4-12-2009

Localized biliary ischemia in patients with hepatic arteriovenous malformations, a newly recognized syndrome occurring in Hereditary Hemorrhagic Telangiectasia Diagnosis and management

Rasha Khoury

Localized biliary ischemia in patients with hepatic arteriovenous malformations, a newly recognized syndrome occurring in Hereditary Hemorrhagic Telangiectasia

Diagnosis and management

A Thesis Submitted to the

Yale University School of Medicine

In Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

By

Rasha Khoury

2008

LOCALIZED BILIARY ISCHEMIA IN PATIENTS WITH HEPATIC ARTERIOVENOUS MALFORMATIONS, A NEWLY RECOGNIZED SYNDROME OCCURING IN HEREDITARY HEMORRHAGIC TELANGIECTASIA: DIAGNOSIS AND MANAGEMENT

Rasha S. Khoury, Guadalupe Garcia-Tsao, Lawrence H. Young, Katharine J. Henderson, Robert I. White, Jr. Yale Vascular Malformation Center, Yale University School of Medicine, New Haven, CT.

The clinical manifestations of hepatic arteriovenous malformations (HAVMs) were elucidated.

A review of the literature was undertaken to better understand how HAVMs specifically affect the biliary system. A retrospective review of the 50 patients with HAVMs seen at the Yale University HHT Center was done, including clinical manifestation, intervention and outcome analysis.

Of 50 adults with HAVM, median age was 64 (range 17-73) and 84% were female. Initially 74% were classified as Type 1, symptomatic heart failure, 16% as Type 2, portal hypertension, and 10% as Type 3, biliary abnormalities. In Type 1 conversion to Type 3 was associated with the highest mortality and in Type 3 invasive procedures precipitated rapid decline and need for transplant +/- death. Of the Type 3s, case reports of two sisters with localized biliary ischemia were presented.

To our knowledge this is the first description of localized biliary HHT involvement, diagnosis and management.

Table of Contents

Introduction

Hereditary Hemorrhagic Telangiectasia (HHT), Osler-Weber-Rendu, is an autosomal dominant disease with variable penetrence characterized by vascular malformations. First described in 1896 by Rendu who recognized the disease as local vascular "incompetence" and recommended applying tannin to control the bleeding associated with it (1) then by Osler in 1901 (2) and Weber in 1907 (3) who described the disease as inherited "vessel inadequacy" rather than a bleeding dyscrasia. When in 1909 Hanes (4) described the dilated vessels without muscular and connective tissue layers under light microscopy he suggested the term Hereditary Hemorrhagic Telangiectasia (HHT) which encompassed the main features of the disorder recognized at that time.

Our contemporary understanding of HHT histopathology builds on Hanes' light microscopy work, demonstrating local dilations of the venules post capillary beds with stress fibers in the cells along the lumen border in the developing telangiectases (5). When these young telangiectases mature the venules dilate significantly and become twisted with excess smooth muscle layers and no elastic fibers. The Yale-HHT center and others view these changes as secondary to the absence of capillaries and direct arteriole-venule connections. On a microscopic scale these telangiectases can be superficial, cutaneous or mucocutaneous, and visible to the naked eye when affecting the hands, face and torso. These areas of directly connected arteries and veins without capillary beds, when large, form the characteristic arteriovenous malformations (AVMs) that appear viscerally throughout multiple systems such as the lungs, brain and liver (6).

The clinical diagnosis of HHT is based on the Curaçao criteria (7). These criteria include epistaxis, telangiectases at characteristic sites (lips, mouth, fingers, nose), visceral

involvement (GI lesions, or lung, brain, liver AVMs) and a first-degree relative with HHT. Inheritance is autosomal dominant with variable penetrance and affects men and women of all ages and ethnic backgrounds (8). About 10-20 in 100,000 individuals worldwide are affected by HHT (9-12) and 1 in 5-8000 in Dakeishi et al (8), with varying manifestations even within the same family. Genetic studies have established HHT as the first human disease defined by a mutation in a member of the (TGF)-β receptor complex. Nearly all patients and families affected by HHT fall into the HHT categories HHT-1 and HHT-2 in reference to mutations mapped to two genes (ENG- endoglin mapped to chromosome 9 (13) and ACVRL1 or ALK-1 mapped to chromosome 12 (14, 15), both belong to the transforming growth factor (TGF)-β receptor superfamily (16). Though the exact mechanism of genetic-vascular-pathology of HHT is not completely understood we do know that (TGF)-β superfamily affects vascular biology through membrane receptors, type I and type II serine/threonine kinases. Once a ligand binds type II receptors, with which the homodimeric membrane protein ENG functions in association, as an auxiliary receptor, they recruit and phosphorylate type I receptors (ALK-1) phosphorylating SMAD proteins and eventually modulating gene transcription by initiating the signaling cascade. HHT is thought to be the result of ENG and ALK-1 haploinsufficiency. Saxena et al (17) suggest that the lack of endoglin may result in the failure to initiate production of extracellular matrix by TGF-beta leading to failure of vascular remodeling and a haphazard arrangement of abnormal telangiectatic vessels.

With variable penetrance the clinical manifestations of HHT are age related, GI and hepatic involvement more prevalent in older patients for example (18), epistaxis

more likely to present in childhood. The genotype-phenotype relationship in HHT has been studied in the last decade and confirmed some clinically noted differences in phenotype distribution based on sex. Studies using genetic sequencing have demonstrated specific variability with respect to gender and subtype, highlighting a predominance of PAVMs (19-21) and HAVMs (21-24) in female patients as well as linking PAVMs with symptomatic HHT-type 1 and HAVM with HHT-type 2. In late 2003 genetic testing for HHT became available, allowing families and providers to test multiple individuals within an affected family. The ability to genotype a family is especially useful in children who have not yet become symptomatic but where early screening and intervention can reduce/prevent catastrophic sequelae. Since the mutation is family specific, affected asymptomatic family members are readily detected and can undergo brain and lung screening. In the case of families with liver involvement, genetic testing may help us identify those individuals that need more careful and less invasive evaluation when presenting with abdominal or RUQ pain or other biliary symptoms.

Clinically HHT manifests with epistaxis in 93% of patients secondary to telangiectases in the nasal mucosa (25). Nosebleeds vary in severity and frequency but onset is mostly in the first two decades of life. 13-44% of patients experience GI bleeding secondary to telangiectases of the stomach and small intestine, these also vary in severity and frequency but onset is usually in the 5^{th} and 6^{th} decades (26, 27). Organ system involvement includes the brain, lungs and liver. CAVM has been reported in 10-23% of HHT patients (28, 29) with a rate of cerebral hemorrhage comparable to non-HHT CAVM population (30). PAVMs are a more variable manifestation that can occur at any point in a patient's life. HHT patients with PAVMs can have single discrete lesions,

multiple discrete lesions or diffuse involvement. PAVMs affect 24%-60% (31-34) of HHT patients and can present with cyanosis, clubbing, dyspnea on exertion and hypoxemia. The treatment of choice for symptomatic PAVMs currently is transcatheter embolotherapy in adults (20, 35-37).

By far the most common visceral HHT involvement, albeit asymptomatic, is the hepatobiliary system. Large prospective studies using non-invasive imaging have shown HAVMs occur in 48% (38) and 73% (39, 40) of HHT patients with symptoms appearing in about 8%-31% (10, 38, 39). With the evolution and use of non-invasive imaging modalities we are likely to diagnose even more patients with liver involvement.

Historically (41) liver involvement was broken down by histologic group: 1) telangiectasia with fibrosis or cirrhosis; 2) cirrhosis without telangiectasia (cirrhosis was thought to be related to superimposed liver disease, e.g. post transfusion hepatitis) and 3) telangiectasia without fibrosis or cirrhosis. Today we understand liver involvement in HHT to be arteriovenous malformations (AVMs) that lead to various forms of shunting: hepatic artery to hepatic vein (Figure 1A), hepatic artery to portal vein (Figure 1B) and portal vein to hepatic vein (Figure 1C). Garcia-Tsao (42) describes these three shunt types as likely occurring simultaneously with singular and likely alternating functional predomination. These shunts lead to the various symptoms characteristic of hepatic involvement: high output cardiac failure (Type 1), portal hypertension (Type 2) and biliary ischemia (Type 3). Symptoms appear to be more common in women than men with onset in the third decade of life. They also have the capacity to occur, exacerbate and remit spontaneously, as evidenced by symptom variation depending on circulatory state as in pregnancy, anemia, atrial fibrillation, etc. Most commonly patients present

with signs and symptoms of high output cardiac failure (shortness of breath and edema without evidence for PAVM or anemia) with fewer patients presenting with portal hypertension (PHT) (ascites, variceal hemorrhage, abdominal pain) and fewer still presenting with biliary symptoms (abdominal pain, cholangitis, encephalopathy). Symptoms can begin with RUQ pain that brings a patient to their provider where hepato or hepatosplenmegaly can be found, a RUQ bruit (or thrill) +/- ascites. Laboratory testing may reveal elevated alkaline phosphatase and GGT, anicteric cholestasis, present in 73% of patients (42, 43). Also –but rare- the following presentations may occur: porto-systemic encephalopathy, abdominal angina and nodular regenerative and focal nodular hyperplasia (44, 45) the latter which can lead to misdiagnosis of cirrhosis, more accurately pseudocirrhosis (46) as well as a misdiagnosis of HCC (47).

Various imaging modalities are useful in the diagnosis of hepatic involvement when a patient is symptomatic but otherwise screening is not recommended given the high prevalence of asymptomatic liver involvement in the HHT population and the tendency for unfamiliar providers to pursue the imaging pathology with invasive procedures that can lead to unfavorable consequences. The gold standard for the diagnosis of HAVM is angiography (48) but the more commonly used and (preferred) non-invasive tests are ultrasonography and CT. Wu (49) showed that arteriovenous shunting and arterioportal shunting can be demonstrated by early/differential enhancement of hepatic veins and portal veins respectively with multidetector CT but also showed that these findings do not necessarily correlate with clinical presentation. The authors found biliary pathology on imaging more prevalent in symptomatic patients compared to asymptomatic patients without displaying biliary symptoms clinically which

Garcia-Tsao et al suggest may be due to an increase in shunting and biliary ischemia further along the time course of liver involvement in HHT. While there is a gold standard for diagnosis of HAVM, there is no predictable course of complications or gold standard for treatment. Consensus recommendations are (50) to aggressively treat symptoms such as heart failure and pulmonary hypertension but also to be conservative with invasive liver procedures (avoiding liver biopsy, ERCP and refraining from the past practice of hepatic artery embolization as a means to control high flow states).

Albeit the least common, the biliary subgroup (Type 3) of HHT hepatic involvement can be particularly aggressive and unpredictable. The patients are at risk for rapidly progressive hepatic failure but outcome can be improved with greater recognition of the disease process and heightened awareness of the clinical, imaging and biochemical presentation of the disease as well as the options for management and definitive treatment. This study reports 2 sisters with HHT and HAVM who presented with "spontaneous localized biliary ischemia", a unique syndrome. Conservative management including percutaneous biliary drainage led to resolution of symptoms. This localized form of symptomatic biliary ischemia is contrasted with the its more generalized form.

Statement of Purpose and Hypothesis

The purpose of this thesis is multifold. A review of the English literature was preformed to better understand and define the biliary subtype of liver involvement in HHT. A retrospective analysis of patients seen at the Yale University HHT Center was done, including clinical manifestation, intervention and outcome analysis. Case reports are presented of two sisters in their third decade with hepatic HHT involvement

presenting with localized biliary ischemia. To our knowledge this is the first description of localized biliary HHT involvement. These results, with a recommendation on diagnosis and management of localized biliary ischemia in HHT patients are presented here.

Subjects and Methods

A. Literature Review

All case reports of patients with biliary symptoms secondary to hepatic AVMs were searched using Medline. Reports prior to 1950 were found by researching references of reviews and reports published after 1950. Only reports in the English language were included. Reports were reviewed and the following data collected: age, gender, presenting symptom (RUQ/abdominal pain; cholangitis/jaundice; nausea/vomiting; weight loss; other including shortness of breath; liver bruit; lab abnormalities (alkaline phosphatase; bilirubin;; biliary abnormality on imaging), intervention preformed, and outcome. This discussion will focus on those with HHT liver involvement Type 3 presenting with RUQ pain.

B. Chart Review

The charts of patients seen and evaluated at the Yale-HHT center in the last 20 years with a diagnosis of liver involvement were reviewed with the approval of the Yale Human Investigation Committee.

The unique presentation of localized biliary ischemia in two patients at the Yale-HHT center will be presented in case report with a discussion on diagnosis and

management. To our knowledge this is the first time this presentation has been recognized prospectively.

Results

In the last 12 years, of the 2500 patients evaluated at the Yale-HHT center, 50 presented with or developed symptoms related to liver involvement. The median age at initial evaluation was 64 years (range 17-73) years and 42/50 (84%) were women. Patients were initially classified into Type 1, symptomatic high cardiac output state (37/50 patients, 74%), Type 2, portal hypertension (8/50 patients, 16%), and Type 3, biliary abnormalities (5/50 patients, 10%) [Young, Garcia, White et al. unpublished data]. Of the type 1 patients, 4 went on to develop biliary ischemia in their final year of life, these are classified as type 1 to type 3 converters and overall had the highest mortality. The focus of this thesis will be the Type 3 group, of whom 100% were female, median age was 39 years (range 31-59). Type 1 and 2 patients were treated medically to either correct or control symptoms: anemia, dyspnea, edema and prevent recurrent atrial fibrillation. Type 3 patients were treated aggressively with antibiotics when infection was suspected and those with biliary pain were given frequent small meals and bile salts as well as analgesics. Two of the Type 3 patients were treated with percutaneous drainage of focal bile collections with excellent outcome, case reports highlighted below. During mean follow-up of 4.8 years, 17/50 (34%) of patients died. In Type 1 patients, 10/37 died at a median of 4 years after initial evaluation due to spontaneous biliary duct necrosis and/or liver hemorrhage (4) of whom 3 converted from type 1 to type 3 in the final year of life, right heart failure with superimposed complications (4), liver necrosis post hepatic

artery embolization (1) and unknown (1). In Type 2 patients, 6/8 died at a median of 4 years due to esophageal varices (1), intractable bleeding from gastrointestinal telangiectases (2), presumed pulmonary emboli (1), pancreatic cancer (1), and lung cancer (1). One of three Type 3 patients died after failed liver transplantation.

The Yale-HHT center has previously presented the largest study on hepatic HHT involvement and noted that progressive disease leading to mortality is frequent but not universal. In that study, Type 1 patients with intractable heart failure who went on to devastating biliary ischemia and necrosis, patient # 3, 4 and 5, had the highest mortality rate. Table 1 illustrates the 3 patients presenting with Type 3 as it had been described up to 2005, and the 3 patients who converted from Type 1 to Type 3 as a final scenario. P1 and P2 are our cases of localized biliary ischemia. All 8 patients presented with RUQ pain apparently precipitated by various types of inflammatory biliary episodes.

Note: P7's sister died at age 29 of Type 3 HHT shortly after OLT for biliary necrosis at an outside hospital (OSH). She initially presented with RUQ pain to OSH where a cholecystectomy was done revealing gangrenous cholecystitis, post-operative complications included persistent sepsis and cholangitis. Initial imaging showed normal caliber bile ducts but quickly developed communicating intrahepatic abscesses with the biliary tree, the patient was transferred to transplant center for evaluation and received OLT but died 2 weeks later as a result of sepsis. Providers attributed her disease process to a cholangitis rather than a Caroli's variant. The liver explant had multiple areas of focal centrilobular necrosis but relatively well preserved and unremarkable vasculature and bile ducts.

Table 2 illustrates the 14 cases reported in the literature of HHT patients with hepatic involvement Type 3. 100% of the patients were female with an age range of 26-62 and a median of 38 years. 11/14 patients presented with RUQ or abdominal pain, 7/14 with jaundice or cholangitis, 4/14 with nausea/vomiting and weight loss, 4/14 with fever and 1/14 with hemobilia. In 2/14 the authors reported the presence of a liver bruit. 10/14 presented with alkaline phosphatase abnormalities and 11/14 with abnormal biliary imaging. The range of time of onset to outcome was 6 hours-15 months with a mean of 5.7 months. Most patients progressed to bacteremia, severe liver function abnormalities and diffuse bile leaks/hepatic abscesses. 11/14 received liver transplant as a definitive treatment for liver failure or imminent failure with excellent outcome. 2 of the 14 died, one of severe and fulminant biliary sepsis (6 hours after onset of pain) and one after hepatic artery ligation and bile leak progression.

Case Reports of Yale HHT patients with focal Type 3 liver involvement

WM: A 39 year-old woman diagnosed with HHT at age 21, from an HHT family with unique liver involvement (sister presented below), began experiencing abdominal pain in August 2006. The pain began in the epigastrium radiating to the RUQ and localized to the RUQ by November 2006. The pain was sharp and unrelated to eating or activity but it did awaken WM at night. It remained manageable until December 2006 when WM presented with severe RUQ pain and mild elevation of liver enzymes (AST/ALT 46/53 and alkaline phosphatase, AP, 72); all other biochemical data was within normal range. On abdominal CT (Figure 2a) the liver had heterogeneous uptake,

particularly in the posterior right lobe. There was no evidence of hepatomegaly or intrahepatic cysts, and no enlargement of the IVC or the hepatic veins. The posterior right lobe of the liver showed a decreased vascular pattern and low attenuation density (diffuse, involving 25-30% of the posterior right lobe) consistent with AVM and ischemia within the liver parenchyma.

By January 2007, the pain became more of a constant discomfort, and WM reported the emergence of the following symptoms: a "racing" heart, shortness of breath, and orthopnea. At that time there were no signs or symptoms of ascites, edema, GI bleeding or encephalopathy. On exam WM had scattered telangiectases but no jaundice. She was normotensive (BP 120/80) with a normal heart rate (88), in contrast to patients with Type 1 hepatic involvement patients who present with wide pulse pressure and large volume pulse. Abdominal exam was notable only for a clear bruit over the liver and particularly in the epigastrium. Laboratory data included: AST/ALT 41/23 and AP 86 (GGT 68). Contrast cardiac echo indicated mild shunt and CT without contrast demonstrated several small PAVMs that did not need treatment at that time. WM was diagnosed with HHT liver involvement and abdominal pain was attributed to biliary ischemia (Type 3) with clinical severity unaccounted for by biochemical data and imaging. Wu et al (49) had previously demonstrated that imaging findings are not predictive of clinical severity in most patients with liver HHT.

At this point it was felt that WM's liver involvement was relatively minor requiring no intervention and would hopefully resolve spontaneously. Were it to continue or get worse, it was recommended WM return to our Center for evaluation and treatment.

In May 2007, WM presented to her local hospital with uncontrollable RUQ pain. A

HIDA scan showed a low gallbladder EF of 21% (suggesting chronic cholecystitis with biliary dyskinesia but without evidence of acute cholecystitis or common bile duct obstruction). One week later abdominal CTA showed a diffusely abnormal liver with multiple enhancing foci throughout both the right and left hepatic lobes likely related to small telangiectases (as described in Garcia et al 2007 the markedly heterogeneous hepatic enhancement pattern of symptomatic HHT involvement). Also seen at this time was a new 3cm (3.0 x 2.1) cyst in the right posterior hepatic lobe with a subcentimeter cyst in the inferior right hepatic lobe. In attempt to continue non-invasive management and minimize complications, WM was placed on a regimen of antibiotics, bile salts and analgesics. Her pain continued to be intermittent but severe, lasting 24-36 hours at a time and she was without fever.

In late June her pain became refractory to the pain regimen, and evolved to continuous throbbing RUQ pain accompanied by low-grade fever. WM was admitted to YNHH and found to have elevated AST/ALT (51/23) and AP (269), her total/direct bilirubin never rose above normal range. Abdominal CTA showed a diffusely abnormal enlarged liver with small vessel AV shunting and a prominent biloma, with no evidence of infarction. Given improving pain control and lack of infection or infarction signs WM was continued on an adequate pain regimen and discharged with outpatient follow-up on HD 7. At the time of discharge AST/ALT 28/19 and AP was 108.

One week later WM was readmitted to the liver service with refractory and worsening RUQ pain, fever and chills. AST/ALT were found to be elevated at 141/115, alkaline phosphatase at 149, and all other biochemical data were within normal range. A repeat abdominal CT (Figure 2b) revealed an enlarging fluid filled lesion in the right

hepatic lobe with a question of infection given the clinical presentation. Meanwhile, transaminases climbed to 154/123 and AP reached 188. It was felt that aspiration and drainage by IR would be beneficial, although we remained concerned about draining the cyst since our previous experience suggested worsening liver function after intervention (Table 1, patients # 3 and 6). We did not appreciate at the time that this may have been a more localized process than we and others had seen previously. On HD 3 the collection was aspirated and found to be sterile. Due to continued pain and fever on HD 5 a second abdominal CT with oral and IV contrast (Figure 2c) was obtained and showed interval increase in the right hepatic lobe fluid collections. On HD 7, due to concern for an abscess and realization that until we drained this biloma WM could not be weaned from PCA and would possibly not recover, IR drained the collection and placed a percutaneous biliary drain (Figure 2d, 2e). WM's pain began to resolve slowly and she was discharged on HD 10 (AST and ALT 23/28 and AP 116 at discharge) with outpatient follow-up, pain regimen and directions for drain self-care. In subsequent months WM suffered a number of episodes of bacteremia secondary to tube change/manipulation but did well with marked reduction in biloma size (Figure 2f-h) and resolution drain output and pain. The tube was capped and removed 3 months after placement. At 3 month follow-up WM remains asymptomatic.

Interestingly WM's sister (EM) presented with a similar clinical picture, at age 31, to an outside hospital. EM is a woman with HHT diagnosed at age 12 in the setting of childhood nosebleeds, never requiring transfusion, and a positive family history for HHT including her two sisters, mother and maternal grandmother. At that time EM did not

have known visceral involvement and her family history specifically did not include known liver involvement at that point.

EM presented in August 2005 with new abdominal pain which was described as band-like in the upper abdomen, dull at first but became sharp during the ensuing months. EM reported having this pain with her two pregnancies in the past, in both cases it resolved spontaneously. On physical exam EM had multiple mucocutaneous telangiectases but no jaundice. Cardiopulmonary exam was unremarkable at that time. Abdominal exam revealed a bruit in the RUQ but no hepatomegaly, ascites, or peripheral edema. EM underwent workup for ulcers and gallstones over the next 3 weeks without a cause identified or pain relief. Abdominal CT revealed a cystic area in the right lobe and was aspirated in her local hospital. Post aspiration her pain became much worse and she developed fevers and chills and was transferred to a tertiary care center. ERCP was performed and demonstrated focal sclerosing cholangitis with post stenotic dilation of the intrahepatic biliary duct (mostly in the posterior segment of the right hepatic lobe). RUQ ultrasound revealed a cystic lesion in the posterior segment of the right hepatic lobe without septation or calcification, and through transmission without solid mass features in the liver and without intrahepatic dilatation. HIDA scan revealed gallbladder dysfunction with an EF of 30.1%. Given the clinical picture and unrelenting RUQ pain EM underwent a laparoscopic cholecystectomy in October 2005. Intra-operative retrograde cholangiography showed the right and left intrahepatic biliary ducts were normal without focal stenosis or occlusion. Branches of the right hepatic duct, however, demonstrated focal stenosis and post stenotic dilation, focal sclerosing cholangitis, consistent with preoperative imaging. This episode of instrumentation likely led to further bacterial

seeding. EM's pain, fevers and nausea persisted, and the clinical team was advised to transfer to a transplant HHT center. Two weeks following aspiration and cholecystectomy, as EM's pain continued to progress (at this point she had lost 30lbs from decreased intake secondary to pain) and signs of infection led to a diagnosis of liver abscess, antibiotics were started. Abdominal CT showed two types of low attenuation changes in the right lobe of the liver: one poorly defined and diffuse (cysts), the other more focal and discrete (ducts), dilated ducts involving the posterior segment of the right lobe of the liver with an appearance similar to what was seen pre cholecystectomy. Her heart was slightly enlarged and a prominent IVC was noted on CT. A percutaneous drain was placed to drain the collection in the right hepatic lobe and P2 was discharged home with outpatient follow-up. During follow-up she was admitted for fever spikes following drain repositioning but overall did well with occasional pain when the catheter was capped.

At 6-week follow-up, post-contrast CT showed a lobulated 3.2 x 7.7cm fluid collection in the central aspect of right lobe of liver with a percutaneous drain in place and duct dilation slightly more inferior in the right lobe of the liver. CXR at that time revealed cardiomegaly. A brief period of drain occlusion during that admission led to worsening pain, fevers and chills without evidence for bacteremia but with repeat CT showing enlargement of several intrahepatic fluid collections surrounding the percutaneous drain. Over the subsequent few months the fever gradually dissipated and the drain was scaled down in size until it was extracted in April 2006 (8 months after initial RUQ pain onset/presentation).

At one year follow-up in April 2007 EM was well, without symptoms. BP and HR were within normal range. On exam EM had multiple telangiectases on lips, sublingual, on chest, back and hands but did not have jaundice. Her lungs were clear. Cardiac exam revealed a holosystolic murmur in the precordium. Abdominal exam revealed a bruit in the RUQ but no ascites, hepatomegaly or peripheral edema. Of note, EM's stool guaiac was positive. GGT was mildly elevated at 74 (normal range 0-51) with all other biochemical data within normal range. Cardiac echo at follow-up showed evidence of late right to left shunting suggesting PAVM. Abdominal CT showed heterogeneous enhancement on arterial phase consistent with arteriovenous shunts, hepatic artery to hepatic vein. Low-density area in the posterior segment of the right lobe could represent interval resolution of a cyst and embolization coils were present. EM's presentation was attributed to focal biliary liver involvement by HHT, with localized biliary ischemia arising secondary to AV shunting and good outcome following percutaneous drainage.

Discussion

Overview of HHT in the liver

The characteristic vascular malformations of HHT of the liver are arteriovenous shunts involving focal sinusoidal ectasia and aberrant direct communications between hepatic arterial branches and ectatic sinusoids. Portal venous shunts between portal and hepatic vein have also been documented by 3-D reconstructions of a human HHT liver (51). These ectatic, dilated vessels have walls of varying thinness and appear in isolation or clusters, in normal or aberrant locations as demonstrated in a mouse model of Acvrl +/- (HHT type 2), the type associated with liver manifestation. Srinivasan et al were able

to confirm lack of vascular integrity with a Von Willebrand factor (VWf) immunostain and showed how these vessels can bleed into surrounding mouse liver tissue (52). The compression and atrophy of adjacent hepatocytes in these areas of vascular malformation seen in the mouse model were later described in the human HHT liver by Blewitt et al in a landmark study (53) that changed the thinking of the HHT liver community as I will discuss below.

HHT hepatic vascular malformations have age-dependent penetrance. Patients can become symptomatic, usually in the third decade, in the setting of AVM growth or new high volume states such as anemia and pregnancy. The direct arteriovenous communications result in a decrease in vascular resistance within the liver. With decreased hepatic vascular resistance, hepatic blood flow increases and a self-perpetuating cycle is set in motion. Total hepatic blood flow increases, associated with decreasing hepatic vascular resistance and leads to increased venous return to the right-sided chambers of the heart, increased cardiac output (CO), increased pulmonary artery and pulmonary capillary wedge pressure. Heart rate can increase secondary to sympathetic activity and with time blood volume will expand in response to the renal-hormonal loop and cause cardiac chamber dilatation as well as hypertrophy. Any state of volume expansion such as anemia which increases CO and enhances existing shunts by decreasing blood viscosity (54), will then exacerbate this cycle.

Normally the hepatic artery accounts for 25-30% of afferent blood flow in the liver, and 45-50% of oxygenation. Branches of the hepatic artery and branches of the portal vein run in parallel within the portal canals/portal tracts where most of the arterial blood then enters a plexus of capillaries known as the peribiliary plexus surrounding and

supplying the bile ducts (before draining into the sinusoids). In HHT, the vascular malformations within the liver (hepatic artery to hepatic vein, hepatic artery to portal vein and portal vein to hepatic vein) despite causing vascular "high flow states" carry blood away from the branches of the hepatic artery (significantly decreasing oxygenation reaching end arterioles and the peribiliary plexus). This relative (or absolute at the extreme) bypass of the peribiliary plexus could explain the infarction of portal tracts, ischemia, stricture and stenosis of bile ducts and eventually the bile cysts, referred to as bilomas. Bilomas are essentially extrahepatic or intrahepatic bile collections outside the biliary system and have been reported secondary to: a) trauma (55, 56) (many are iatrogenic (55) and can occur after intra-abdominal surgery (57-59), ERCP (60), percutaneous transhepatic cholangiography (55) b) complication of transarterial embolization (61-63), percutaneous ethanol intratumor injection for HCC (64) c) hepatic infarction (65, 66) d) gallbladder infection (67) e) biliary stone (68) f) bile duct ischemia (61) and g) AVM (69). The scenario of peribiliary ischemia that arises with AVM growth and dynamic shift across the hepatic shunts is therefore one of "poverty amidst plenty" as described by Saluja and White (70) and others (42, 53, 69).

World experience with liver HHT Type 3

Various models have been proposed to explain biliary ischemia in HHT patients. The overall incidence of the latter is so rare and scattered across institutions that most reports involve only one or two cases. The largest case series to date includes 5 patients with biliary ischemia among 19 HHT patients reported at the Yale-HHT Center (42). Table 2 illustrates the 14 cases that have been reported in the English-language literature

from centers other than the Yale-HHT center. One hundred percent of patients reported are female, with a median age of 38 (range 26-65), and the most common presenting symptom of abdominal pain and/or abdominal bruit and hepatomegaly (Table 2). The most common laboratory abnormalities were elevated alkaline phosphatase levels from 2-10 times the upper limit of normal and the most common imaging abnormalities were biliary pathology on ultrasound, CT or MRI. These cases span 17 years and reflect the change in understanding and management of these biliary HHT patients.

In 1990 Ball et al (71) described the first case of hepatolithiasis (soft brown caliculi in the hepatic ducts with surrounding parenchymal necrosis) in a 62-year-old female HHT patient with HAVM and rapid death from septic shock. Ball et al proposed that abnormalities in hepatic blood flow led to hepatic fibrosis and nodular regeneration and went on to explain (as Mendoza et al suggested in 1995(72)) that nodular transformation is secondary to large anomalous arteries hyperperfusing portions of the parenchyma, which in turn causes stenosis and compression of large intrahepatic bile ducts leading to biliary stasis. Stasis and superimposed infection then precipitate stone formation (lithiasis).

In 1995, Bauer et al (73) presented the case of a 33-year old woman with HHT and liver failure requiring transplantation, the liver explant was shown to have bile stained foci of necrosis centered around portal tracts, with the portal collagenous skeleton isolated and detached. Bauer et al suggested arterial ischemia secondary to AVM shunts as an etiology for the portal necrosis and biliary stricture leading to bile stasis and superinfection. This they compared to portal necrosis and biliary sludge seen in liver

transplantation where the biliary tree sustains ischemic injury as a consequence of storage at 4 degrees centigrade (74).

McInroy et al in 1998 (75) presented a 31-year-old woman with recurrent RUQ pain and fever who underwent invasive diagnostic procedures that precipitated deteriorating liver function, RUQ syndrome and eventually diffuse hepatic ischemia and multiple abscesses requiring transplantation. The authors presented the explanted liver and showed that while the intrahepatic biliary ducts were necrosed the extrahepatic ducts were maintained, a scenario described by Zajko in liver transplant literature. The authors attributed this to the difference in blood supply, with the intrahepatic ducts being supplied by the hepatic artery which is vulnerable to the AVM shunting of HHT and the extrahepatic ducts with multiple extrahepatic blood suppliers -more than seven arteries including the cystic artery, posterior superior pancreaticoduodenal artery, right hepatic artery, and retroportal artery-. The conclusion as mentioned by Bauer et al earlier is that biliary ischemia is likely secondary to intrahepatic vascular shunting due to the AVMs.

Biliary ischemia in the setting of hepatic AVMs is likely a dynamic continuum with mild manifestation of chronic cholangitis (70-80% of hepatic HHT patients have some degree of cholestasis (76) and with biliary necrosis at the extreme. Factors that reduce oxygen delivery to these compromised ducts (anemia, pregnancy, GI bleeding) will push the continuum to its extreme.

Certainly the occasional onset of biliary necrosis post hepatic artery embolization (HAE) supports this theory of peribiliary ischemia secondary to AVM shunts. HAE is functional ligation of the hepatic artery with spiral coils or poly vinyl alcohol particles initially undertaken as a treatment for high output cardiac failure with the aim of arresting

flow into the (hepatic artery to hepatic vein) shunt and resolving the high flow state. In instances of concomitant portal vein to hepatic vein shunts the portal vein cannot supply the peribiliary plexus or liver parenchyma with sufficient oxygenated blood and biliary ischemia and necrosis result. In 1998 Odorico et al (77)reported two female patients 47 and 48 years old with biliary ischemia secondary to hepatic artery embolization. Initially they presented with chronic abdominal pain, weight loss and multiple hepatic AVMs on CT and angiography, but unlike previous cases, normal liver function tests. Both patients underwent hepatic artery or branch embolization with temporary relief of pain followed by onset of RUQ syndrome, sepsis and large biloma formation. In both cases the authors considered percutaneous or surgical drainage of the collections but deferred for two reasons: a) bleeding risk and b) the diffuse appearance of multiple bilomas throughout the presumably necrosed liver parenchyma. In the setting of intrahepatic biliary sepsis and liver failure both patients underwent successful liver transplant and were alive at 9 and 12-month follow-up. Odorico et al emphasized the deleterious effects of hepatic artery embolization in these patients with hepatic AVMs (mortality close to 20% in a meta-analysis of the literature) with complications including parenchymal necrosis and liver failure. A similar outcome was noted by Hillert et al (2001) (78) in a 39 year-old gravid woman with diffuse abdominal pain during her second pregnancy necessitating cesarean section at 29 weeks for non-reassuring cardiotocogram. The patient went on to develop persistent pain post delivery, hemobilia, and an uncontrollable upper GI bleed and underwent a Billroth resection (pylorectomy with end to end anastomosis of the remaining stomach with the duodenum), ERCP and hepatic artery embolization and then deterioration of liver function and sepsis necessitating transplant. The explant had

multiple bilateral cystic lesions characteristic of diffuse purulent and chronic cholangitis with post-infectious cystic dilations, necrosis of mucosa of small and large bile ducts and destruction of most of the parenchyma (not unlike what Blewitt et al (53) later described spontaneous biliary ischemia secondary to HAVM, telangiectases rupture and liver cell "disintegration").

With hepatic artery embolization or ligation (79, 80), blood flow within the peribiliary plexus is even more compromised. The effect of transarterial embolization had also been documented in HCC patients where the vessels in the peribiliary plexus are lost or show coagulation necrosis adjacent to or within the necrotic bile ducts (61). These cases of post-HAE biliary ischemia are analogous to our cases of spontaneous biliary ischemia in setting of AVM shunts ("poverty amidst plenty") and to the sequelae of hepatic artery thrombosis post liver transplant where clinical presentation consists of fulminant hepatic necrosis, bile leak or relapsing bacteremia/septicemia (81, 82).

Zajko et al (1987) (83) present post-liver transplant patients who developed biliary strictures, both intra and extra hepatic, after hepatic artery occlusion (14/31 patients). 3 of the 14 developed bilomas. 4 of the 14 presented with biliary obstruction symptoms leading to imaging and the remaining 9 were known to have the HA occlusion prior to discovery of the strictures (early diagnosis). Strictures are described as anastamotic and nonanastamotic with the latter more likely due to ischemia and the former to scar formation and retraction. They are the result of under or arrested perfusion of the peribiliary plexus effectively severing the end arterial supply. In sever ischemia at the time of transplantation (or in response to inflammation of the biliary tract), necrosis

results and bile leaks can be seen. In most of these cases Zajko et al preformed percutaneous drainage until liver re-transplant was possible.

Biliary ischemia and necrosis also occurs as a spectrum of focal to diffuse depending on the anatomy of the vascular malformations and the resultant interruption of blood flow and oxygenation. Boillot et al in 1999 (84) presented a case of a 36-year-old gravid woman with marked diffuse hepatic necrosis and abscesses following cholecystectomy, ERCP and cesarean section who ultimately received a liver transplant as there was no other way to treat the disseminated hepatic sepsis secondary to superinfection.

In the same year Chen et al (1999) (69) reported a 26-year-old female patient with protracted RUQ pain, fever and jaundice, an elevated alkaline phosphatase 7 times the upper limit of normal and a focal biloma on imaging. ERCP was done and revealed normal sized intrahepatic ducts with some extravasation at the right hepatic ducts. They deferred percutaneous drainage for fear of bleeding risk but they did intervene surgically with an open laparotomy, cyst aspiration, hepatic artery ligation and liver biopsy. This was done prior to the shift in thinking regarding the risk-benefit imbalance of HAE. Initially the biloma was sterile and small but likely became infected and progressed in size with instrumentation. The patient died at an outside hospital ultimately of an unknown cause but with evidence of biloma progression 11 months prior to death. While Chen at el, agreeing with Bauer (73) and Mendoza (72), support the theory that the biloma was related to bile duct ischemia, they do not attribute RUQ pain to the biloma as it was not large enough to have an expansive effect on the liver capsule,

also when it later recurred post hepatic artery ligation the patient did not complain of pain. They do conclude with a recommendation for ERCP or percutaneous drainage for this focal presentation and certainly we know now that percutaneous drainage when possible is optimal but that ERCP has led to various degrees of biliary ischemia exacerbation. Later in 2006, Klepchick et al (85) reported another case of focal biliary ischemia in a 31 year-old woman with RUQ pain, diagnosed with biliary dyskinesia who underwent cholecystectomy and returned with pain and fever, alkaline phosphatase 7 times the upper limit of normal and collections later found to be focal groups of dilated bile ducts. As with our patient interventional radiology was asked to drain the collections, found to be sterile, reduced in size and then followed by pain recurrence. The pattern of focal segmental bile duct dilatation led the authors to suggest a "Caroli's variant" as an etiology for the biliary presentation in this HHT liver.

Azoulay et al in 2002 (86) from France reported 3 female patients, 38, 49 and 38-years-old (2 of them sisters) with repeated episodes of cholangitis and abdominal pain, with alkaline phosphatase abnormalities in the 200-300 range. The two sisters underwent cholecystectomy and both developed abscesses post-op that required repeated drainage. Ultimately the three patients received liver transplant (the quick move to treat these biliary patients with liver transplant maybe because the authors were reporting from a hepatobiliary and liver transplant unit). The authors propose that nodular transformation (described by Wanless at al 1986 (44) have described nodular transformation as a variant of nodular regenerative hyperplasia secondary to abnormal blood flow), fibrosis and biliary ischemia induced by the AV malformations. They suggest nodular transformation

can cause compression or stricture of large bile ducts favoring stasis, infection and lithiasis (as described by Ball (71) and Mendoza (72)).

Yet another theory proposed by Hatzidakis et al (2002) (87) is that of "external" or mechanical compression of bile ducts. The authors propose external vascular compression by the hepatic AVMs on the bile ducts, based on anatomical proximity on imaging, as a cause for their focal dilatation. Similar mechanical rather than ischemic/fibrotic etiology is ascribed to biliary obstruction in extrahepatic portal hypertension caused by periportal varices by compressing the extrahepatic bile ducts.

Yale experience with liver HHT Type 3

The Garcia-Tsao et al paper in 2000 (42) on Liver involvement and HHT based on the Yale-HHT experience was the first paper to highlight a large number of HHT liver patients 5/19 with biliary sequelae, 2 of those with right upper quadrant pain as their initial presentation as well as alkaline phosphatase abnormalities. All 5 patients had alkaline phosphatase abnormalities and bile duct pathology on imaging similar to Caroli's disease and sclerosing cholangitis. Garcia refers to the latter as secondary sclerosing cholangitis and attributes the development of biliary strictures (a process described with hepatic artery instillation of chemotherapeutic drugs (88) as well as post-liver transplant (83) which induces the formation of bile collections/cysts/bilomas directly to the bile duct ischemia caused by the AV shunting. Garcia further suggests vascular malformations at the ductal plate (Caroli-like) could contribute to abnormal biliary duct system development. Caroli's variant is a congenital disorder of insufficient reabsorption of

ductal plates resulting in multifocal segmental dilatation of large intrahepatic bile ducts. A retrospective review of liver biopsy histology from these 5 patients with respect to the following features revealed: ectatic vessels in 4; periductal fibrosis in 3 and bile-duct necrosis in 1 (versus none in the portal hypertension group); sinusoidal fibrosis in 0 (versus most in the portal hypertension group); nodularity, absent in 1, nodular hyperplasia (regeneration alternating with atrophy) in 3, true cirrhosis in 1; fibrosis along ecstatic vessels in 2. The histology reflects predominant shunts in either patient subgroup; hepatic artery to hepatic vein +/- portal vein and resultant relative ischemia of the peribiliary plexus versus hepatic artery to portal vein shunts and resultant increase in resistive indices in sinusoids and post sinusoids, increased flow with adjacent relative (and chronic) ischemia leading to atrophy adjacent to hyperplasia, nodular hyperplasia and portal hypertension.

A paper that changed our thinking about pathophysiology of HHT of the liver was published in 2003 (53). Blewitt et al described a 34-year-old patient with RUQ pain, normal liver function tests initially with only mild rise in AP to upper limit of normal. The patient underwent cholecystectomy and liver biopsy. Post-op minor acoustic changes were seen on ultrasound followed by development of definite cystic changes and an alkaline phosphatase 13 times the upper limit of normal. The patient ultimately received a liver transplant and did very well. The authors agreed with Bauer (73)and McInroy (75) who suggested biliary necrosis of bile ducts due to AV shunting may lead to liver damage (all three of these cases started with some form of biliary inflammation) but also offer an explanation for hepatic disruption based on histology, proposing rupture of the periportal telangiectases as the precursor step to bile duct necrosis. Periportal telangiectases are

delicate, susceptible to rupture as they get larger and if they coalesce as they rupture they could dissect into the liver parenchyma, accentuate AV shunting by changing the dynamics of flow and cause ischemic insult to hepatocytes and bile ducts leaving other telangiectases without hepatocyte support, liable to rupture and so on. Effectively the liver cells "fall apart" in what they dub "disintegration". Blewitt et al suggest in addition that these AVMS create localized shunt areas of high flow and high pressure leading to a relative ischemia that causes in turn atrophy of liver cell plates, a drop in mechanical portal canal support, decreasing support for telangiectatic vessels that then become more fragile and liable to rupture into the liver parenchyma; a process of hepatic collapse, labeled by the authors "hepatic disintegration". The micrographs presented in Blewitt et al show liver cells falling apart as a result of telangiectatic rupture/hemorrhage and likely relative ischemia, probably just short of necrosis. While the hemorrhages in the micrographs appear real it is difficult to see the break in the vessel wall since they are usually very thin and when they bleed the liver tissue is covered in blood. Dr. Garcia-Tsao suggests that an elastic tissue stain or trichrome stain could show the vessel wall and the breaks within the wall, however these were not shown in the Blewitt paper.

Pregnancy in the Type 3 liver HHT patient

A number of case reports relate to the exacerbation of hepatic vascular shunt sequelae in gravid HHT patients (78, 84) likely linked to the expansion of circulatory volume. Cardiac output in pregnancy increases 30-50% initially due to an increase in stroke volume (SV) and subsequently due to a rise in heart rate (HR) of about 10bpm. Most of the increase in cardiac output (CO) occurs before 20 weeks though it continues

into the third trimester and plateaus at 32 weeks. The increase in oxygen consumption occurs mostly in the second half of pregnancy reaching 20-30% above the non-gravid state at term. There is also an increase in blood volume to 45% of non-gravid women. The expansion of plasma volume precedes that of red cell volume creating a dilutional effect but the rise in hemoglobin and CO compensates for the rise in oxygen requirement. Pregnancy itself may also increase the AVM chance of bleeding secondary to estrogen effect on vascular fragility, although the exact mode of action of sex hormones and their role is unclear. In a double blind RCT 50ug ethinylestradiol and 1mg norethisterone resulted in significant reduction of transfusion requirements for HHT patients (89). The exact mechanism remains unclear however and keeping in mind that HHT patients are at risk for thromboembolic disease these hormonal agents must be used with caution.

Treatment

The Yale-HHT experience with Type 3 hepatic involvement illustrates the unpredictable and non-linear clinical course as well as the dilemma in management. To our knowledge this is the first case report of patients (two sisters) with localized biliary ischemia in the setting of hepatic AVMs and remission with percutaneous drainage. While it is difficult to identify sentinel signs that differentiate their clinical picture from that of those with more diffuse biliary ischemia it is clear that these two patients benefited from the conservative approach to their management. The description of hepatic disintegration by Blewitt et al, and possibly the cause of death in our P__ led us to proceed very carefully with P1 and 2. Refractory RUQ pain, elevated alkaline phosphatase to 3x upper limit of normal and hemodynamic parameters (HR and BP)

within normal range set these patients apart from the Type 1 to Type 3 converters but did not help differentiate them from the Type 3s with diffuse ischemia.

Certainly conservative/medical/goal directed-symptom relief is always the first step. Eliminating the hepatic AVM's feeding artery has been attempted via hepatic artery ligation (90-92) or embolization (93-97) with varying degrees of success and failure. The US HHT community decidedly moved away from these procedures in 2000 given the unpredictable complication profile. While hepatic artery ligation is invasive and less selective in its blockade (with embolization one can eliminate selective smaller branches). Embolization is associated with a number of complications from reflux of the embolization material outside the target area, to total ischemia to the area and necrosis/infarct of parenchymal tissue. Adverse outcomes include abdominal pain, gastrointestinal bleeding, abscesses, biliary ischemia, acute liver failure requiring emergency liver transplantation and death. For the 24 cases reported overall morbidity was 42% and overall mortality 17% (42, 77, 79, 92-95, 97-103). Revascularization and AVM recurrence have also been documented post HE (92). In Europe hepatic artery embolization remains a treatment option but admittedly done with caution and at centers with transplant capabilities should they be needed. The most likely explanation for this wide range of response to the embolization reflects the diversity of vascular malformation configurations within the HHT liver. Whiting et al explain that patients with hepatic artery to hepatic vein communications may tolerate embolization better than patients in whom there are also portal vein to hepatic vein communications given that in the setting of AVMs the portal vein is likely only to hypoperfuse the liver. The authors exclude

partial hepatectomy or lobectomy as an option given the extensive vascular network precludes safe surgical resection.

That said, currently the treatment for severe liver involvement (as well as post HE complications), intractable heart failure, severe portal hypertension, refractory ascites and acute diffuse biliary necrosis is liver transplantation. Many HHT patients will not be eligible given their age or co-morbidities (diffuse PAVMs for example) in which case a risk-benefit analysis should guide the clinician with regard to treatment course.

Conclusion

If these patients with symptomatic hepatic HHT type 3 are identified early in the course of the disease, monitored carefully and cautiously avoiding any invasive liver procedures especially when presenting with abdominal pain and/or alkaline phosphatase abnormalities and bile leaks on imaging, it may be possible to stave off the need for the extreme intervention of liver transplant. The HHT community has decidedly moved away from hepatic artery embolization and ligation given the evidence that these procedures can exacerbate biliary ischemia and hepatic failure (77, 92). Although the literature remains divided with some groups presenting prospective on embolization with good outcome. Chavan et al (104) present the largest such series, 15 patients treated with staged hepatic artery embolization with good outcome; 5/5 patients with abdominal pain relieved and 10/11 with increased cardiac output and/or cardiac failure improved (from around 12 to 8). They do suggest that patients with preexistent cirrhosis be excluded (this patient in their series died).

The Type 3 patient's symptoms (RUQ pain, fever, jaundice) will often remit spontaneously or with correction of anemia, termination of pregnancy, etc. We have documented the first case of localized biliary ischemia in a HHT patient with Type 3 liver involvement and conclude that avoiding invasive procedures but pursuing percutaneous draining of symptomatic bile leaks seen on imaging maybe be life saving. These patients need to be monitored closely in coordination with a transplant center in the event that percutaneous drainage fails and/or hepatic failure is inevitable. That said appropriate transplant guidelines for these patients need to be developed by the global HHT community to protect them in cases of slipping along the biliary ischemia continuum towards biliary necrosis, although many of these patients concomitantly have diffuse PAVMs that would preclude them from transplant. Some advances have been made in this area, Garcia-Tsao et al in 2006 suggested a MELD (model for end stage liver disease) exception for HHT patients. While the authors found insufficient objective evidence to grant HHT patients with/nearing liver failure automatic priority they did propose priority be assigned based on a case by case review by the regional review board where a score of 40 is given to patients with acute biliary necrosis and a score of 22 to patients with medically refractory heart failure and an addition of 10% mortality risk to the score 3 month interval review (105). Overall the medical community is recognizing the spectrum of visceral HHT involvement and the need for preventive care, screening when appropriate and cautious management.

References

1. Rendu, H. 1896. Epistaxis repetees chez un sujet porteur de petits angiomes cutanes et muquez. *Gazette des Hopitaux Civils et Militaires*:1322.

2. Osler, W. 1901. On a family form of recurring epistaxis, associated with multiple telangiectases of the skin and mucous membranes. *Bulletin of the Johns Hopkins Hospital* **12**:333.

3. Weber, F. 1907. Multiple hereditary developmental angiomata (telangiectases) of the skin and mucous membranes associated with recurring haemorrhages. *Lancet* **ii**:160.

4. Hanes, F. 1909. Multiple hereditary telangiectases causing hemorrhage (hereditary hemorrhagic telangiectasia). *Bulletin of the Johns Hopkins Hospital* **20**:63.

5. Braverman, I.M., Keh, A., and Jacobson, B.S. 1990. Ultrastructure and three-dimensional organization of the telangiectases of hereditary hemorrhagic telangiectasia. *J. Invest. Dermatol.* **95**:422-427.

6. Guttmacher, A.E., Marchuk, D.A., and White, R.I.,Jr. 1995. Hereditary hemorrhagic telangiectasia. *N. Engl. J. Med.* **333**:918-924.

7. Shovlin, C.L., Guttmacher, A.E., Buscarini, E., Faughnan, M.E., Hyland, R.H., Westermann, C.J., Kjeldsen, A.D., and Plauchu, H. 2000. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am. J. Med. Genet.* **91**:66-67.

8. Dakeishi, M., Shioya, T., Wada, Y., Shindo, T., Otaka, K., Manabe, M., Nozaki, J., Inoue, S., and Koizumi, A. 2002. Genetic epidemiology of hereditary hemorrhagic telangiectasia in a local community in the northern part of Japan. *Hum. Mutat.* **19**:140-148.

9. Jessurun, G.A., Kamphuis, D.J., van der Zande, F.H., and Nossent, J.C. 1993. Cerebral arteriovenous malformations in The Netherlands Antilles. High prevalence of hereditary hemorrhagic telangiectasia-related single and multiple cerebral arteriovenous malformations. *Clin. Neurol. Neurosurg.* **95**:193-198.

10. Plauchu, H., de Chadarevian, J.P., Bideau, A., and Robert, J.M. 1989. Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. *Am. J. Med. Genet.* **32**:291-297.

11. Guttmacher, A.E., McKinnon, W.C., and Upton, M.D. 1994. Hereditary hemorrhagic telangiectasia: a disorder in search of the genetics community. *Am. J. Med. Genet.* **52**:252-253.

12. Kjeldsen, A.D., Vase, P., and Green, A. 1999. Hereditary haemorrhagic telangiectasia: a population-based study of prevalence and mortality in Danish patients. *J. Intern. Med.* **245**:31-39.

13. McAllister, K.A., Grogg, K.M., Johnson, D.W., Gallione, C.J., Baldwin, M.A., Jackson, C.E., Helmbold, E.A., Markel, D.S., McKinnon, W.C., and Murrell, J. 1994. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. *Nat. Genet.* **8**:345-351.

14. Johnson, D.W., Berg, J.N., Gallione, C.J., McAllister, K.A., Warner, J.P., Helmbold, E.A., Markel, D.S., Jackson, C.E., Porteous, M.E., and Marchuk, D.A. 1995. A second locus for hereditary hemorrhagic telangiectasia maps to chromosome 12. *Genome Res.* **5**:21-28.

15. Johnson, D.W., Berg, J.N., Baldwin, M.A., Gallione, C.J., Marondel, I., Yoon, S.J., Stenzel, T.T., Speer, M., Pericak-Vance, M.A., Diamond, A. et al. 1996. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. *Nat. Genet.* **13**:189-195.

16. Proux, A., Tapiero, S., Girszyn, N., Levesque, H., and Marie, I. 2007. Liver involvement in hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber disease). Report of one case and review of the literature. *Rev. Med. Interne* **28**:775-779.

17. Saxena, R., Hytiroglou, P., Atillasoy, E.O., Cakaloglu, Y., Emre, S., and Thung, S.N. 1998. Coexistence of hereditary hemorrhagic telangiectasia and fibropolycystic liver disease. *Am. J. Surg. Pathol.* **22**:368-372.

18. Buscarini, E., Buscarini, L., Civardi, G., Arruzzoli, S., Bossalini, G., and Piantanida, M. 1994. Hepatic vascular malformations in hereditary hemorrhagic telangiectasia: imaging findings. *AJR Am. J. Roentgenol.* **163**:1105-1110.

19. Dines, D.E., Seward, J.B., and Bernatz, P.E. 1983. Pulmonary arteriovenous fistulas. *Mayo Clin. Proc.* **58**:176-181.

20. White, R.I.,Jr, Lynch-Nyhan, A., Terry, P., Buescher, P.C., Farmlett, E.J., Charnas, L., Shuman, K., Kim, W., Kinnison, M., and Mitchell, S.E. 1988. Pulmonary arteriovenous malformations: techniques and long-term outcome of embolotherapy. *Radiology* **169**:663-669.

21. Letteboer, T.G., Mager, J.J., Snijder, R.J., Koeleman, B.P., Lindhout, D., Ploos van Amstel, J.K., and Westermann, C.J. 2006. Genotype-phenotype relationship in hereditary haemorrhagic telangiectasia. *J. Med. Genet.* **43**:371-377.

22. Argyriou, L., Pfitzmann, R., Wehner, L.E., Twelkemeyer, S., Neuhaus, P., Nayernia, K., and Engel, W. 2005. ALK-1 mutations in liver transplanted patients with hereditary hemorrhagic telangiectasia. *Liver Transpl.* **11**:1132-1135.

23. Lesca, G., Olivieri, C., Burnichon, N., Pagella, F., Carette, M.F., Gilbert-Dussardier, B., Goizet, C., Roume, J., Rabilloud, M., Saurin, J.C. et al. 2007. Genotype-phenotype correlations in hereditary hemorrhagic telangiectasia: data from the French-Italian HHT network. *Genet. Med.* **9**:14-22.

24. Reilly, P.J., and Nostrant, T.T. 1984. Clinical manifestations of hereditary hemorrhagic telangiectasia. *Am. J. Gastroenterol.* **79**:363-367.

25. AAssar, O.S., Friedman, C.M., and White, R.I.,Jr. 1991. The natural history of epistaxis in hereditary hemorrhagic telangiectasia. *Laryngoscope* **101**:977-980.

26. Longacre, A.V., Gross, C.P., Gallitelli, M., Henderson, K.J., White, R.I.,Jr, and Proctor, D.D. 2003. Diagnosis and management of gastrointestinal bleeding in patients with hereditary hemorrhagic telangiectasia. *Am. J. Gastroenterol.* **98**:59-65.

27. Korzenik, J.R. 1996. Hereditary hemorrhagic telangiectasia and other intestinal vascular anomalies. *Gastroenterologist* **4**:203-210.

28. Fulbright, R.K., Chaloupka, J.C., Putman, C.M., Sze, G.K., Merriam, M.M., Lee, G.K., Fayad, P.B., Awad, I.A., and White, R.I.,Jr. 1998. MR of hereditary hemorrhagic telangiectasia: prevalence and spectrum of cerebrovascular malformations. *AJNR Am. J. Neuroradiol.* **19**:477-484.

29. Willemse, R.B., Mager, J.J., Westermann, C.J., Overtoom, T.T., Mauser, H., and Wolbers, J.G. 2000. Bleeding risk of cerebrovascular malformations in hereditary hemorrhagic telangiectasia. *J. Neurosurg.* **92**:779-784.

30. Easey, A.J., Wallace, G.M., Hughes, J.M., Jackson, J.E., Taylor, W.J., and Shovlin, C.L. 2003. Should asymptomatic patients with hereditary haemorrhagic telangiectasia (HHT) be screened for cerebral vascular malformations? Data from 22,061 years of HHT patient life. *J. Neurol. Neurosurg. Psychiatry.* **74**:743-748.

31. Kjeldsen, A.D., Vase, P., and Green, A. 2000. Hereditary hemorrhagic telangiectasia. A population-based study on prevalence and mortality among Danish HHT patients. *Ugeskr. Laeger* **162**:3597-3601.

32. Dines, D.E., Arms, R.A., Bernatz, P.E., and Gomes, M.R. 1974. Pulmonary arteriovenous fistulas. *Mayo Clin. Proc.* **49**:460-465.

33. Puskas, J.D., Allen, M.S., Moncure, A.C., Wain, J.C.,Jr, Hilgenberg, A.D., Wright, C., Grillo, H.C., and Mathisen, D.J. 1993. Pulmonary arteriovenous malformations: therapeutic options. *Ann. Thorac. Surg.* **56**:253-7; discussion 257-8.

34. Haitjema, T., Disch, F., Overtoom, T.T., Westermann, C.J., and Lammers, J.W. 1995. Screening family members of patients with hereditary hemorrhagic telangiectasia. *Am. J. Med.* **99**:519-524.

35. Terry, P.B., White, R.I.,Jr, Barth, K.H., Kaufman, S.L., and Mitchell, S.E. 1983. Pulmonary arteriovenous malformations. Physiologic observations and results of therapeutic balloon embolization. *N. Engl. J. Med.* **308**:1197-1200.

36. White, R.I.,Jr. 1996. Pulmonary arteriovenous malformations and hereditary hemorrhagic telangiectasia: embolotherapy using balloons and coils. *Arch. Intern. Med.* **156**:2627-2628.

37. Lee, D.W., White, R.I.,Jr, Egglin, T.K., Pollak, J.S., Fayad, P.B., Wirth, J.A., Rosenblatt, M.M., Dickey, K.W., and Burdge, C.M. 1997. Embolotherapy of large pulmonary arteriovenous malformations: long-term results. *Ann. Thorac. Surg.* **64**:930-9; discussion 939-40.

38. Buscarini, E., Danesino, C., Olivieri, C., Lupinacci, G., and Zambelli, A. 2005. Liver involvement in hereditary haemorrhagic telangiectasia or Rendu-Osler-Weber disease. *Dig. Liver Dis.* **37**:635-645.

39. Ianora, A.A., Memeo, M., Sabba, C., Cirulli, A., Rotondo, A., and Angelelli, G. 2004. Hereditary hemorrhagic telangiectasia: multi-detector row helical CT assessment of hepatic involvement. *Radiology* **230**:250-259.

40. Memeo, M., Stabile Ianora, A.A., Scardapane, A., Buonamico, P., Sabba, C., and Angelelli, G. 2004. Hepatic involvement in hereditary hemorrhagic telangiectasia: CT findings. *Abdom. Imaging* **29**:211-220.

41. Martini, G.A. 1978. The liver in hereditary haemorrhagic teleangiectasia: an inborn error of vascular structure with multiple manifestations: a reappraisal. *Gut* **19**:531-537.

42. Garcia-Tsao, G., Korzenik, J.R., Young, L., Henderson, K.J., Jain, D., Byrd, B., Pollak, J.S., and White, R.I.,Jr. 2000. Liver disease in patients with hereditary hemorrhagic telangiectasia. *N. Engl. J. Med.* **343**:931-936.

43. Haitjema, T., Westermann, C.J., Overtoom, T.T., Timmer, R., Disch, F., Mauser, H., and Lammers, J.W. 1996. Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease): new insights in pathogenesis, complications, and treatment. *Arch. Intern. Med.* **156**:714-719.

44. Wanless, I.R., and Gryfe, A. 1986. Nodular transformation of the liver in hereditary hemorrhagic telangiectasia. *Arch. Pathol. Lab. Med.* **110**:331-335.

45. Marteau, P., Poupon, R., Chazouilleres, O., and Darnis, F. 1986. Rendu-Osler disease and focal nodular hyperplasia of the liver. *Gastroenterol. Clin. Biol.* **10**:856.

46. Cooney, T., Sweeney, E.C., Coll, R., and Greally, M. 1977. 'Pseudocirrhosis' in hereditary haemorrhagic telangiectasia. *J. Clin. Pathol.* **30**:1134-1141.

47. Buscarini, E., Danesino, C., Plauchu, H., de Fazio, C., Olivieri, C., Brambilla, G., Menozzi, F., Reduzzi, L., Blotta, P., Gazzaniga, P. et al. 2004. High prevalence of hepatic focal nodular hyperplasia in subjects with hereditary hemorrhagic telangiectasia. *Ultrasound Med. Biol.* **30**:1089-1097.

48. Garcia-Tsao, G. 2007. Liver involvement in hereditary hemorrhagic telangiectasia (HHT). *J. Hepatol.* **46**:499-507.

49. Wu, J.S., Saluja, S., Garcia-Tsao, G., Chong, A., Henderson, K.J., and White, R.I.,Jr. 2006. Liver involvement in hereditary hemorrhagic telangiectasia: CT and clinical findings do not correlate in symptomatic patients. *AJR Am. J. Roentgenol.* **187**:W399-405.

50. Buscarini, E., Plauchu, H., Garcia Tsao, G., White, R.I.,Jr, Sabba, C., Miller, F., Saurin, J.C., Pelage, J.P., Lesca, G., Marion, M.J. et al. 2006. Liver involvement in hereditary hemorrhagic telangiectasia: consensus recommendations. *Liver Int.* **26**:1040-1046.

51. Sawabe, M., Arai, T., Esaki, Y., Tsuru, M., Fukazawa, T., and Takubo, K. 2001. Three-dimensional organization of the hepatic microvasculature in hereditary hemorrhagic telangiectasia. *Arch. Pathol. Lab. Med.* **125**:1219-1223.

52. Srinivasan, S., Hanes, M.A., Dickens, T., Porteous, M.E., Oh, S.P., Hale, L.P., and Marchuk, D.A. 2003. A mouse model for hereditary hemorrhagic telangiectasia (HHT) type 2. *Hum. Mol. Genet.* **12**:473-482.

53. Blewitt, R.W., Brown, C.M., and Wyatt, J.I. 2003. The pathology of acute hepatic disintegration in hereditary haemorrhagic telangiectasia. *Histopathology* **42**:265-269.

54. Radu, C., Reich, D.L., and Tamman, R. 1992. Anesthetic considerations in a cardiac surgical patient with Osler-Weber-Rendu disease. *J. Cardiothorac. Vasc. Anesth.* **6**:461-464.

55. Vazquez, J.L., Thorsen, M.K., Dodds, W.J., Quiroz, F.A., Martinez, M.L., Lawson, T.L., Stewart, E.T., and Foley, W.D. 1985. Evaluation and treatment of intraabdominal bilomas. *AJR Am. J. Roentgenol.* **144**:933-938.

56. Becker, C.D., Gal, I., Baer, H.U., and Vock, P. 1996. Blunt hepatic trauma in adults: correlation of CT injury grading with outcome. *Radiology* **201**:215-220.

57. Howdieshell, T.R., Purvis, J., Bates, W.B., and Teeslink, C.R. 1995. Biloma and biliary fistula following hepatorraphy for liver trauma: incidence, natural history, and management. *Am. Surg.* **61**:165-168.

58. Moss, G. 1996. Raising the outcome standards for conventional open cholecystectomy. *Am. J. Surg.* **172**:383-385.

59. Ralph-Edwards, T., and Himal, H.S. 1992. Bile leak after laparoscopic cholecystectomy. *Surg. Endosc.* **6**:33-35.

60. Dupas, J.L., Mancheron, H., Sevenet, F., Delamarre, J., Delcenserie, R., and Capron, J.P. 1988. Hepatic subcapsular biloma. An unusual complication of endoscopic retrograde cholangiopancreatography. *Gastroenterology* **94**:1225-1227.

61. Kobayashi, S., Nakanuma, Y., Terada, T., and Matsui, O. 1993. Postmortem survey of bile duct necrosis and biloma in hepatocellular carcinoma after transcatheter arterial chemoembolization therapy: relevance to microvascular damages of peribiliary capillary plexus. *Am. J. Gastroenterol.* **88**:1410-1415.

62. Chung, J.W., Park, J.H., Han, J.K., Choi, B.I., Han, M.C., Lee, H.S., and Kim, C.Y. 1996. Hepatic tumors: predisposing factors for complications of transcatheter oily chemoembolization. *Radiology* **198**:33-40.

63. Hagiwara, A., Yukioka, T., Shimazaki, S., Megawa, T., and Matuda, H. 1993. Delayed hemorrhage following transcatheter arterial embolization for blunt hepatic injury. *Cardiovasc. Intervent. Radiol.* **16**:380-383.

64. Kohno, E., Chen, S., Numata, K., Nakamura, S., Tanaka, K., Endo, O., Inoue, S., and Takamura, Y. 1992. A case of biloma: complication of percutaneous ethanol injection therapy for hepatocellular carcinoma. *Nippon Shokakibyo Gakkai Zasshi* **89**:2719-2724.

65. Peterson, I.M., and Neumann, C.H. 1984. Focal hepatic infarction with bile lake formation. *AJR Am. J. Roentgenol.* **142**:1155-1156.

66. Middleton, J.P., and Wolper, J.C. 1984. Hepatic biloma complicating sickle cell disease. A case report and a review of the literature. *Gastroenterology* **86**:743-744.

67. Hahn, S.T., Park, S.H., Shin, W.S., Kim, C.Y., and Shinn, K.S. 1995. Gallbladder tuberculosis with perforation and intrahepatic biloma. *J. Clin. Gastroenterol.* **20**:84-86.

68. Yoshikawa, J., Akimoto, M., Matsui, O., Miura, S., and Takashima, T. 1994. Right perirenal biloma due to a common bile duct stone: CT demonstration. *Radiat. Med.* **12**:281-283.

69. Chen, C.H., Yang, P.M., Sheu, J.C., Huang, G.T., Tsang, Y.M., Lee, P.H., and Chen, D.S. 1999. Intrahepatic bilomas associated with hepatic arteriovenous malformation. *Hepatogastroenterology* **46**:443-447.

70. Saluja, S., and White, R.I. 2004. Hereditary hemorrhagic telangiectasia of the liver: hyperperfusion with relative ischemia--poverty amidst plenty. *Radiology* **230**:25-27.

71. Ball, N.J., and Duggan, M.A. 1990. Hepatolithiasis in hereditary hemorrhagic telangiectasia. *Arch. Pathol. Lab. Med.* **114**:423-425.

72. Mendoza, A., Oliff, S., and Elias, E. 1995. Hereditary haemorrhagic telangiectasia and secondary biliary cirrhosis. *Eur. J. Gastroenterol. Hepatol.* **7**:999-1002.

73. Bauer, T., Britton, P., Lomas, D., Wight, D.G., Friend, P.J., and Alexander, G.J. 1995. Liver transplantation for hepatic arteriovenous malformation in hereditary haemorrhagic telangiectasia. *J. Hepatol.* **22**:586-590.

74. Portmann, B., and Wight, D. 1987. Pathology of liver transplantation. In *Liver Transplantation.* R. Calne, editor. Grune & Stratton. Orlando, FL. 437.

75. McInroy, B., Zajko, A.B., and Pinna, A.D. 1998. Biliary necrosis due to hepatic involvement with hereditary hemorrhagic telangiectasia. *AJR Am. J. Roentgenol.* **170**:413-415.

76. Bernard, G., Mion, F., Henry, L., Plauchu, H., and Paliard, P. 1993. Hepatic involvement in hereditary hemorrhagic telangiectasia: clinical, radiological, and hemodynamic studies of 11 cases. *Gastroenterology* **105**:482-487.

77. Odorico, J.S., Hakim, M.N., Becker, Y.T., Van der Werf, W., Musat, A., Knechtle, S.J., D'Alessandro, A.M., and Kalayoglu, M. 1998. Liver transplantation as definitive therapy for complications after arterial embolization for hepatic manifestations of hereditary hemorrhagic telangiectasia. *Liver Transpl. Surg.* **4**:483-490.

78. Hillert, C., Broering, D.C., Gundlach, M., Knoefel, W.T., Izbicki, J.R., and Rogiers, X. 2001. Hepatic involvement in hereditary hemorrhagic telangiectasia: an unusual indication for liver transplantation. *Liver Transpl.* **7**:266-268.

79. Bourgeois, N., Delcour, C., Deviere, J., Francois, A., Lambert, M., Cremer, M., Rickaert, F., and Lecocq, E. 1990. Osler-Weber-Rendu disease associated with hepatic involvement and high output heart failure. *J. Clin. Gastroenterol.* **12**:236-238.

80. Wachsberg, R.H., Cho, K.C., and Raina, S. 1994. Liver infarction following unrecognized right hepatic artery ligation at laparoscopic cholecystectomy. *Abdom. Imaging* **19**:53-54.

81. Kaplan, S.B., Zajko, A.B., and Koneru, B. 1990. Hepatic bilomas due to hepatic artery thrombosis in liver transplant recipients: percutaneous drainage and clinical outcome. *Radiology* **174**:1031-1035.

82. Colonna, J.O.,2nd, Shaked, A., Gomes, A.S., Colquhoun, S.D., Jurim, O., McDiarmid, S.V., Millis, J.M., Goldstein, L.I., and Busuttil, R.W. 1992. Biliary strictures complicating liver transplantation. Incidence, pathogenesis, management, and outcome. *Ann. Surg.* **216**:344-50; discussion 350-2.

83. Zajko, A.B., Bron, K.M., Campbell, W.L., Behal, R., Van Thiel, D.H., and Starzl, T.E. 1987. Percutaneous transhepatic cholangiography and biliary drainage after liver transplantation: a five-year experience. *Gastrointest. Radiol.* **12**:137-143.

84. Boillot, O., Bianco, F., Viale, J.P., Mion, F., Mechet, I., Gille, D., Delaye, J., Paliard, P., and Plauchu, H. 1999. Liver transplantation resolves the hyperdynamic circulation in hereditary hemorrhagic telangiectasia with hepatic involvement. *Gastroenterology* **116**:187-192.

85. Klepchick, P.R., and McLean, G.K. 2006. SIR 2006 film panel case: "Caroli's variant" hereditary hemorrhagic telangiectasia of the liver. *J. Vasc. Interv. Radiol.* **17**:1091-1094.

86. Azoulay, D., Precetti, S., Emile, J.F., Ichai, P., Gillon, M.C., Duclos-Vallee, J.C., Visda, S., Adam, R., Castaing, D., Samuel, D. et al. 2002. Liver transplantation for intrahepatic Rendu-Osler-Weber's disease: the Paul Brousse hospital experience. *Gastroenterol. Clin. Biol.* **26**:828-834.

87. Hatzidakis, A.A., Gogas, C., Papanikolaou, N., Samonakis, D., Kofteridis, D., and Gourtsoyiannis, N.C. 2002. Hepatic involvement in hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease). *Eur. Radiol.* **12 Suppl 3**:S51-5.

88. Ludwig, J., Kim, C.H., Wiesner, R.H., and Krom, R.A. 1989. Floxuridine-induced sclerosing cholangitis: an ischemic cholangiopathy? *Hepatology* **9**:215-218.

89. Van Cutsem, E. 1993. Georges Brohee Prize. Oestrogen-progesterone, a new therapy of bleeding gastrointestinal vascular malformations. *Acta Gastroenterol. Belg.* **56**:2-10.

90. Graham, W.P., Eiseman, B., and Pryor, R. 1964. Hepatic artery aneurysm with portal vein fistula in a patient with familial hereditary teleangiectasia. *Ann. Surg.* **159**:362.

91. Radtke, W.E., Smith, H.C., Fulton, R.E., and Adson, M.A. 1978. Misdiagnosis of atrial septal defect in patients with hereditary telangiectasia (Osler-Weber-Rendu disease) and hepatic arteriovenous fistulas. *Am. Heart J.* **95**:235-242.

92. Neumann, U.P., Knoop, M., Langrehr, J.M., Keck, H., Bechstein, W.O., Lobeck, H., Vogel, T., and Neuhaus, P. 1998. Effective therapy for hepatic M. Osler with systemic hypercirculation by ligation of the hepatic artery and subsequent liver transplantation. *Transpl. Int.* **11**:323-326.

93. Hisamatsu, K., Ueeda, M., Ando, M., Koike, K., Matsuo, N., Matsu-ura, K., Ueda, H., Hirohata, M., and Imai, M. 1999. Peripheral arterial coil embolization for hepatic arteriovenous malformation in Osler-Weber-Rendu disease; useful for controlling high output heart failure, but harmful to the liver. *Intern. Med.* **38**:962-968.

94. Whiting, J.H.,Jr, Morton, K.A., Datz, F.L., Patch, G.G., and Miller, F.J.,Jr. 1992. Embolization of hepatic arteriovenous malformations using radiolabeled and nonradiolabeled polyvinyl alcohol sponge in a patient with hereditary hemorrhagic telangiectasia: case report. *J. Nucl. Med.* **33**:260-262.

95. Whiting, J.H.,Jr, Korzenik, J.R., Miller, F.J.,Jr, Pollak, J.S., and White, R.I.,Jr. 2000. Fatal outcome after embolotherapy for hepatic arteriovenous malformations of the liver in two patients with hereditary hemorrhagic telangiectasia. *J. Vasc. Interv. Radiol.* **11**:855-858.

96. Miller, F.J.,Jr, Whiting, J.H., Korzenik, J.R., and White, R.I. 1999. Caution with use of hepatic embolization in the treatment of hereditary hemorrhagic telangiectasia. *Radiology* **213**:928-930.

97. Brohee, D., Franken, P., Fievez, M., Baudoux, M., Henuzet, C., Brasseur, P., and Struyven, J. 1984. High-output right ventricular failure secondary to hepatic arteriovenous microfistulae. Selective arterial embolization treatment. *Arch. Intern. Med.* **144**:1282-1284.

98. Gothlin, J.H., Nordgard, K., Jonsson, K., and Nyman, U. 1982. Hepatic telangiectasia in Osler's disease treated with arterial embolization. Report of 2 cases. *Eur. J. Radiol.* **2**:27-30.

99. Caselitz, M., Wagner, S., Chavan, A., Gebel, M., Bleck, J.S., Wu, A., Schlitt, H.J., Galanski, M., and Manns, M.P. 1998. Clinical outcome of transfemoral embolisation in patients with arteriovenous malformations of the liver in hereditary haemorrhagic telangiectasia (Weber-Rendu-Osler disease). *Gut* **42**:123-126.

100. Derauf, B.J., Hunter, D.W., Sirr, S.A., Cardella, J.F., Castaneda-Zuniga, W., and Amplatz, K. 1987. Peripheral embolization of diffuse hepatic arteriovenous malformations in a patient with hereditary hemorrhagic telangiectasia. *Cardiovasc. Intervent. Radiol.* **10**:80-83.

101. Roman, C.F., Cha, S.D., Incarvito, J., Cope, C., and Maranhao, V. 1987. Transcatheter embolization of hepatic arteriovenous fistula in Osler-Weber-Rendu disease--a case report. *Angiology* **38**:484-488.

102. Rambusch, E.G., Chavan, A., Harms, C.P., Tietge, U., Ocran, K., Strassburg, C., Wagner, S., Galanski, M., Creutzig, A., and Manns, M.P. 1996. Hereditary hemorrhagic telangiectasia with hepatic involvement and including gastric vessels. A case report. *Vasa* **25**:352-357.

103. Nikolopoulos, N., Xynos, E., and Vassilakis, J.S. 1988. Familial occurrence of hyperdynamic circulation status due to intrahepatic fistulae in hereditary hemorrhagic telangiectasia. *Hepatogastroenterology* **35**:167-168.

104. Chavan, A., Caselitz, M., Gratz, K.F., Lotz, J., Kirchhoff, T., Piso, P., Wagner, S., Manns, M., and Galanski, M. 2004. Hepatic artery embolization for treatment of

patients with hereditary hemorrhagic telangiectasia and symptomatic hepatic vascular malformations. *Eur. Radiol.* **14**:2079-2085.

105. Garcia-Tsao, G., Gish, R.G., and Punch, J. 2006. Model for end-stage liver disease (MELD) exception for hereditary hemorrhagic telangiectasia. *Liver Transplanation* **12**:S108.

Figure 1: Normal liver (modified from Garcia-Tsao 2007, presentation) to compare with 3 types of shunts in HHT liver presented on the following pages.

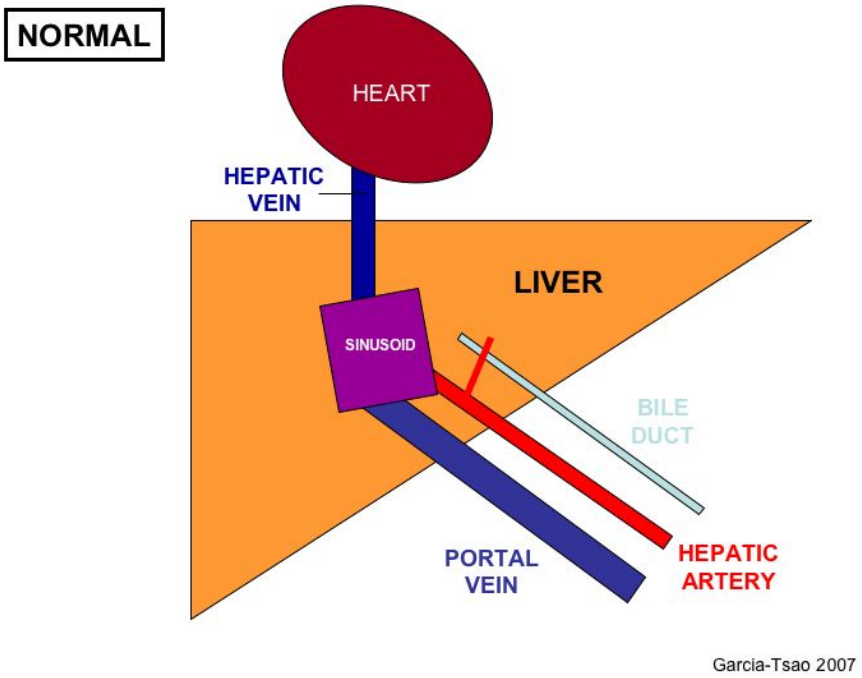

Figure 1a: Diagram of hepatic artery to hepatic vein shunt (modified from Garcia-Tsao 2007, presentation). When this shunt predominates sequelae can include high output cardiac failure and biliary ischemia.

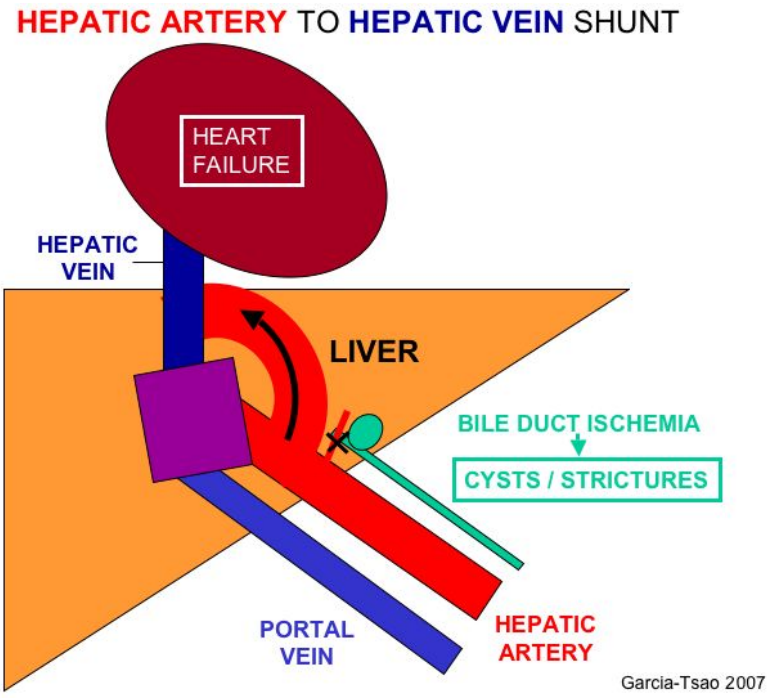

Figure 1b: Diagram of hepatic artery to portal vein shunt (modified from Garcia-Tsao 2007, presentation). When this shunt predominates sequelae can include liver fibrosis, portal hypertension, varices and splenomegaly.

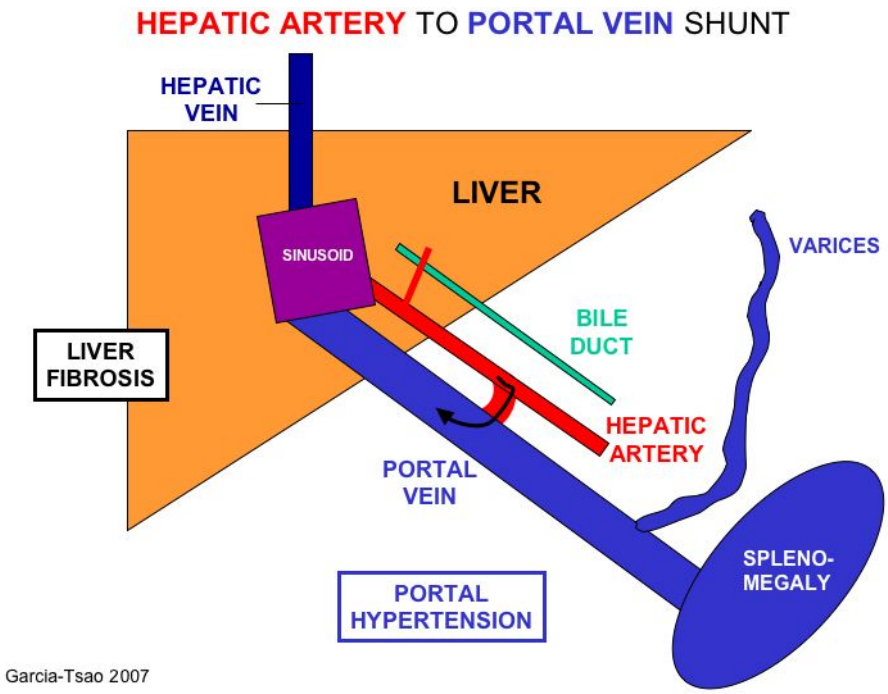

Figure 1c: Diagram of portal vein to hepatic vein shunt (modified from Garcia-Tsao 2007, presentation). When this shunt predominates sequelae can include hepatic encephalopathy.

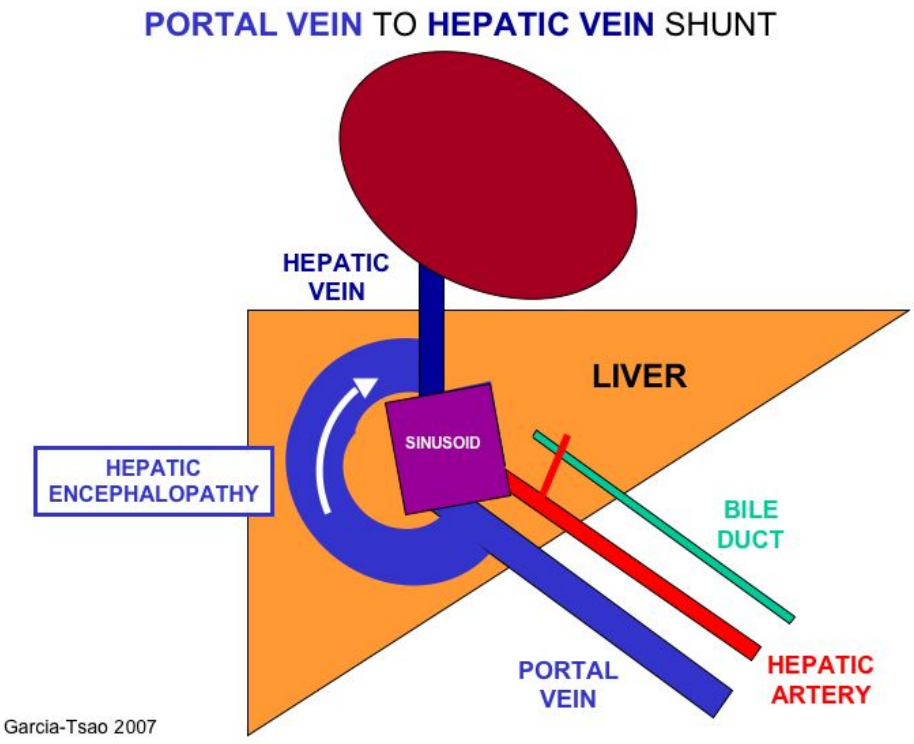

Figure 2a: Initial abdominal CT at outside hospital in December 2006, 4 months after onset of RUQ pain.
The liver is hypervascular compatible with HHT, no biloma.

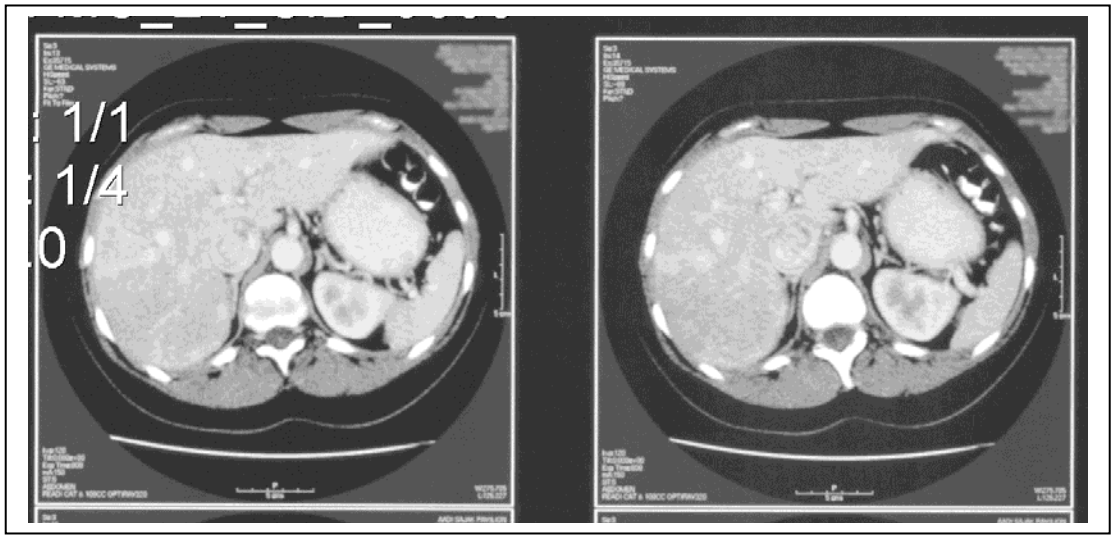

Figure 2b: 7 months after initial CT and with continued symptoms, abdominal CT showing new biloma.

Figure 2c: Repeat abdominal CT 3 days later showing biloma progression.

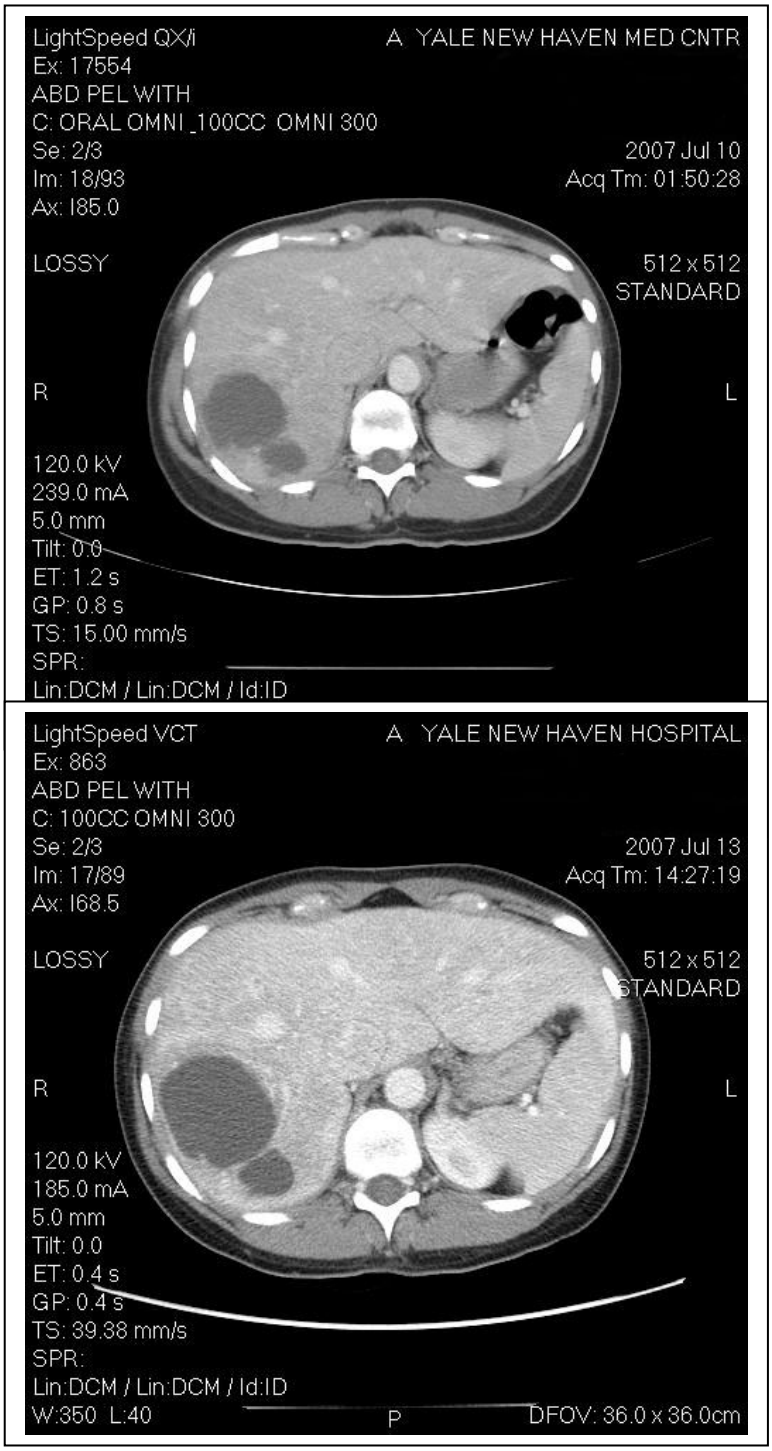

Figure 2d: Percutaneous biliary drainage catheter in place.

Figure 2e: Contrast injection via biliary drainage catheter demonstrating size of biloma. With pain control the patient was discharged home.

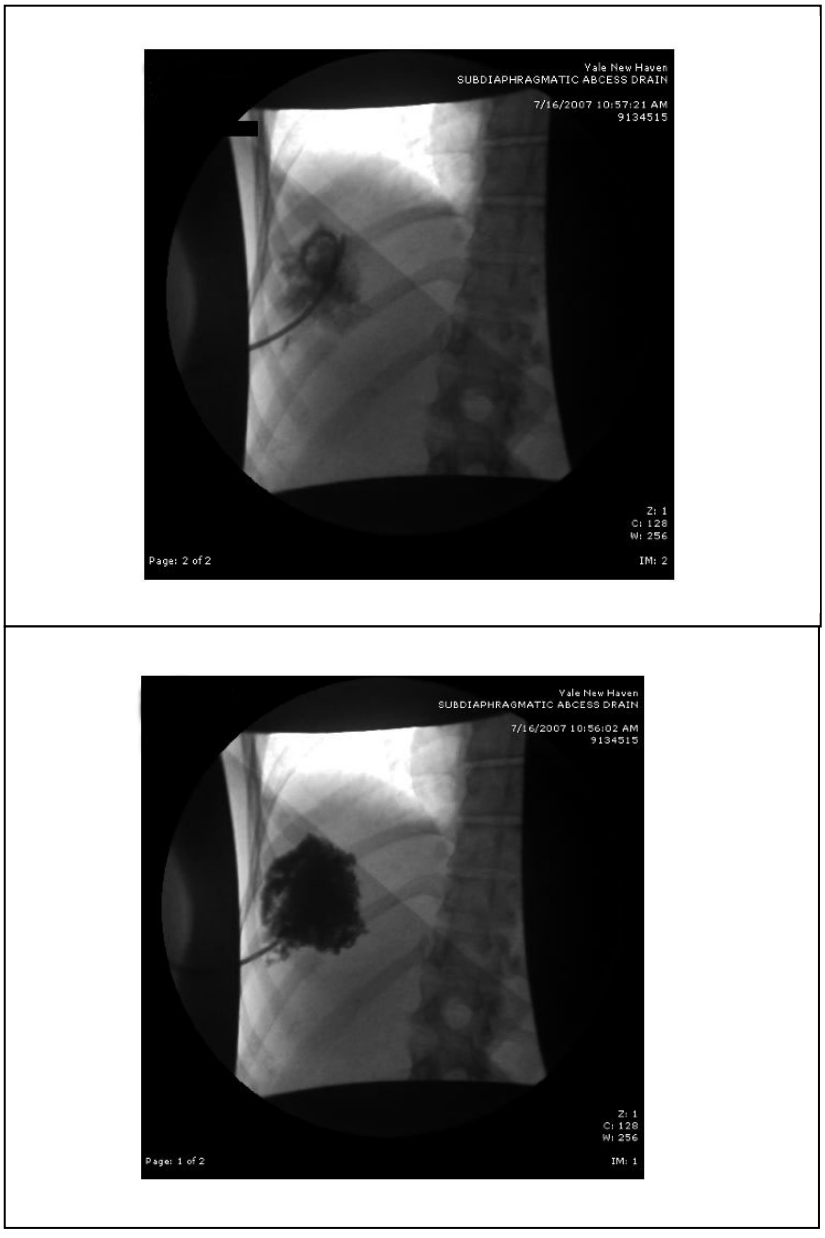

Figure 2f: Cholangiogram 1week post discharge at scheduled follow-up. No interval change in size of biloma.

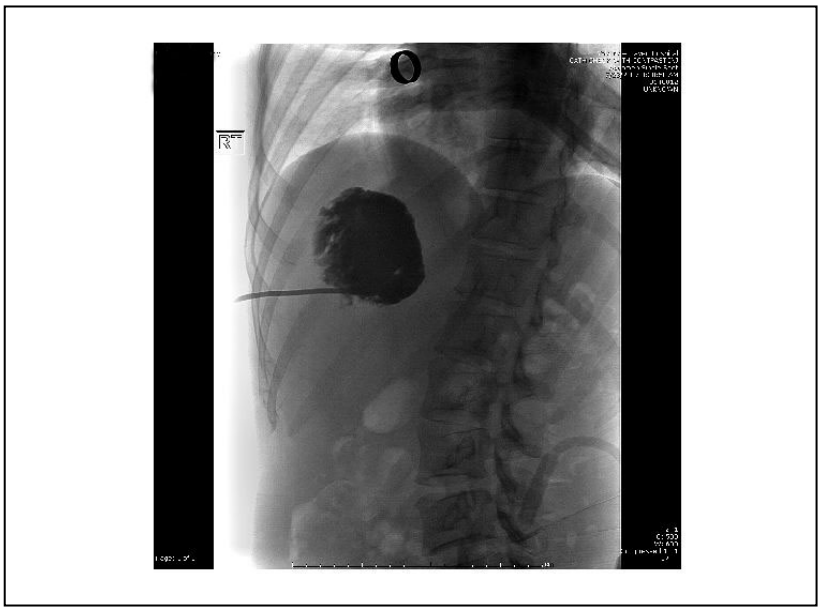

Figure 2g: 5 week follow-up outpatient cholangiogram demonstrating reduction in size of biloma following drainage.

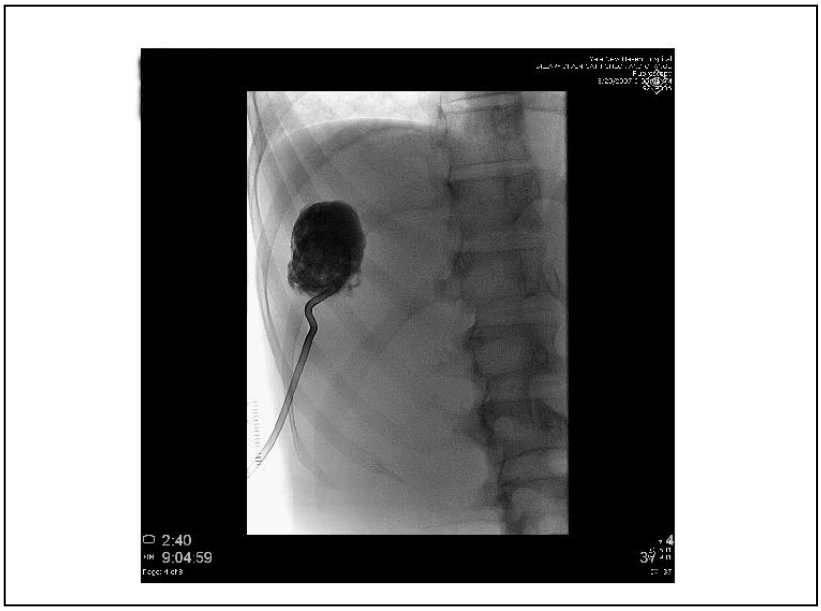

Figure 2h: 10 week follow-up demonstrating marked reduction in biloma size. Concomitantly patient had reduction in biliary drainage and improved clinically. 4 weeks later catheter was removed when bile drainage was no longer present, patient was without pain and remains asymptomatic 3 months after removal.

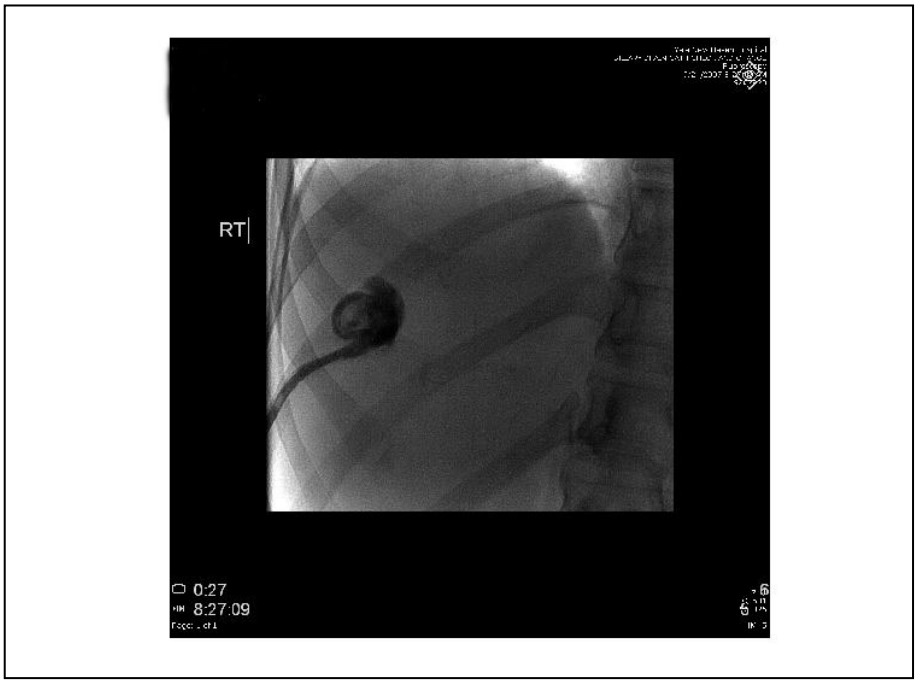

Figure 3: Laboratory abnormalities in patient WM with localized biliary ischemia.
X axis: time course (Jan-Sept 2007)
Y axis: absolute value. AST: aspartate aminotransferase; ALT: alanine amino transferase; Bili: total bilirubin; AlkPhos: alkaline phosphatase; HD: hospital day.

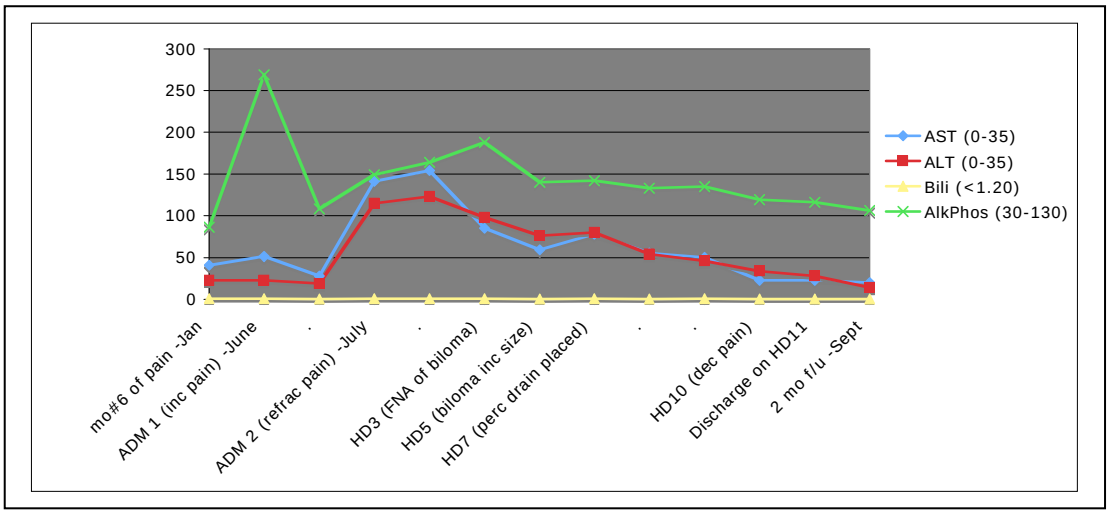

TABLE 1: HHT Type 3 patients at Yale: 8 patients.

Case	Age	Sex	Presenting symptom			Lab abnormality		Imaging		PMH/ Other	Time course (onset-outcome yrs)	Intervention	Sequelae	Outcome
			RUQ/abd pain	N/v, wt loss	Other	AP	Bili> 2.0 mg/dL	Cysts (#)	HA (mm)					
P1	39	F	y	y		y (269)	n	y (1)	na	PAVM	1	Perc drain	Localized biliary ischemia	Alive
P2	31	F	y	y		y (200-400)	n	y (1)	na	h/o episode while gravid	2	Perc drain	Localized biliary ischemia	Alive
P3	61	F	y			y (200-300 then 1530)		y (1)[b]	5	Mild HF	9[a]	Urgent perc drain	Hepatic infarct	Dead (70)
P4	33	F	y		Back pain, SOB	y (171 → 1127)	n	y (1)[c]	10	HF, diffuse severe PAVM, and CAVM	17[a]	Bile salts + analgesia	Intrahepatic hemorrhage	Dead (34)
P5	42	F	y		SOB	y (200-400)	y (2.2)	y (multiple)[d]	13	HF, diffuse severe PAVM, and CAVM	6[a]	Bile salts + analgesia	Hepatic disintegration and hemorrhage	Dead (48)
P6	37	F	y	y		y (700-1000s)		y[e]	na	Marfan's	2	Lap chole, liver bx, ERCP, bile salts and analgesia, OLT		Dead (38)
P7	47	F	y			nl until liver bx (1000s → 174 spontaneously		y (multiple)	11.5		7	Liver bx, bile salts and analgesia.	Spontaneous remission	Alive
P8	59	F	y		Back pain, hepatic	y (200-300)	n	y (1)	na	HF	6	MRCP, antibiotics	Spontaneous remission	Alive

					encephalopathy									

RUQ: right upper quadrant; Abd pain: abdominal pain; jaun/chol: jaundice/cholangitis; n/v: nausea/vomiting; wt loss: weight loss; AP: alkaline phosphatase; Bili: bilirubin; AVM: arteriovenous malformation; PAVM: pulmonary arteriovenous malformation; CAVM: cerebral arteriovenous malformation; PMH: past medical history; HF: heart failure; perc: percutaneous; Lap chole: laparoscopic cholecystectomy; Liver bx: liver biopsy; ERCP: endoscopic retrograde cholangiopancreatography;MRCP: Magnetic resonance cholangiopancreatography.

a P3-P5 are Type 1 to Type 3 converters and had been followed for their HF for many years prior to onset of biliary ischemia. P3 (8/9 yrs type 1), P4 (14/17 yrs type 1) P5 (5/6 yrs type 1). Type 1 to 3 conversion is associated with the highest mortality in our series.

b Also developed an area of hepatic infarct in the anterior segment of the right hepatic lobe.

c Also developed multiple wedge shaped filling defects in the right lobe pole.

d Also developed liver hemorrhage and subcapsular hematoma.

e Also developed intra-hepatic ductular abnormalities with dilated ducts and truncated small tapering ducts.

f Also bile duct dilation

TABLE 2: HHT Type 3 patients in the world literature: 14 reported cases

Case	Age	Sex	Presenting symptom			Lab abnormality		Imaging	PMH/ Other *	Time course (onset-outcome) months	Intervention	Sequelae	Outcome
			RUQ/abd pain	N/v, wt loss	Other	AP	Bili>2.0 mg/dL	Biliary abnl					
Ball (1990)[71]	62	F	y	y	fever	y (1167)	n	y		6 (hrs)	Abx		Dead
Bauer (1995)[73]	33	F	y	y	doe, melena	y (231→ 1361)	n	y		8	Abx, OLT		Alive at 24 mo
McInroy (1998)[75]	31	F	y		fever	y (671)	y (2.02)	y	Biliary inflam	3	Abx, ERCP, liver bx, OLT		Alive
Odorico (1998)[77]	48	F	y	y				y (post AE)	Biliary inflam	4	AE (pancreatoduodenal a.), OLT	Bacteremia and LFT abnl post AE	Alive at 12 mo
	47	F	y	y		y (post AE)		y (post AE)		2	ERCP, AE (hepatic), chole (gangrenous), OLT	Bacteremia and LFT abnl post AE	Alive at 9 mon
Boillot (1999)[84]	36	F	y[a]				y	y		5	Chole, c-section @28wk, OLT	Icterus and hepatic abscesses post chole	Alive at 65 mo
Chen (1999)[69]	26	F	y		fever	y (864)	n	y		15	ERCP, HA ligation	Bacteremia post ligation, biloma progression	Dead
Hillert (2001)[78]	39	F	y[a]		hemobilia			y		10	C-section @29wk, endoscopy and billroth I, ERCP and AE (hepatic), OLT	Post HAE: AP 2083, tbili 8.5 → 20, bilomas	Alive at 12 mo
Azoulay (2002)[86]	38	F				y (203)	344 um/L				Chole, ERCP, repeated perc drain, OLT		Unknown
	49	F				y (337)	249 um/L				OLT		Unknown
	38	F				y (145)	24 um/L				Chole, ERCP, perc drain, OLT		Unknown
Blewitt (2003)[53]	34	F	y			y (131)		y		3	Chole, liver bx,		Alive at 36

											OLT		mo
Dominguez (2005)	32	F	y		fever	n		y		3	Chole, OLT	Post-op AP 499→ 2212, Tbili 2.8	Alive at 3 mo
Klepchick (2006)[85]	31	F	y				n	y		4	Chole, perc drain	Post-op AP 790	Unknown

RUQ: right upper quadrant; Abd pain: abdominal pain; jaun/chol: jaundice/cholangitis; n/v: nausea/vomiting; wt loss: weight loss; AP: alkaline phosphatase; Bili: bilirubin; AVM: arteriovenous malformation; PAVM: pulmonary arteriovenous malformation; CAVM: cerebral arteriovenous malformation; PMH: past medical history; HF: heart failure; perc: percutaneous; Lap chole: laparoscopic cholecystectomy; Liver bx: liver biopsy; ERCP: endoscopic retrograde cholangiopancreatography;MRCP: Magnetic resonance cholangiopancreatography; Abx: antibiotics; AE: arterial embolization; blank: not mentioned

a Boillot and Hillert report two patients with onset of symptoms during pregnancy.

* no mention of PAVM/CAVM