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CASE REPORT

Hereditary Hemorrhagic Telangiectasia of the Liver Complicated by Ischemic Bile Duct Necrosis and Sepsis: Case Report and Review of the Literature

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Abbreviation
HHT Hereditary hemorrhagic telangiectasia

Introduction

Hereditary hemorrhagic telangiectasia (HHT) or Osler–Weber–Rendu syndrome is an autosomal dominant disorder with a prevalence of 1–20/100,000 population [1]. Mutations in the genes for endoglin (ENG) and for activin A receptor type II-like kinase 1 (ALK-1), located on chromosomes 9 and 12, respectively, have been associated with HHT [2, 3]. The homozygous state appears to be lethal [4]. According to the Curacao diagnostic criteria for HHT, a definite or probable diagnosis is made if three or two out of the following four criteria, respectively, are met [5]:

1. Epistaxis (spontaneous recurrent nosebleeds)
2. Telangiectasias (oral cavity, nose, lips, fingers)
3. Visceral lesions (arteriovenous malformations: pulmonary, liver, gastrointestinal, cerebral, spinal)
4. A first-degree relative with HHT

Two major phenotypes of HHT have been reported; type 1 and type 2.

HHT type 1 is associated with pulmonary arteriovenous malformations. The genetic abnormality involves a mutation in the gene for ENG [2].

In HHT type 2, there is a high incidence of liver involvement. However, the abnormalities appear later and tend to be milder. The genetic abnormality involves a mutation in the gene for ALK-1 [2].

A genotype–phenotype relationship for localization and age distribution of telangiectasias in HHT has been detected. Mucosal and dermal telangiectasias have been reported to occur in descending order of frequency in the following sites: nasal mucosa, oral mucosa, facial skin, and hands. In HHT type 1, oral and nasal mucosal telangiectasias appear earlier in life, whereas in HHT type 2 dermal telangiectasias are more frequent and appear earlier in life. In both HHT type 1 and HHT type 2, increasing age has been associated with increased number of sites affected [6].

Liver involvement has been reported in up to 31% of the affected patients [2, 4, 7], predominantly in HHT type 2. However, radiological signs of liver involvement are detectable in up to 74% of patients and vary according to the radiological technique used. In particular, liver involvement has been reported in 32–41% of patients by Doppler ultrasound [8, 9] and in 74% of patients by

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multidetector-row helical computed tomography (CT) [10]. However, only a minority (<10%) of patients has been reported to be symptomatic.

Common symptoms secondary to liver involvement include right heart failure and pulmonary hypertension as a result of hyperdynamic circulation, cholestasis, biliary ischemia due to arteriovenous shunting resulting in necrosis, sepsis, and manifestations of portal hypertension.

Interestingly, recurrent arteriovenous malformations have been reported up to ten years after liver transplantation [2, 11].

We report a case of a 32-year-old Caucasian female at 33 weeks gestation with HHT who developed fulminant hepatic failure and septic shock 2 months after the induction of vaginal delivery. The explant revealed vascular malformations and biliary necrosis. She ultimately required liver transplantation.

We have conducted a literature review with a focus on the spectrum of liver involvement in HHT, including the risks of biliary necrosis and infarction with resultant infection, the role of pregnancy as a contributing factor to hepatic decompensation in HHT, the experience with liver transplantation in HHT, and the importance of its timely consideration.

For the purposes of this report, we conducted a computer-based search of MEDLINE (National Library of Medicine, Bethesda, MD) to identify studies that were published in English-language peer-review journals between the years 1974 and 2009. We complemented this computer-based search by cross-referencing published articles. Although we reviewed all studies, this report is not an exhaustive compendium of the current literature.

Case Presentation

A 32-year-old Caucasian female, gravida 5, para 3 (one spontaneous abortion), at 33 weeks gestation was admitted to an outside hospital complaining of right upper quadrant abdominal pain, nausea, and intermittent vomiting. The pain had been episodic, sharp in quality, radiating to the back, at times 8/10 in intensity, and aggravated by food intake. It continued for approximately 3 weeks, and became worse over the last 3 days prior to admission. She had lost approximately 24 lbs during this period. In addition, she had been complaining of occasional chills. She remained afebrile during her presentation.

Her past medical history was significant for two attacks of biliary colic over the past month prior to presentation. She had been admitted both times to an outside hospital for a few days, diagnosed with gallbladder gallstones, and had been treated with antibiotics and pain medication. She had also experienced chronic recurrent epistaxis.

Her past surgical history was significant for a spontaneous abortion followed by cervical dilatation and curettage.

Her family history was significant for colon cancer (unknown at what age it was diagnosed) and HHT in her father, manifested by episodic epistaxis. Her father had been diagnosed at an outside hospital. It is unclear why the entire family had not been screened for HHT.

She denied alcohol abuse and she had been smoking approximately three cigarettes a day over the past few years. She denied intravenous drug use. She was married and had three healthy children.

She had no known drug allergies; she was on prenatal vitamin, iron sulfate, and Zantac.

On physical examination, her vital signs were stable. She was afebrile. She was icteric. Her lung fields were clear to auscultation, she had regular heart rate and rhythm, normal S1 and S2 with III/VI systolic ejection murmur at the left lower sternal border, which was non-radiating. The abdomen was tender mainly at the right upper quadrant with voluntary guarding; no Murphy's sign was elicited; there was no rebound tenderness. The bowel sounds were normal, no abdominal bruits were appreciated, liver and spleen were not palpable, and there was no shifting dullness to percussion or fluid thrill. An enlarged uterus was felt above the umbilicus. There was no lower extremity edema.

Laboratory tests revealed: white bloody cell (WBC) count 20,300/mm^3 with 4% bands, Hgb 11.6 gr/dl, Hct 34.5%, PLT 219,000/mm^3, albumin 2.0 gr/dl, and INR 2.2. ALT 250 IU/l, AST 494 IU/l, alkaline phosphatase 327 IU/l, and total bilirubin 4.1 mg/dl. Creatinine 1.2 mg/dl and amylase 164 IU/l. Viral serologies for hepatitis A, B, and C were all negative; a-1 antitrypsin, ceruloplasmin, serum iron, total iron binding capacity, and serum ferritin were all within the limits of normal. Autoimmune markers (ANA, AMA, ASMA, LKMA) were all negative.

Right upper quadrant abdominal ultrasound with Doppler revealed mild gallbladder wall thickening, gallbladder calculi, and trace pericholecystic fluid, which was concerning for acute cholecystitis. The liver was echogenic, consistent with fatty infiltration, and the intrahepatic blood vessels examined by Doppler were normal with appropriately directed flow. No signs of hepatic arteriovenous malformations were recognized by Doppler.

Intravenous fluids and antibiotics were initiated followed by the induction of vaginal delivery. Subsequently, she underwent endoscopic retrograde cholangiopancreatography, which revealed common bile duct stones. Endoscopic sphincterotomy was performed and multiple small stones and sludge were removed.

CT scan of the abdomen with contrast revealed innumerable hypervascular linear structures throughout the liver, an enlarged hepatic artery, as well as early filling and enlargement of the hepatic veins. The liver was not

cirrhotic in morphology, no fatty infiltration was reported and the spleen was not enlarged. A small amount of ascites was detected in the left upper quadrant and minimally adjacent to the liver.

One month after delivery, she underwent elective laparoscopic cholecystectomy at an outside hospital. It appears that, at the time, the patient was stable enough to undergo the procedure without evidence of infection or liver failure, and that the extent of arteriovenous malformations was not appreciated. Macroscopically, the liver appeared abnormal with multiple circular reddish lesions on the liver surface, consistent with arteriovenous malformations. The presence of dilated blood vessels in the region of the porta hepatis and close to the gastroesophageal junction raised concern for portal hypertension. Despite clear evidence of HHT, a liver biopsy was performed at the outside hospital, which revealed aberrant thin-walled vessels in the lobules and in the portal tracts, nodular regenerative hyperplasia, diffuse microvesicular and macrovesicular steatosis involving <10% of the hepatocytes, and multifocal patchy subsinusoidal fibrosis.

Two months after delivery, she presented to our institution with progressive malaise, nausea and vomiting, scleral jaundice, and changes in mental status. No hospital admissions or laboratory work was noted between cholecystectomy and admission to our institution. Her vital signs were stable and she was afebrile. Her physical examination was remarkable for scleral icterus, diffuse abdominal tenderness with abdominal wall edema, shifting dullness to percussion, positive fluid thrill, and grade 2 pitting edema in both lower extremities.

Laboratory work revealed WBC 14,300/mm^3 with 8% bands, Hgb 11.1 gr/dl, Hct 32.6%, PLT 227,000/mm^3, albumin 1.1 gr/dl, and INR 2.4. ALT 33 IU/l, AST 184 IU/l, alkaline phosphatase 580 IU/l, and total bilirubin 4.1 mg/dl. Creatinine 2.7 mg/dl.

Initial blood, urine, and ascitic fluid cultures prior to the initiation of antibiotics did not grow any organisms.

Repeat abdominal CT scan revealed diffuse fatty infiltration of the liver, prominence of hepatic vasculature, diffuse multiple bilobar small enhancing nodules, increased ascites, and abdominal subcutaneous edema.

Magnetic resonance imaging (MRI) of the brain did not reveal any evidence of arteriovenous malformations.

She was treated with intravenous fluids and albumin; 3 l of ascitic fluid were removed. Over the next day, she became increasingly encephalopathic, and her ammonia level had risen to 174 μmol/l. She required intubation and transfer to the intensive care unit. A diagnosis of fulminant liver failure (FHF) was made, and she was subsequently listed for transplantation. Over the next 24 h, she developed septic shock secondary to vancomycin-resistant enterococcus and linezolid was started. Despite intensive therapy, her PLT count dropped to 27,000/mm^3, bilirubin rose to 6.8 mg/dl, and she became markedly acidotic (pH = 7.1). PT and PTT remained prolonged, despite transfusions of fresh frozen plasma. The picture was consistent with the development of disseminated intravascular coagulation.

Transthoracic echocardiogram revealed borderline dilated left ventricle with an ejection fraction of 40–45% and pulmonary hypertension (pulmonary artery pressure 37 mmHg). The normal pulmonary artery pressure in a person living at sea level has a mean value of 12–16 mmHg. Pulmonary hypertension is present when the mean pulmonary artery pressure exceeds 25 mmHg at rest or 30 mmHg with exercise.

The following day, she underwent liver transplantation, but after donor liver implantation, she developed an intracardiac thrombus and a subsequent cardiac arrest. All attempts at resuscitation failed and she expired (after 7.1 h of total operative time).

Pathological examination of the enlarged native liver revealed severe steatosis, multiple abnormal venous channels/shunts and arteriovenous malformations, areas of congestion and hemorrhage, focal central vein sclerosis, and focal hepatic venous obliteration with marked congestion and hemorrhage, consistent with HHT (Figs. 1 and 2). There was also severe ischemic cholangiopathy with widespread bile duct necrosis, bile extravasation, and nearby tissue necrosis, containing colonies of gram-positive coccoid bacteria.

Discussion

Liver involvement in HHT has been described in multiple case reports [7, 12–14] and case series [8–10]. As

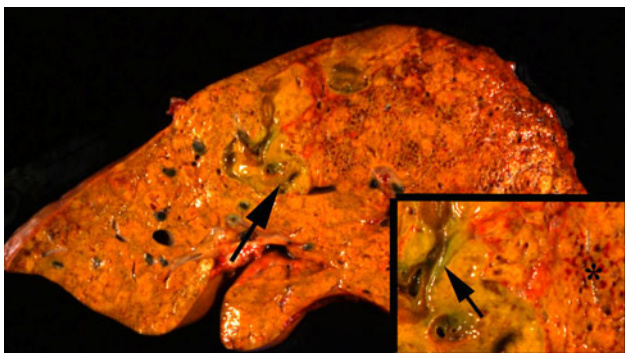

Fig. 1 The 2,121-g, 27.5 × 25.0 × 7.5-cm native hepatectomy specimen showed a smooth capsule, but cross-sectioning revealed obvious necrosis of the biliary tree, marked by the *green* bile staining of the necrotic bile duct walls. The cut surface was variegated (*yellow*) from steatosis and (*red*) from congestion and focal necrosis. The area marked by the *arrow* is shown at higher magnification in the inset. Note the necrotic bile duct (*arrow*) and areas of parenchymal congestion and hemorrhage (*). (Color figure online)

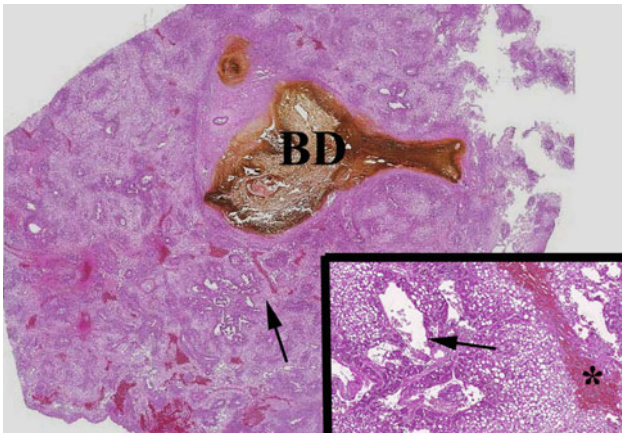

Fig. 2 Microscopic examination of the liver showed obvious necrosis of the bile ducts (*BD*), which were filled with biliary sludge and contained colonies of bacteria. The parenchyma showed severe panlobular steatosis and was interrupted by multiple arterio-venous shunts and centrilobular congestion and hemorrhage and perivenular fibrosis. The area highlighted by the *arrow* is shown at higher magnification in the inset, which illustrates the abnormal shunt vessel (*arrow*), severe steatosis, and areas of centrilobular congestion and hemorrhage (*)

demonstrated in this case, there are abnormal vascular intrahepatic shunts (hepatic artery to hepatic vein, hepatic artery to portal vein, portal vein to hepatic vein) that may result in high-output cardiac failure, pulmonary and portal hypertension, and biliary injury.

Right heart failure and pulmonary hypertension are more commonly manifested by malaise and dyspnea, predominantly on exertion [15]. Both of these symptoms can also be attributed to iron deficiency anemia secondary to blood loss from occult or gross gastrointestinal bleeding.

The opening of the arteriovenous fistulas causes a decrease in arterial pressure as blood shifts to the venous system and an increase in cardiac output [15]. This is further precipitated by the presence of anemia, mainly due to blood loss from mucocutaneous telangiectasias and visceral arteriovenous malformations. Left ventricular afterload decreases, venous resistance decreases, and the sympathetic system is activated, leading to an increase in heart rate [15]. Subsequently, serum angiotensin is increased, causing a decrease in renal blood flow and a decrease in urinary output [15]. The resulting hyperdynamic circulation places the heart at risk for hypertrophic cardiomyopathy [15]. Liver transplantation is warranted before irreversible pulmonary hypertension develops [2].

At our institution, it is the policy to perform a stress echocardiogram as part of pretransplantation evaluation, followed by right heart catheterization if pulmonary artery pressure is elevated. One should keep in mind that pulmonary hypertension may be a contra-indication to liver transplantation.

The opening of pulmonary arteriovenous malformations can lead to hypoxemia, which can be manifested by cyanosis, shortness of breath, and clubbing.

Portal hypertension develops as a result of pseudocirrhosis [4, 16]. It has been postulated that abnormalities in blood flow with resultant ischemia lead to the development of hepatic fibrosis and reactive nodular changes, which, in turn, lead to portal hypertension and the development of porto-systemic collaterals [13]. In addition to pseudocirrhosis, portal hypertension is precipitated by the opening of arterioportal fistulas [13].

Nodular regeneration with fibrotic changes may result in direct bile duct injury with intrahepatic bile duct narrowing, bile stasis, stone formation, and infections [13].

Our patient presented with a cholestatic hepatitis prior to the development of hepatic decompensation.

Ischemic changes of the biliary system may lead to ischemic cholangitis, biliary infarction with rupture of bile ducts, extravasation of bile, and the development of sepsis [1]. Ischemic changes due to shunt physiology may lead to infarction of hepatocytes, with resultant hemorrhage and hepatocyte necrosis, cystic degeneration of the liver parenchyma, and infection [1, 16], as occurred in this case. The danger of the formation of septic emboli should be taken into account.

The role of screening family members using Doppler ultrasound should be stressed. Liver involvement has been reported in 32–41% of patients by Doppler ultrasound [8, 9].

Liver biopsy should be avoided in cases of proven or suspected HHT [17].

Pregnancy, which is associated with a hyperdynamic circulation, may have triggered the hepatic decompensation in our case. It has been reported that the number and size of arteriovenous fistulas increase during pregnancy [18]. Additional factors that may increase the risk of hyperdynamic circulation include blood volume increase by 30–40% at 24 weeks of gestation [4, 18], as well as reduced vascular tone [18] and reduced concentration of vasoconstricting substances in late pregnancy [18].

Liver transplantation has been reported to be effective in the reversal of cardiopulmonary changes and the elimination of hepatobiliary infections in patients with HHT and hepatic involvement. The largest study to date has been reported by the European Liver Transplant Registry in 2006 [19]. Forty patients who underwent liver transplantation for hepatic complications of HHT were analyzed. One-, 5-, and 10-year actuarial patient and graft survival rates were 82.5%. Of the eight patients who died, seven died in the perioperative period (one due to intraoperative bleeding, one on day 2 due to heart failure, one on day 4 due to cerebral bleeding, one on day 4 due to primary non-function, one on day 6 due to upper pulmonary

arteriovenous malformation bleeding, one on day 12 due to gastric arteriovenous malformation bleeding, one on day 14 due to bleeding during retransplantation performed for acute rejection) and one died 127 months after liver transplantation due to chronic rejection in the setting of non-compliance. The quality of life was markedly improved in all 32 surviving patients.

However, up to now, no definite criteria have been established to determine the optimal timing for liver transplantation in hepatic HHT [17]. Liver transplantation is obviously indicated in patients with ischemic biliary necrosis and in those with intractable high-output cardiac failure or portal hypertension [17].

Other therapeutic options such as transarterial embolization, ligation, and resection are not preferred due to the possible development of ischemic necrosis of the liver and infection [2, 4, 17, 19]. Likewise, transjugular intrahepatic portosystemic shunt (TIPS) is contraindicated because of the possible exacerbation of heart failure [17] and worsening pulmonary hypertension.

Interestingly, the regression of cutaneous and gastrointestinal telangiectasias has been reported with sirolimus and aspirin [20]. It has been postulated that sirolimus has a direct inhibitory action on the vascular endothelial growth factor (VEGF), while aspirin may have an indirect inhibitory action on VEGF by suppressing cyclooxygenase-2 [20]. The resolution of arteriovenous malformations with the reversal of high-output cardiac failure has also been reported with bevacizumab, a VEGF antibody [21].

Our patient had HHT with hepatic involvement and survived four pregnancies but succumbed to the fifth, which probably played an important role in the rapid deterioration of her liver, causing severe ischemic biliary injury and sepsis. Massive hepatic involvement in this disease should be considered as an indication for transplant before the development of irreversible changes.

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