venous phase, before (left column) and after treatment (right column). Pre-treatment imaging demonstrates dilatation of the intrahepatic ducts (arrows) and multiple well-defined hypointense/hypodense lesions in keeping with intrahepatic bilomas (arrowheads). Peripheral rim enhancement is observed in Patient 3 (left column), suggestive of superimposed infection. Following treatment, there is resolution of the bilomas and near-complete resolution of the intrahepatic biliary dilatation (right column). Incidental note made of two hepatic hemangiomas (*) in patient 1.

At follow-up, three months after initiation of bevacizumab, the patient was remarkably clinically improved, with a 7-kg weight gain, complete resolution of abdominal pain, resolution of all symptoms of heart failure and no recurrent sepsis. The bilirubin and INR had normalized, and the C-reactive protein had improved significantly. Though there was further elevation of ALP, GGT, AST, and ALT, compared to pretreatment, this was clinically felt to reflect the consequences of the severe biliary ischemia pretreatment. Epistaxis and gastrointestinal bleeding were markedly improved and no further blood transfusions were needed. Cardiac echocardiography revealed a reduction of CI to 3.0 L/min/m^2. Liver MRI showed marked diminution of biliary