Case Report

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

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

Paraskevi A. Vlachou[1], Errol Colak[1], Alexander Koculym[1], Anish Kirpalani[1], Tae Kyoung Kim[2], Gideon M. Hirschfield[3,4,*,†], Marie E. Faughnan[5,6,*,†]

[1]*Department of Diagnostic Imaging, St. Michael's Hospital, 30 Bond Street, Toronto, ON, Canada M5B 1W8;* [2]*Department of Diagnostic Imaging, Toronto General Hospital, 200 Elizabeth St., Toronto, ON, Canada M5G 2C4;* [3]*Department of Medicine, Division of Gastroenterology, University of Toronto, Toronto, Canada;* [4]*Centre for Liver Research, Institute of Biomedical Research, NIHR Biomedical Research Unit, University of Birmingham, Birmingham B15 2TT, UK;* [5]*Department of Medicine, Division of Respirology, Toronto HHT Centre, St. Michael's Hospital, Toronto, Canada;* [6]*Keenan Research Centre of the Li Ka Shing Knowledge Institute of St. Michael's Hospital, 30 Bond Street, Toronto, ON, Canada M5B 1W8*

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

Keywords: Hereditary hemorrhagic telangiectasia; Anti-VEGF; Cholangitis.
Received 5 December 2012; received in revised form 23 January 2013; accepted 11 February 2013

* Corresponding authors. Addresses: Centre for Liver Research, NIHR Biomedical Research Unit, University of Birmingham, UK (G.M. Hirschfield). Division of Respirology, St. Michael's Hospital, 30 Bond Street, Toronto, ON, Canada M5B 1W8 (M.E. Faughnan).
E-mail addresses: g.hirschfield@bham.ac.uk (G.M. Hirschfield), faughnanm@smh.ca (M.E. Faughnan).
† GMH and MEF contributed equally to the management of patients and jointly directed this work.

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.

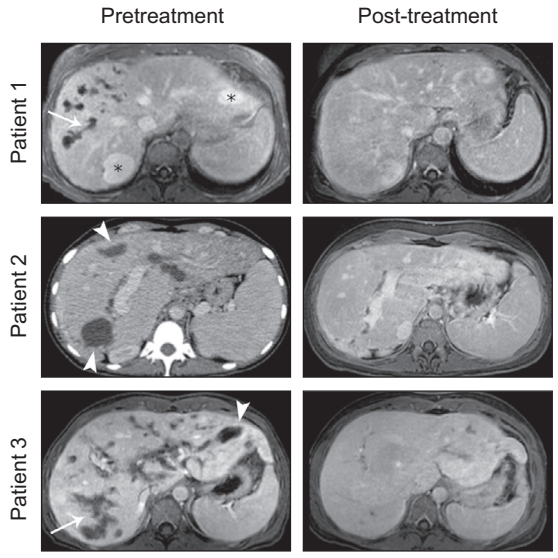

Fig. 1. Radiologic improvement in biliary disease after treatment with intravenous anti-vascular endothelial growth factor in patients with hereditary hemorrhagic telangiectasia. Contrast-enhanced T1-weighted MRI images and contrast-enhanced CT image (Patient 2, left column) obtained during the portal 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

dilatation, near resolution of the bilomas, improvement of telangiectasias and shunting and normalization of hepatic size and arterial flow volume (decreased to 0.3 L/min from 1.3 L/min) (Fig. 1). The patient was continued on a three-monthly maintenance dose of bevacizumab 5 mg/kg for twelve months and remains well nine months following discharge. Given her excellent response to bevacizumab, she was not listed for liver transplantation.

Patient 2

A 32-year-old woman with HHT presented with a three-month history of right upper quadrant pain, weight loss, melena, and recurrent spontaneous epistaxis. She had a known definite clinical diagnosis of HHT based on the presence of all four Curaçao criteria (diagnosis of HHT in a first degree relative, recurrent spontaneous epistaxis, multiple typical mucocutaneous telangiectasias and pulmonary VMs) and she had been confirmed to harbor the known familial *ACVRL1* mutation. Physical examination revealed a high-flow cardiac murmur, hepatomegaly, and a hepatic bruit. Haematology testing demonstrated anemia (Hb 64 g/L) requiring transfusion but normal liver biochemistry. Liver MRI showed hepatic artery dilatation, multiple hepatic telangiectasias and systemic arteriovenous shunting. In addition, there was marked segmental intrahepatic biliary dilatation, intraductal filling defects and multiple bilomas. Phase contrast MRI yielded flow volumes of 4.0 L/min in the celiac artery (normal <2 L/min). Despite endoscopic treatment of bleeding gastric telangiectasias, she required further transfusions and continued to suffer from paroxysms of pain despite analgesia. She was admitted with fever, leukocytosis and positive blood cultures for *Enterococcus*, which was attributed to cholangitis. Computed tomography demonstrated multiple new bilomas and progression of intrahepatic biliary dilatation and stricturing. The patient was treated first with piperacillin-tazobactam for 8 days, then changed to meropenem, and subsequently vancomycin, for ongoing fever, for another 14 days, with resolution of the fever while on vancomycin. She underwent endoscopic treatment of multiple stomach angiodysplasias and was transfused in order to maintain a Hb above 100 g/L, a total of 13 units of packed red blood cells, as well as receiving 4 units of fresh frozen plasma. Given refractory pain, anorexia, low-grade gastrointestinal bleeding, anemia, and worsening bilomas, she was started on a course of bevacizumab with the same regimen as detailed for patient 1. This was started while she was afebrile on antibiotics and she received the first three doses prior to discharge. She was also referred for assessment for liver transplantation. After the second dose of bevacizumab, she required no further transfusions; after the third dose she was discharged home.

At follow-up, three months following initiation of bevacizumab, the abdominal pain, febrile episodes and melena had resolved. She had gained weight, the severity of epistaxis had improved and she no longer required blood transfusions. Cardiac echocardiography showed a normal CI of 2.5 L/min/m^2 (from the elevated 5.3 L/min/m^2 pre-bevacizumab). Liver MRI revealed marked improvement in biliary dilatation, resolution of bilomas, improvement of telangiectasias and hepatic parenchymal heterogeneity and reduction in celiac arterial flow (1.7 L/min) (Fig. 1). The patient was continued on a maintenance dose of bevacizumab as indicated for patient 1. She has regained her weight and remains asymptomatic one year following discharge from hospital, with progressive weaning from analgesics, and no present indication for liver transplantation.

Patient 3

A 25-year-old woman with HHT was admitted with 6 kg weight loss, fevers, fatigue and refractory epigastric and right upper quadrant pain. She had a known definite clinical diagnosis of HHT based on the presence of all four Curaçao criteria (diagnosis of HHT in a first degree relative, recurrent spontaneous epistaxis, multiple typical mucocutaneous telangiectasias and hepatic VMs) and she had been confirmed to harbor the known familial *ACVRL1* mutation. She developed seizures presumed secondary to portosystemic shunting and was managed with anti-seizure medications, ursodeoxycholic acid and lactulose. Physical examination revealed a hyperdynamic precordium, and a hepatic bruit. Laboratory analysis demonstrated cholestasis and Hb 110 g/L. Cardiac echocardiography showed normal biventricular size and systolic function but increased CI of 4.6 L/min/m^2. Liver MRI demonstrated marked dilatation of the hepatic artery, diffuse telangiectasias, arteriosystemic venous shunting, irregular intrahepatic biliary dilatation with areas of focal stricturing, and multiple bilomas. Given the severity of the presentation and complications, the patient was started on bevacizumab with the same protocol as detailed for patient 1. She was also assessed for liver transplantation. She was discharged home after the second dose. At follow-up, three months after initiation of bevacizumab, the patient's weight had stabilized, the pain had improved and there was no recurrence of hepatic encephalopathy or seizure activity. Cardiac echocardiography showed a reduction of CI to 3.4 L/min/m^2. Laboratory evaluation showed mild elevation of cholestatic liver enzymes and repeat MRI revealed unchanged biliary dilatation and bilomas with imaging features indicative of superimposed infection. Multiple intraductal filling defects were present, concerning for sloughed biliary epithelium. A focal, likely ischemic stricture was also noted in the gallbladder body. Given only partial improvement after the first six doses of bevacizumab, she was continued on a monthly maintenance dose of bevacizumab for three months, and then every three months for twelve months.

Whilst listed for liver transplantation, she continued bevacizumab, and six months later had an episode of bacterial cholangitis, managed with antibiotics and endoscopic intervention. By 8 months, the patient's clinical status had significantly improved with resolution of abdominal pain, fatigue and weakness, weight gain and a return to exercise. Her hepatic bruit resolved and liver enzymes fell, with her CI decreased to 2.9 L/min/m^2. Liver MRI showed near-complete resolution of the biliary findings with improvement of the arteriosystemic shunting (Fig. 1). The patient was kept (and continues) on a maintenance dose of bevacizumab (5 mg/kg) every three months and remains well one year following her initial presentation, no longer being listed for liver transplantation.

Discussion

We report three patients with HHT, for whom their predominant clinical presentation was with ischemic cholangiopathy. In these patients, anti-vascular endothelial growth factor therapy not only obviated the need for liver transplantation in the first year of follow-up, but also resolved biliary features sufficiently to be

demonstrable radiologically, in a striking manner given that reversal of biliary disease is rarely reported [11]. Our report therefore provides helpful, albeit relatively short term, information of benefit to patients with HHT and biliary disease, as well as more broadly to investigators who seek to understand further mechanisms by which the biliary tree can be damaged by vascular insufficiency. Our patients received therapy without incident, but remain under active follow-up given the recognized risks of bevacizumab.

Biliary abnormalities are variably seen in HHT ranging from 26% to 46% of those usually with symptomatic disease [3,4]. Patients are usually female, presenting in the third decade with symptoms of abdominal/right upper quadrant pain and fatigue, symptoms related to cholangitis, and/or a cholestatic biochemistry profile [3,12,13]. The biliary phenotype is believed to arise from hepatic arterial-venous shunting resulting in stealing/bypassing of blood from the biliary tree, causing hypoperfusion of the peribiliary plexus, bile duct ischemia with subsequent fibrosis, formation of strictures and focal biliary dilatations. In severe ischemic injury, biliary necrosis occurs with bile extravasating into the adjacent hepatic parenchyma causing bilomas [3,4,12,13], which can potentially lead to hepatic disintegration [13]. Patterns of biliary abnormalities related to HHT resemble Caroli's disease with cystic dilatations of the intrahepatic bile ducts or sclerosing cholangitis with irregular, multifocal biliary strictures, sparing the extrahepatic ducts [3,4,12]. On imaging, our patients had a dilated common hepatic artery and extensive hepatic VMs. All patients had multifocal intrahepatic biliary strictures and bilomas but normal-appearing extrahepatic bile ducts. Two of our patients had intraductal filling defects, likely biliary casts from desquamation of the ischemic biliary epithelium and intraductal calculi or hemorrhage. Liver biochemistry is not necessarily reflective of the degree of biliary injury in the acute setting, and in our series of patients changes in liver biochemistry became more evident over time, presumably reflecting a degree of biliary damage and repair, in spite of evident clinical and radiologic improvement.

VEGF is a regulator of angiogenesis and patients with HHT have elevated plasma concentrations and tissue expression of VEGF [7]. Anti-VEGF antibodies such as bevacizumab have been shown to decrease angiogenesis by inhibiting endothelial growth and simultaneously cause regression of aberrant vessels by promoting endothelial death [14]. We speculate that bevacizumab by causing regression of existing hepatic capillaries and inhibition of neovascularization within hepatic arteriovenous malformations, reduced hepatic arteriovenous shunting in our patients, thereby reversing arterial steal/peribiliary plexus hypoperfusion. Although bevacizumab can have serious side effects, such as severe hemorrhage, arterial and venous thromboembolism, gastrointestinal perforation, and wound complications, our patients tolerated the treatment well and did not suffer any complications. To date, liver transplantation for complicated hepatic HHT remains the only curative option for life-threatening complications such as ischemic biliary necrosis that fails to respond to intensive medical therapy. Ischemic cholangiopathy with superimposed infection, as was the case in two of our patients, has a high mortality, and transplantation is difficult in the setting of uncontrolled systemic sepsis. Procedures, such as transarterial embolization of hepatic VMs are generally avoided, as they carry a high risk of hepatic or biliary necrosis, particularly in patients with biliary presentation of hepatic VMs [6]. Our patients remain well but naturally longer term outcomes other than those reported to date, are not yet available, and this limitation to our observation needs to be acknowledged.

In conclusion, we present three patients with severe biliary manifestations from HHT who were successfully managed with intensive medical therapy in the form of prolonged anti-vascular endothelial growth factor, and for whom clear reversible cholangiopathy is evident. This is an important treatment option for patients to be considered, although further studies are needed to adequately assess long-term safety, efficacy, as well as wider applicability of this pharmacologic modality.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contributions

PAV and GMH wrote the initial draft, and coordinated revisions; all authors contributed to the final version.

References

[1] Guttmacher AE, Marchuk DA, White Jr RI. Hereditary hemorrhagic telangiectasia. N Engl J Med 1995;333:918–924.
[2] Ianora AA, Memeo M, Sabba C, Cirulli A, Rotondo A, Angelelli G. Hereditary hemorrhagic telangiectasia: multi-detector row helical CT assessment of hepatic involvement. Radiology 2004;230:250–259.
[3] Garcia-Tsao G, Korzenik JR, Young L, Henderson KJ, Jain D, Byrd B, et al. Liver disease in patients with hereditary hemorrhagic telangiectasia. N Engl J Med 2000;343:931–936.
[4] Wu JS, Saluja S, Garcia-Tsao G, Chong A, Henderson KJ, White Jr RI. Liver involvement in hereditary hemorrhagic telangiectasia: CT and clinical findings do not correlate in symptomatic patients. AJR Am J Roentgenol 2006;187:W399–W405.
[5] Buscarini E, Leandro G, Conte D, Danesino C, Daina E, Manfredi G, et al. Natural history and outcome of hepatic vascular malformations in a large cohort of patients with hereditary hemorrhagic teleangiectasia. Dig Dis Sci 2011;56:2166–2178.
[6] Faughnan ME, Palada VA, Garcia-Tsao G, Geisthoff UW, McDonald J, Proctor DD. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. J Med Genet 2011;48:73–87.
[7] Sadick H, Riedel F, Naim R, Goessler U, Hormann K, Hafner M, et al. Patients with hereditary hemorrhagic telangiectasia have increased plasma levels of vascular endothelial growth factor and transforming growth factor-beta1 as well as high ALK1 tissue expression. Haematologica 2005;90:818–828.
[8] Bose P, Holter JL, Selby GB. Bevacizumab in hereditary hemorrhagic telangiectasia. N Engl J Med 2009;360:2143–2144.
[9] Dupuis-Girod S, Ginon I, Saurin JC, Marion D, Guillot E, Decullier E, et al. Bevacizumab in patients with hereditary hemorrhagic telangiectasia and severe hepatic vascular malformations and high cardiac output. JAMA 2012;307:948–955.
[10] Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 2000;91:66–67.
[11] Erkelens GW, Vleggar FP, Lesterhuis W, van Buuren HR, van der Werf SD. Sclerosing pancreato-cholangitis responsive to steroid therapy. Lancet 1999;354:43–44.
[12] McInroy B, Zajko AB, Pinna AD. Biliary necrosis due to hepatic involvement with hereditary hemorrhagic telangiectasia. AJR Am J Roentgenol 1998;170:413–415.
[13] Blewitt RW, Brown CM, Wyatt JI. The pathology of acute hepatic disintegration in hereditary haemorrhagic telangiectasia. Histopathology 2003;42:265–269.
[14] Carmeliet P. Angiogenesis in life, disease and medicine. Nature 2005;438:932–936.