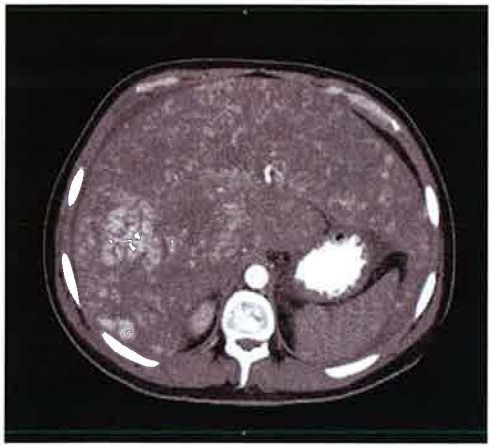
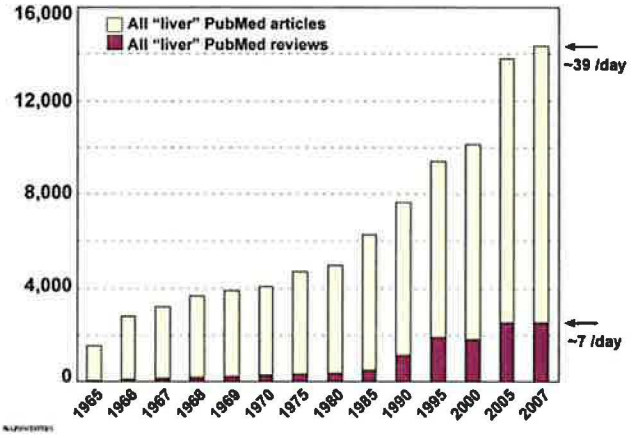
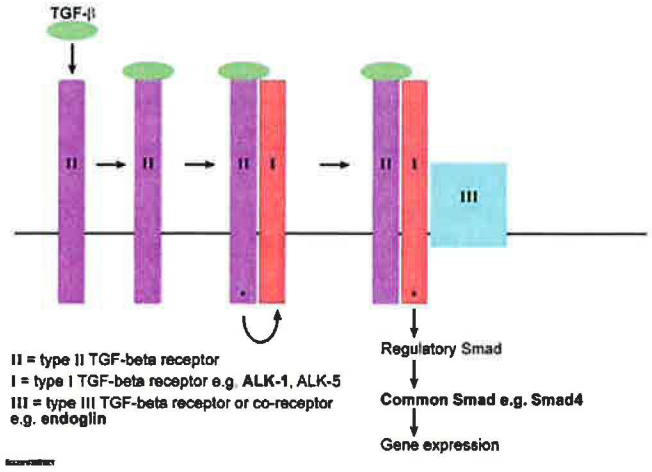
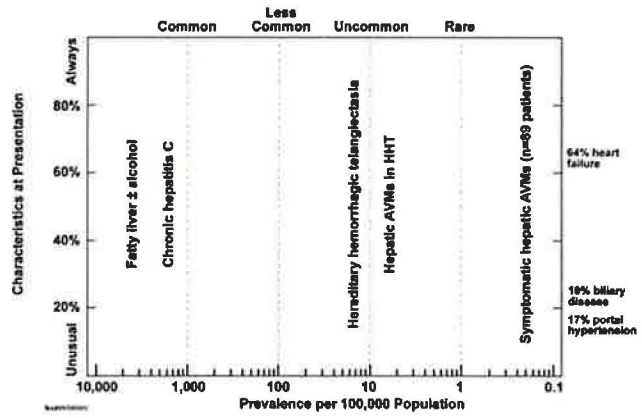
Osler's Liver Disease

Lessons Learned from a Patient









"It Takes a Village....." Hillary Rodham Clinton

Friday, 13 February, 2009
Solo Grand Rounds #13

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This is to acknowledge that the author, Jennifer A. Cuthbert, M.D. has neither financial interests nor other relationships with commercial concerns related directly or indirectly to this presentation.

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Professor of Internal Medicine, Director, Web Curriculum

Clinical Interests:
Ascites, genetic liver disease, acute hepatitis

	Date	Title
1	May 1981	Hepatic Abscess "…the chief aid to the diagnosis of hepatic abscess is the knowledge that it may occur…" Taylor, 1902: Guy's Hosp Rep 56:109 Comment: Weeks of full time preparation and panic ~4 weeks after promotion from Faculty Associate (staff) to tenure-track Assistant Professor. Multiple slide projectors, a media nightmare
2	1984	1984 Delta Agent: Hepatitis D?
3	1985	Hepatic Transplantation
4	1988	Spontaneous Bacterial Peritonitis
5	1989	Hepatitis C
6	1991	Hepatitis B: Molecular Variants with Clinical Significance? Comment: Just the slides, no text 3 years after promotion to Associate Professor, 2 children, ages 5 and 3 years old Single slide projector, a deadline nightmare
7	1993	Hepatitis C Update: Progress and Problems
8	1994	Wilson('s) Disease: A New Gene and an Animal Model for an Old Disease
9	1997	HLA-H: Final Piece in the Hemochromatosis Puzzle? "…when you have eliminated the impossible, whatever remains, however improbable, must be the truth" Sherlock Holmes [Sir Arthur Conan Doyle, 1859-1930, physician and man of letters]
10	1999	Hepatitis A: Ancient Disease, Emerging Threat? A virus is "…a piece of nucleic acid surrounded by bad news" Peter Medawar, Nobel laureate 1983
11	2001	Hepatitis E: Sporadic and Fulminant Disease in Texas Comment: Text with references Associate Dean and Web Curriculum Director My own slide maker, a last minute nightmare
12	2004	Why Am I Yellow? Answers from Shakespeare and HUGO "All the world's a stage,…..And one man in his time plays many parts, His acts being seven ages,…" From: "As You Like It." Wm. Shakespeare
13	February 2009	Osler's Liver Disease: Lessons Learned from a Patient "It Takes a Village…." Hillary Rodham Clinton

Chief Complaint: Jaundice and generalized weakness

HPI:
The patient is a 28 year old man referred for evaluation of jaundice and "liver mass" from an outside hospital. He reported 30 lb weight loss over 3 months, malaise, fatigue, weakness. This was accompanied by easy bruising, bleeding for 3 months; peripheral edema and abdominal distension. He also experienced dyspnea, chest pain and subjective fevers.

PH: None. **FH:** No liver disease. **SH:** 6-8 beers / wk, none for 6 months

Physical Examination:
Vital signs: Pulse 78, BP 118/78, respiratory rate 24; Weight 80.5 Kg (177 lb), height 5' 3" – 5' 7", BMI = 27.7 – 31.4 (depending on height)
He had mild icterus, hepatomegaly and peripheral edema but no "fluid wave" was appreciated and no palpable spleen. On his left hip there was an ecchymosis. Similar findings were reported by the primary team and the consultants.

Laboratory Investigations:

Table I: Standard "Liver Tests"

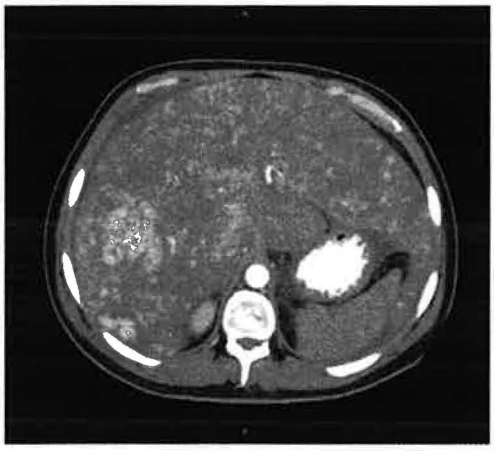
	6/9	6/30	7/9	7/21	7/25	7/30
Bilirubin mg/dL	6.2	9.4	27.5	27.3	27.8	34.5
Alk Phos U/L	91	65	95	128	91	91
GGT U/L	203	104		156	162	203
AST U/L	43	49	108	106	84	43
ALT U/L	20	45	87	89	73	20
Albumin g/dL	3.6	2.6	3.5	3.1	2.7	2.5
Total protein g/dL	6.6	5.3	6.5	6.2	5.8	5.3
INR	2.1	2.8	2.1	1.9	1.9	1.8
Creatinine	0.7	0.5	0.9	1.3	1.0	3.1
MELD (Mayo)	18	20	25	28	26	37
Admission	1	1	OPC	2	2	3

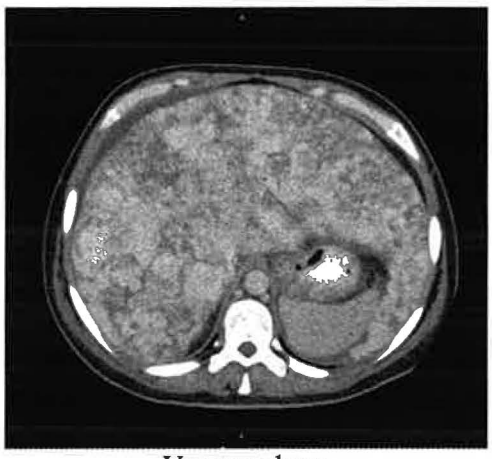
Viral: HBsAg negative, HBV DNA <357 IU/mL; HCV antibody negative, HCV RNA <50 IU/L, rheumatoid factor <10
Autoimmune: ANA negative, smooth muscle antibody negative; mitochondrial antibody negative
Genetic: α1 anti-trypsin 143 mg/dL, ceruloplasmin 19 mg/dL, iron 105 µg/dL, TIBC could not be calculated, ferritin 621 ng/mL
Tumor: α fetoprotein 20 ng/mL

Table II: Hematology

	6/9	6/24	7/5	7/21	7/25	7/30
WBC /μL	6,100	5,580	6,600	5,490	5,290	6,800
Hemoglobin g/dL	10.3	6.9	8.6	5.9	8.7	7.8
MCV fL	97	96	95	94	93	91
Platelets /μL	89,000	57,00	37,000	150,000	137,000	45,000
Haptoglobin mg/dL		<5				<5
D-dimer mg/L		41				19
Admission	1	1	1	2	2	3

Imaging:
Ultrasound: Large liver, nodular contour, appearance consistent with diffusely infiltrating mass, ?hepatocellular carcinoma
CT abdomen #1: Innumerable hypervascular lesions concerning for hepatocellular carcinoma


Arterial phase


Venous phase

Hospital Course – 1st Admission
Pathology:
Bone marrow biopsy = No evidence of lymphoma

Radiology review:
CT consistent with diffuse hepatic involvement in hereditary hemorrhagic telangiectasia (HHT)

HHT = hereditary hemorrhagic telangiectasia = Osler's disease

telangiectasia = permanent dilation of pre-existing blood vessels
tela = Latin, "something woven", "web"
angi = Greek, angeion, vessel, usually a blood vessel
ectasia = Greek, ektasis, dilation

telangiectasis, plural telangiectases = the lesion produced by telangiectasia

"…..coarse or fine red line or as a punctum with radiating limbs (spider)…." Dorland's Medical Dictionary

Sir William ***Osler***, Canadian-born physician, 1849-1919
McGill University (MD and returned as professor, 1874 – 1884)
University of Pennsylvania (1884 – 1889)
Johns Hopkins University (1889 – 1905)
University of Oxford (1905 – 1919)
Frederick Parkes ***Weber***, British physician, 1863-1962
Henri Jules Louis ***Rendu***, French physician, 1844-1902

Osler-Weber-Rendu = geopolitical i.e. from an Anglo-Saxon perspective; 29,100 Google®s
Rendu-Osler-Weber = chronological; 82,300 Google®s

History:
Eponymous clinical descriptions published by Rendu (1896), Osler (1901) and Weber (1907). There are earlier descriptions considered consistent with the diagnosis but the author's are only remembered in reviews.

Genetics:
Autosomal dominant, prevalence 1-2:10,000. In some areas, the prevalence is significantly higher. A positive family history is one of the 4 criteria for diagnosis. This may affect the recognition of new mutations.

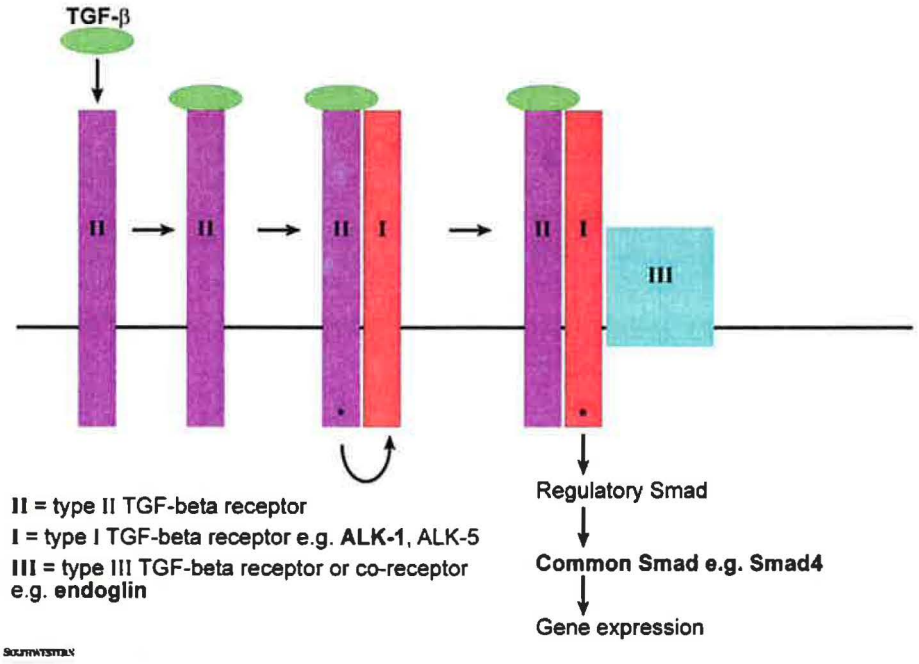
Identification of mutated genes:
ENG encodes endoglin (HHT1) on chromosome 9, 9q33-q34.1
ACVRL1 encodes activin A receptor II-like 1 (HHT2) on chromosome 12, 12q11-q14
ORW3 (HHT3) – linked to chromosome 5, 5q31.3-q32, unidentified gene
HHT4 – linked to chromosome 7, 7p14, unidentified gene
SMAD4 encodes Smad4 (JPHT juvenile polyposis and hereditary telangiectasia) on chromosome 18, 18q21.1
BMPR2 encodes bone morphogenetic protein receptor, type II (PPH primary pulmonary hypertension) on chromosome 2, 2q33-q34

Mechanism of disease:
In HHT, there is interference with TGF-beta signaling in endothelial cells of blood vessels. Based on studies in mice, the manifestations arise from haploinsufficiency, i.e. one copy of the gene is not enough. The alternative mechanism, a dominant negative process, appears to be much less likely but cannot be excluded. The gene products from some specific mutations may act in this latter manner.

Mice lacking two copies of either *ENG* (HHT1) or *ACVRL1* (HHT2) are not viable. In heterozygote knock-out mouse models, a phenotype similar to that of human HHT can be observed. However, the findings are dependent on the genetic background of the mouse strain. In many strains, no abnormalities are observed.

ENG gene = endoglin protein = HHT1
Endoglin – covalently-linked homodimer interacts with heterodimerized TGFß receptors, mutations commonly in extra-cellular domain

ACVRL1 gene = activin A receptor type II-like 1 = HHT2
ALK-1 protein – type I cell surface receptor for TGFß, mutations commonly in kinase domain



Signaling pathway for TGFß (* = kinase activity)

TGFß binds to the type II receptor. Binding recruits the type I receptor into a heterodimer e.g. ALK-1 (HHT2) or ALK-5. The Type II receptor serine / threonine kinase activates type I receptor kinase and initiates downstream signals.

Endoglin (HHT1) interacts with the receptor-ligand complex as an auxiliary or co- receptor for ALK-1. Smad4 (JPHT) is one of the downstream signals. The signaling pathway is involved in "angiogenesis and vascular integrity". Failure of normal signaling, the result of mutations in the genes encoding endoglin, ALK-1 or other specific proteins, leads to abnormal vasculature.

Phenotype:
Telangiectases are apparent first, presenting as epistaxis. GI telangiectases become clinically important later. Arteriovenous malformations take longer to evolve. Significant shunting from AVMs leads to increased cardiac output and eventually cardiac failure

Genotype-Phenotype in HHT
Family studies: One genetic mutation, more than one clinical pattern
"Variable penetrance and expressivity" = other genes
HHT1 differs from HHT2 e.g. symptomatic hepatic AVMs almost exclusively in HHT2 (1 case in HHT1)
Gender differences within HHT1 and HHT2 e.g. hepatic AVMs more common in women
5 families with one specific HHT2 mutation & hepatic AVMs

HHT – Diagnosis:
Diagnostic criteria established in 2000

1. Epistaxis: Spontaneous, recurrent nose bleeds
2. Telangiectases: multiple, at characteristic sites
3. Visceral:
   Telangiectases (GI) or arterio-venous malformations
   Pulmonary, hepatic, cerebral and spinal AVMs
4. Family history

"Definite" = 3 criteria
"Possible" or "suspected" = 2 criteria
"Unlikely" = 1 criterion

Does our patient have HHT?

History review:

No family history of bleeding disorder
Epistaxes recent (last 3 months), not life-long
No visible telangiectases, spider nevi on hands

Imaging for HHT:

CT brain and CT chest: No abnormal vessels, lytic T6
Echo: Normal LV and RV systolic function. No R → L shunt on bubble study

Back to the patient: More Hospital Course – 1st Admission

Bleeding = total 10 units pRBCs, 14 units FFP

RLE pain and swelling consistent with hemorrhage
DIC? haptoglobin <5 mg/dL, d-dimers 41.3 mg/L, platelet count 49,000 /μL
Attributed to multiple hemangiomata (Kasabach-Merritt picture)

Imaging

CT abdomen #2: No evidence of hemoperitoneum; increased ascites; multiple lytic lesions throughout pelvis and spine at T6, T11, T12 & L3

Portal hypertensive ascites treated with sodium restriction and diuretics

Table III: Ascites

	Admit #1 7/3	Admit #3 7/30	Admit #3 8/2
Serum albumin g/dL	2.6	2.5	3.6
Ascites albumin g/dL	0.5	0.4	1.1
SAAG	2.1	2.1	2.5
Ascites total protein	1.0	0.8	1.7
WBC /μL	29	5,050	1,415
Polys %	41	90	75
Lymphs %	48	6	13
Mono/macros %	11	4	12
RBC /μL	7,400	12,000	10,150
Culture	Not done	*E. coli*	*E. coli*

What is the Diagnosis?

Radiology = Hereditary hemorrhagic telangiectasia
Clinical = "Unlikely" because only one criterion, visceral arterio-venous malformations
Is there an alternative diagnosis?
Does HHT explain the observations, e.g. lytic lesions in pelvis and spine?

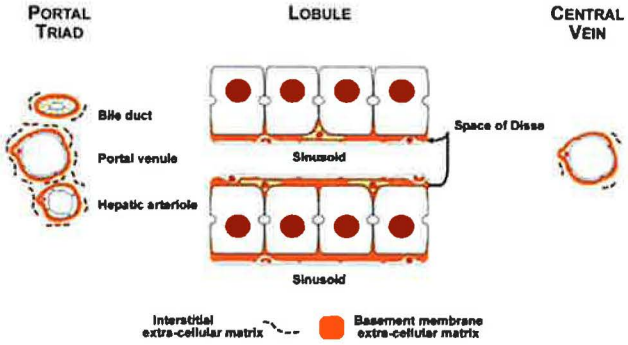
What next? Back to PubMed

HHT – Clinical Heterogeneity:
Manifestations of HHT are not present at birth
Epistaxis usually earliest, often in childhood, occurs in >90%
Mucocutaneous and GI telangiectases increase with age, occur in ~80%
AVMs:
- Pulmonary and hepatic most frequent
- Cerebral (10%) and spinal (1%) less frequent

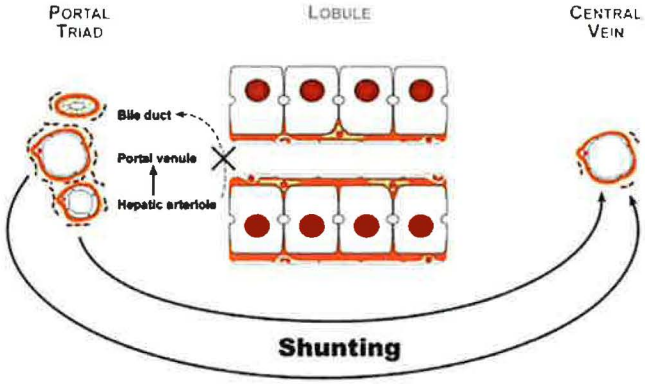
Genotype-phenotype relationships

Liver Involvement in HHT:
Asymptomatic liver AVMs found in 41 – 78% of patients with HHT using sensitive imaging techniques
Symptomatic hepatic AVMs are rare, only 89 cases in the literature through 2007, 73/89 (82%) women
Clinical presentations include:
- High output heart failure, 57/89 (64%) for which out patient lacked evidence
- Portal hypertension, 15/89 (17%)
- Biliary disease, 17/89 (19%)

Anatomic Pathology of Hepatic AVMs in HHT:
Abnormal connections between blood vessels
Shunting from one blood vessel to another
Hepatic artery to hepatic vein = shunting, i.e. bypass hepatocytes; ischemic bile ductular epithelium
Hepatic artery to portal vein = increased flow in portal venous system = portal hypertension
Portal vein to hepatic vein = shunting, i.e. bypass hepatocytes



Hepatic blood vessels



Abnormal connections & consequences

Heart Failure & Hepatic AVMs:
Heart failure is the commonest pattern on presentation for patients with symptomatic hepatic AVMs in HHT. The heart failure is high output in type and is the direct result of the shunting of blood from the hepatic arteriole or portal venule in the portal triad to the centrilobular hepatic venules, bypassing the liver sinusoids and the lining hepatocytes. Presenting symptoms include dyspnea, orthopnea, ascites and edema. There may be a thrill or bruit auscultated in the epigastrium or right upper quadrant. When measured, more than 90% of the reported cases had either a cardiac output >8 L/min or cardiac index >6 L/min/m^2.

Of the 57 patients presenting with heart failure reviewed in reference PMID: 17239481, 84% were female and the average age at presentation was 52 years, with a range of 28 – 77 years.

Portal Hypertension & Hepatic HHT:
Pressure is proportional to flow times resistance to flow. Portal hypertension, an increase in portal venous pressure, results from an increase in portal venous blood flow or from increased resistance to flow. Shunting from the hepatic arteriole to the portal venule usually accompanies the development of portal hypertension in HHT. Presenting symptoms include ascites and hematemesis from variceal hemorrhage.

Of the 15 patients presenting with portal hypertension and reviewed in reference PMID: 17239481, 53% were female and the average age at presentation was 62 years, with a range of 41 – 84 years.

The combination of a nodular liver + portal hypertension usually = cirrhosis, but not in these patients. The nodular liver in HHT is the result of either nodular regenerative hyperplasia or focal nodular hyperplasia.

The pathogenesis of nodule formation & "pseudocirrhosis" is as follows:

1. Perfusion abnormalities from blood shunting → regeneration
2. Fibrosis around abnormal blood vessels

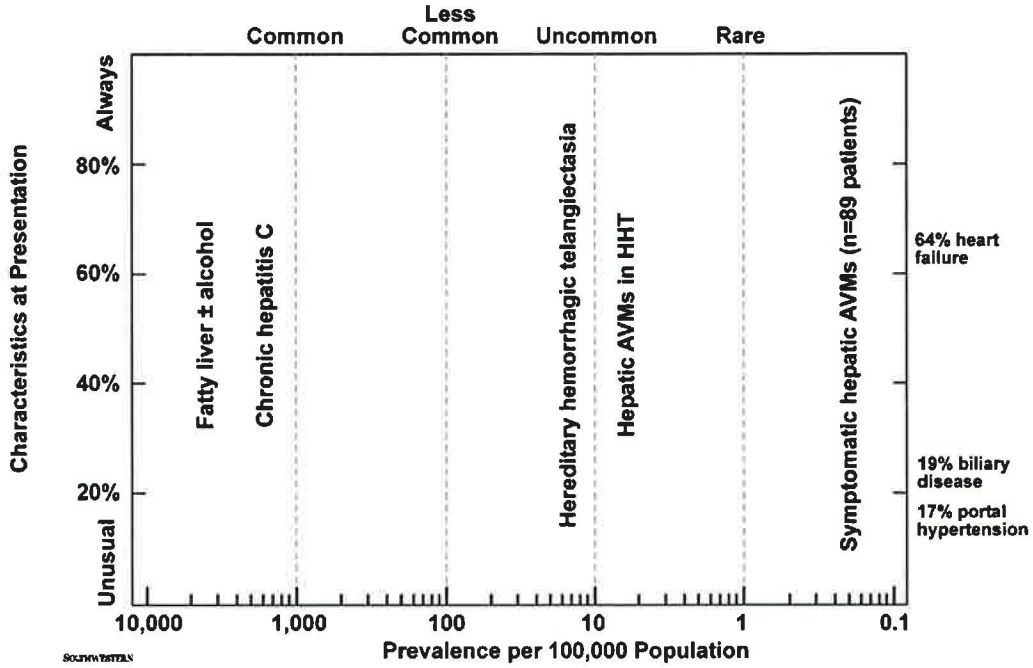
Biliary Presentation & Hepatic AVMs:
The bile ductules in portal triads are dependent on hepatic arterioles for their blood supply. When there is shunting from the hepatic arteriole to portal or hepatic venules, the bile ductular cells can develop ischemic injury. Possible consequences of ischemia include biliary necrosis and secondary sclerosing cholangitis. Patients present with right upper quadrant pain accompanied by jaundice and cholestasis. Cholangitis may occur.

Of the 17 patients presenting with biliary disease and reviewed in reference PMID: 17239481, all were female and the average age at presentation was 39 years, with a range of 31 – 65 years.

Does the Diagnosis of HHT "Fit"?

Yes =	**Maybe =**	**No =**
Nodular liver Portal hypertension, presentation with ascites Radiologic appearance	Equal youngest with symptomatic hepatic AVMs Male sex (18%)	No family history No epistaxis before 3 months ago (coagulopathy) No mucocutaneous telangiectases

Back to the patient: More Hospital Course – 1st Admission
Transjugular liver biopsy:
Free hepatic vein pressure = 21 mm Hg
Wedged hepatic vein pressure = 31 mm Hg
= evidence of portal hypertension (gradient 10 mm Hg)
= increased right-sided pressures, from transfusion, FFP etc. before biopsy?

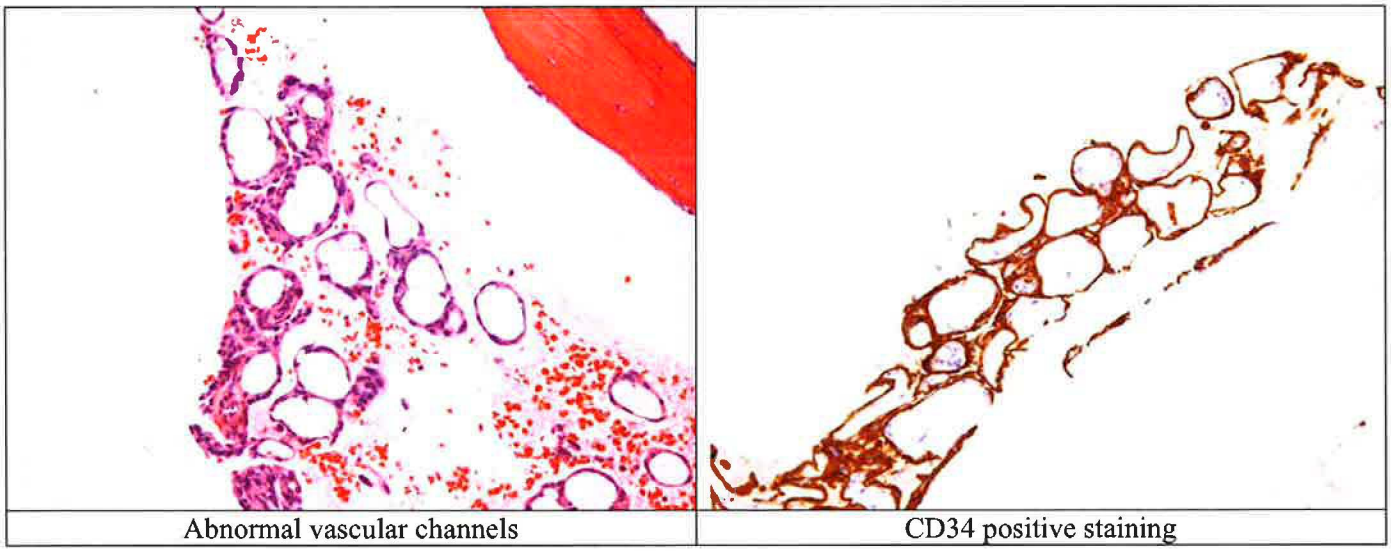


Prevalence and characteristic presentation in hepatic HHT

Pathology:
Radiologic biopsies, total length 2.2 cm
Gross distortion of normal liver architecture
Hepatocytes in small nodules surrounded by bands of fibrous tissue consistent with cirrhosis
Replacement of normal sinusoidal network by dilated vascular channels lined by benign CD34+ endothelium
No evidence of malignancy (angiosarcoma, hepatocellular carcinoma, epithelioid hemagioendothelioma)

Comment: consistent with hereditary hemorrhagic telangiectasia if other clinical findings are confirmatory

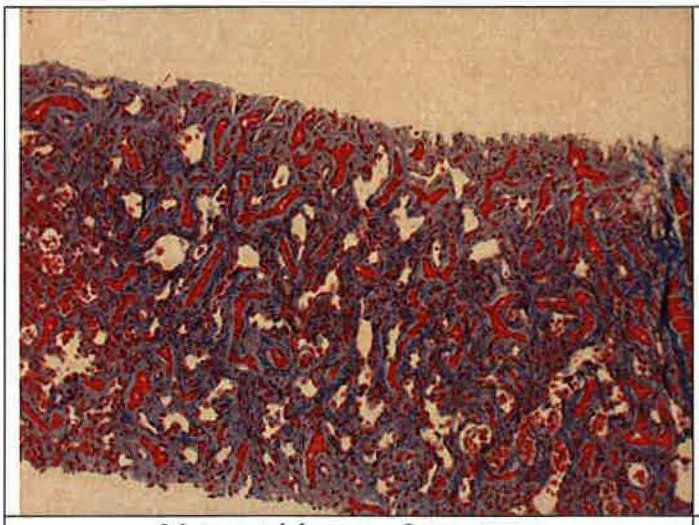
Bone marrow biopsy:



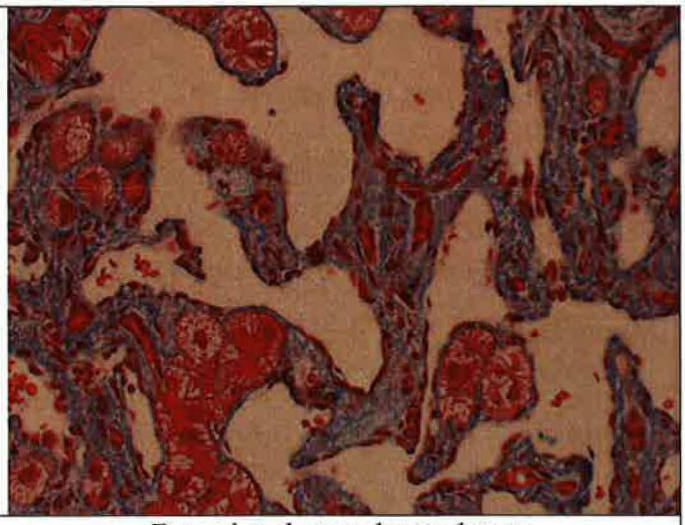
Abnormal vascular channels | CD34 positive staining

CD34 = hematopoietic and endothelial progenitor cell marker
Note: Normal hepatic sinusoidal endothelium is negative for certain endothelial antigens such as CD34, whereas portal venous and hepatic venous endothelial cells are positive.

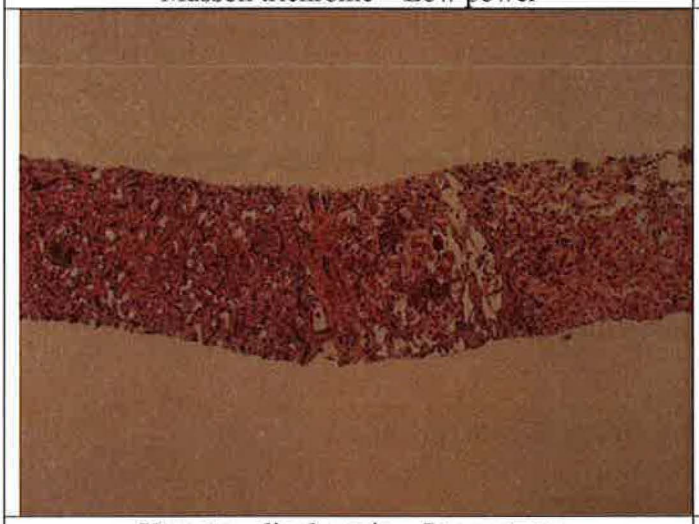
Liver biopsy:



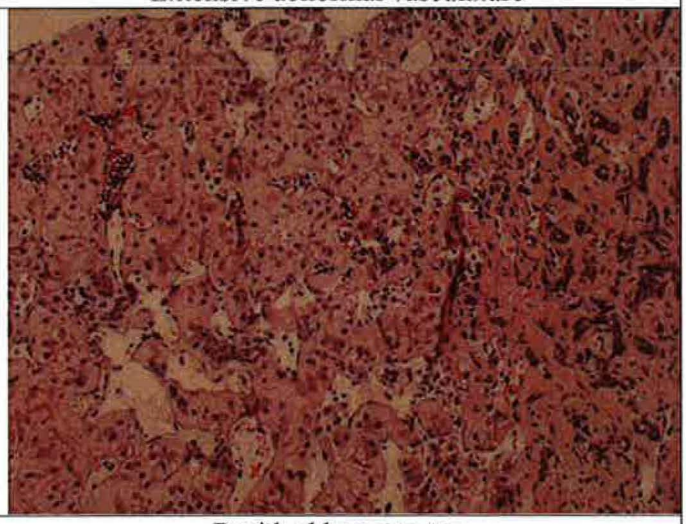
Masson trichrome – Low power



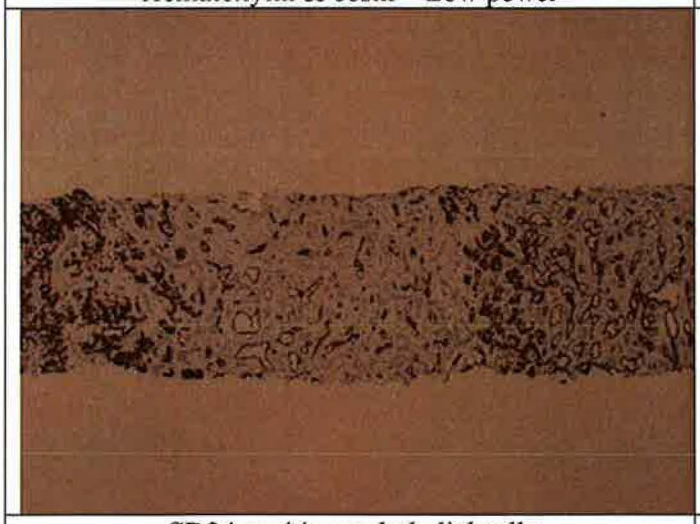
Extensive abnormal vasculature



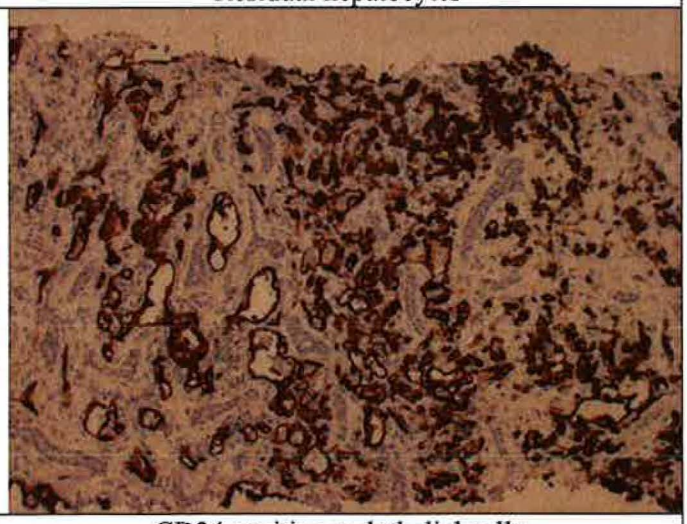
Hematoxylin & eosin – Low power



Residual hepatocytes



CD34 positive endothelial cells



CD34 positive endothelial cells

2nd Admission
Chief complaint: Gingival bleeding and fatigue

HPI: Bleeding from gums and nose

Physical examination: Tachycardia and abdominal bruit, palpable hepatomegaly and splenomegaly (?), no ascites clinically

Laboratory investigations: Anemia, no thrombocytopenia, jaundice, hyponatremia, increased creatinine

Hospital Course:
Endoscopy = EGD – non-bleeding esophageal varices, portal hypertensive gastropathy, colonoscopy – normal
Anemia – Transfused 4 units pRBCs and remained stable
Hyponatremia – Responded to free water restriction
Acute renal failure – ? Volume depletion, improved
Hyperbilirubinemia – First evident at follow-up after initial hospitalization, not explained
Hepatic encephalopathy – Asymptomatic hyperammonemia responded to lactulose Rx

3rd and Final Admission
Chief complaint: Generalized abdominal pain, fever

HPI: Returns to ED 5 days after discharge with 1 day of abdominal pain, dyspnea, weakness, fatigue and increasing abdominal distention

Physical examination: Tachycardia, systolic flow murmur, icteric, abdomen distended, palpable hepatomegaly

Laboratory investigations: Anemia, thrombocytopenia, low-grade DIC, acute kidney injury; peritonitis

Hospital Course:
Spontaneous bacterial peritonitis – Treated with antibiotics and intravenous albumin x2
Anemia – Transfusion with packed red blood cells and plasma
Abdominal CT – New layering effect consistent with hemoperitoneum
Acute kidney injury likely 2° acute tubular necrosis, CRRT for volume (anuric), complicated by hypotension
Discontinuation of Rx

Autopsy – Principal Findings:
Liver
- Benign anastomosing vascular network replacing normal tissue
- Extensive hepatic fibrosis
- Cholestasis, ascites, esophageal varices

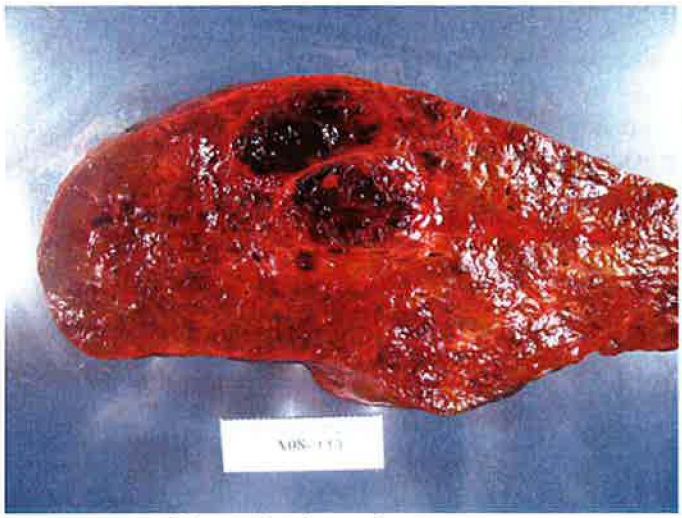
Bone marrow
- Benign anastomosing vascular network replacing normal tissue

Intestine
- Extensive hemorrhage, no evidence of vascular abnormalities

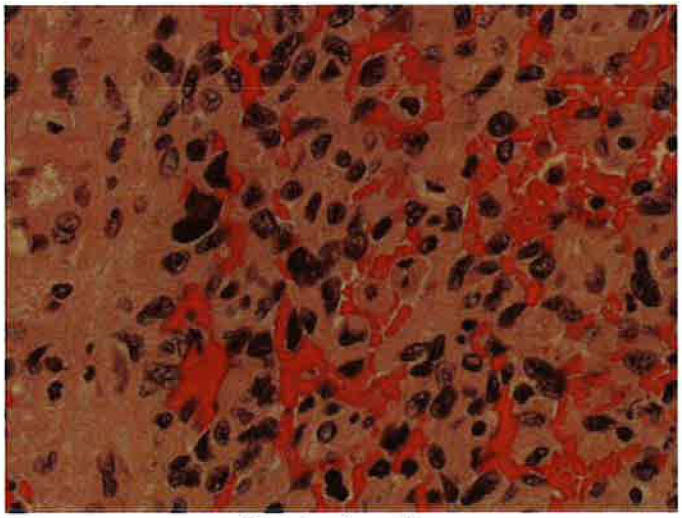
Kidney
- Acute tubular necrosis

Autopsy – Unexpected Finding:
Liver

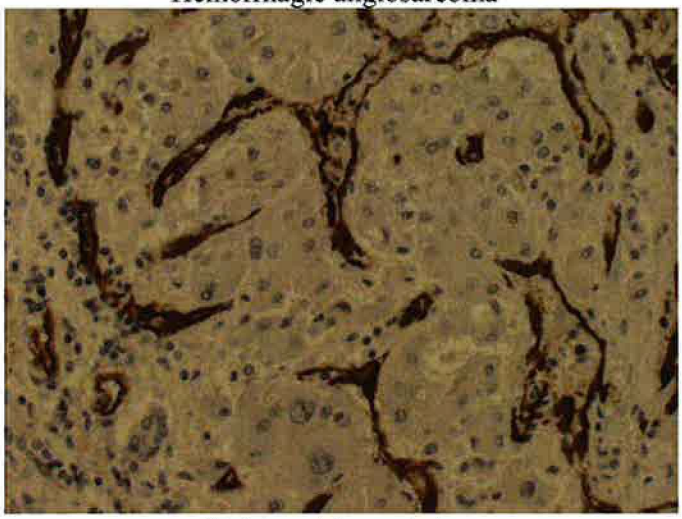
Multifocal angiosarcoma



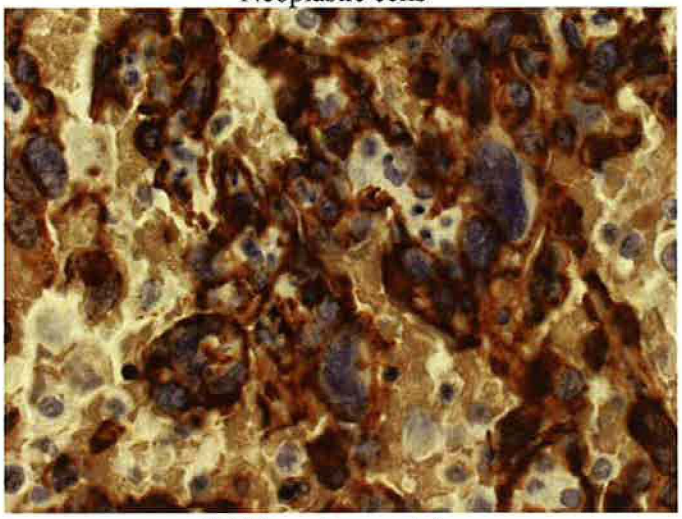
Hemorrhagic angiosarcoma



Neoplastic cells



CD34 positive staining



CD34 positive staining

Hepatic AVMs in HHT: Consensus: 6th HHT International Scientific Conference, Lyon 2005

Recommendations of an expert panel on hepatic involvement:

- Doppler ultrasound accurate and suitable for screening
- Substantial morbidity and mortality in patients with symptoms
- Avoid biopsy
- FNH and NRH up to 100-fold higher than general population
- Intensive medical therapy for high output cardiac failure and portal hypertension
- Liver transplantation

Lessons: Idioms
Idiom = Figurative meaning

Apply the common English idiom "look before you leap" to patient care
Look at the data before you make a decision
Look online before you leap in with assumptions about what to do next

Apply another common English idiom "practice what you preach"
The road to mismanagement is paved with wrong assumptions – Back to Basics lecture (Cuthbert)

Lessons: Aphorisms
Aphorism = Original thought in an easily memorable form

"…pus somewhere, …pus nowhere else, …pus there" where "there" was under the diaphragm. Harold Barnard, 1868 – 1908, surgeon, The London Hospital
Blood somewhere, blood nowhere else, blood under the diaphragm

"It takes a village…" Hillary Rodham Clinton
The village in this case is the health care team
We benefit from directly interacting with the team members, particularly "Visual Arts" practitioners

Dedications:

To Dr. Burton Combes
He interviewed me by telephone in the Southern hemisphere spring of 1976 and offered me a research fellowship
He became a trusted advisor and colleague
He is still a trusted advisor and colleague

To the patients at Parkland – I continue to love coming to work each day to teach and practice

To the others with whom I interact at Parkland – thank you for your patience as well as your patients

Grand Rounds = "Instant" Expert
The past
Surround yourself in a topic, becoming an expert
Maybe tackle something new and different from an outsider's perspective

The current
Stick to what you know and embroider it
Get a "twofer" by having the new knowledge add to your research, patient care or education missions
Get a "threefer" by having it published

The future? I cannot predict

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