Case Presentation

Kasher Meron Michal MD

Meir Hospital, Kfar sava, Israel

On Presentation

- 62y old male, born in South Africa
- Osler Weber Rendu, Hereditary Hemorrhagic Telangiectasia (HHT)
  - Recurrent Epistaxis. Anemia. No known pulmonary or visceral telangiectasia.
  - Iron supplements, occasionally transexamic acid
- DM, treated with diet only

On Presentation

- RUQ pain. Dyspnea. Night sweating

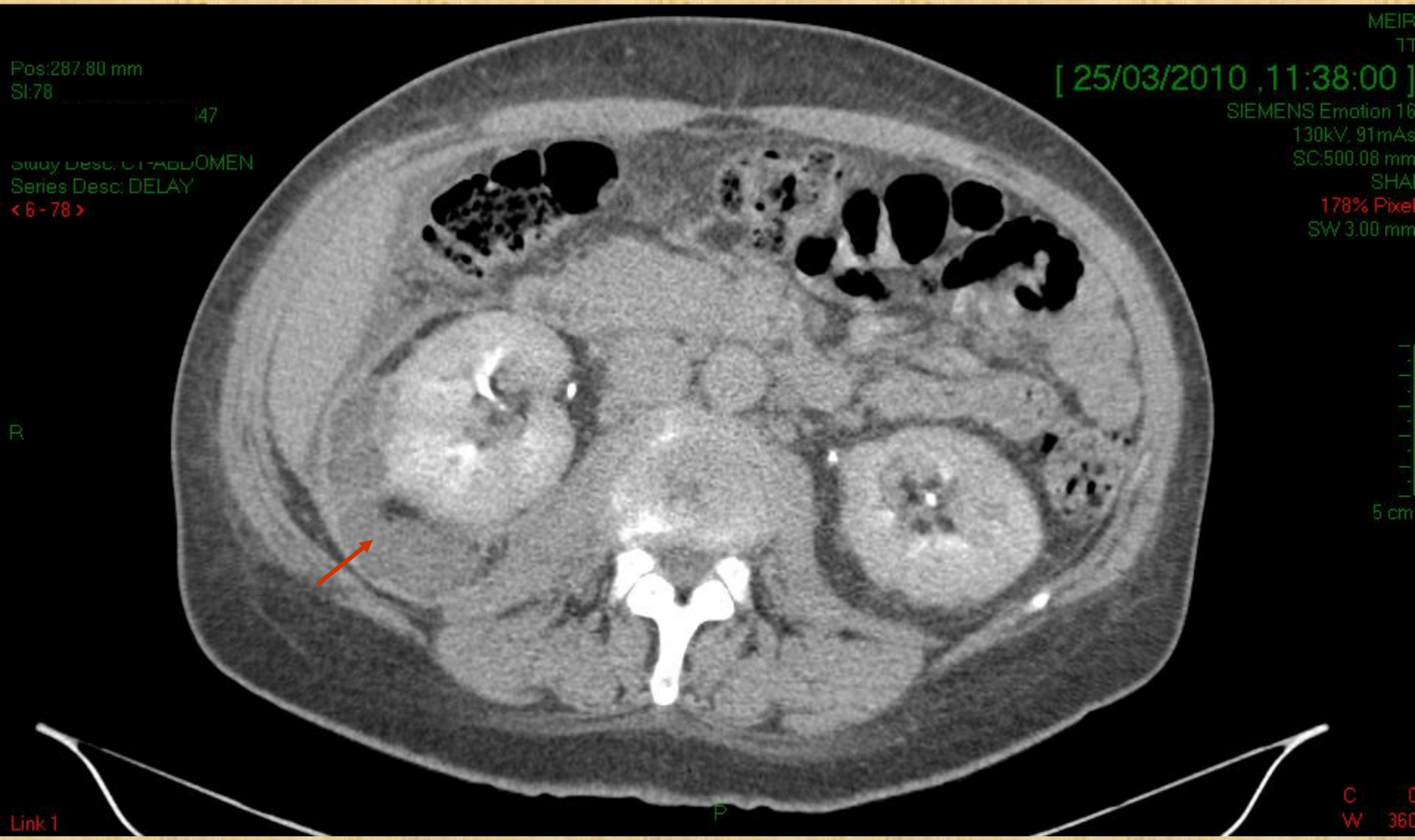
- PE:
- BP 132/87 HR 140/min T 37.5°c P.O. O2sat 94% RA
  Tachypnea. Clear breathing sounds
  RUQ tenderness++
  hepatomegaly
  JVP++, mild leg edema
- Leukocytosis 16K, Hb 10g/dL, creat. 0.8 mg/dL
- Elevated LFT – ALP GGT LDH.
- Glucose 500. HbA1C 12%

Differential Diagnosis

- Cholecystitis,Choledocholithiasis
- Liver malignancy
- RLL pneumonia
- High output cardiac failure
- Hematoma
- Rt heart failure
- Myocardial Infarction, Inferior wall
- PE

Initial Imaging Workup

- CXR normal
  ECG- sinus tachycardia LAH.
  Normal troponin levels
- **US**- normal liver, no cholecystitis.
  Biliary tracts are not enlarged.
  5cm collection in lower pole of Rt kidney
- **CT abdomen** – Rt kidney hematoma, subcapsular.
  Extended hepatic artery.
  Liver-normal parenchyma.


Pos:287.80 mm
SI:78
Series Desc: DELAY
< 6 - 78 >
[25/03/2010 ,11:38:00]
SIEMENS Emotion 16
130kV, 91mAs
SC:500.08 mm
178% Pixel
SW 3.00 mm
5 cm
R
P
Link 1

During Admission2

- Fever 38.1°c, clinical impression of sepsis:
  - Empirical Abx: ceforuxim, roxithromycin
- Signs of acute rt. heart failure-
  - Pulmonary scan –
    PE not likely, severe ventilation abnormality.
  - Echocardiography (TTE)-
    No pericardial fluid. No TR. RVH, extended IVC, biatrial enlargement. Good LV function.
  - Pulmonary shunt?
    Contrast ECHO– shunt
    CT angiogarphy- pleural infiltrates, no substantial AVM

During Admission3

- MSSA on blood cultures. Switched to Cefazoline.
- TEE- no vegetations

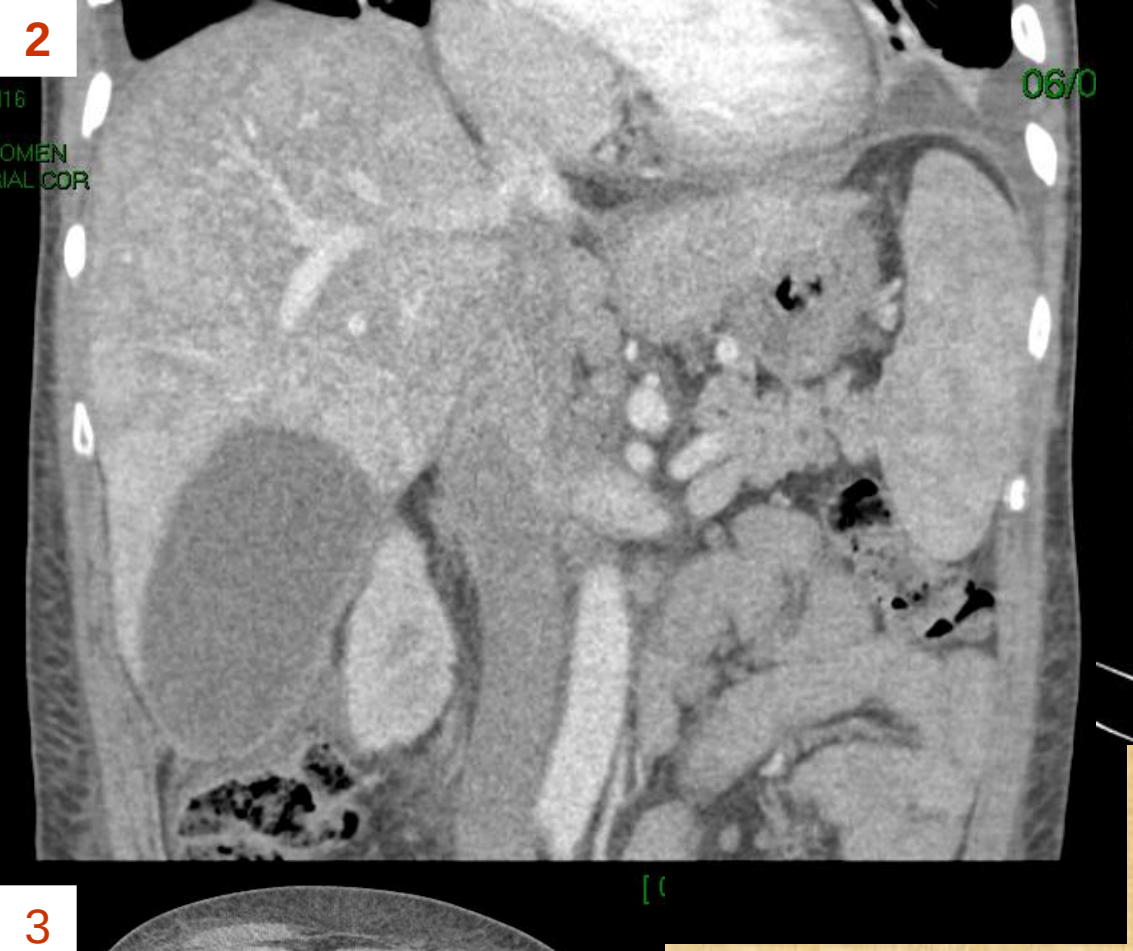
- 6 days later – still MSSA in blood cultures- PERSISTENT BACTEREMIA
- No fever. Still night sweating. CRP-18 →11

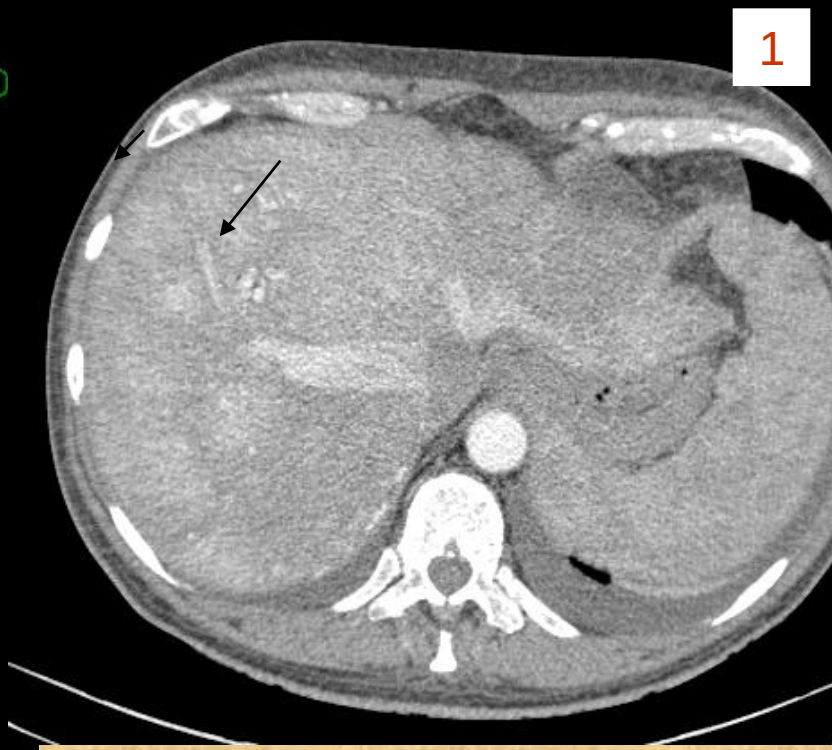
- CHF therapy, Diuretics
- Clinical improvement

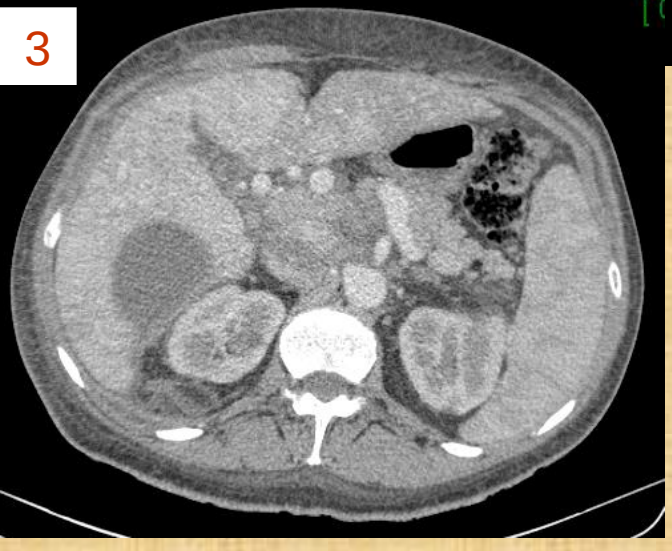
	טווח ויחידות / תאריך	10/05/2010 10:00	27/04/2010 10:19	11/04/2010 09:57	06/04/2010 10:45	28/03/2010 09:57	
SODIUM	135 - 145 mEq/L	139	138	136	137	139	
POTASSIUM	3.5 - 5.1 mEq/L	4.1	4.3	4.3	4.6	4.6	
GLUCOSE	70 - 100 mg/dL	**108**	**120**	**180**	**112**	**182**	
PROTEIN-TOTAL	6.0 - 8.2 gr/dL		6.9	6.6	6.3	**5.3**	
ALBUMIN	3.5 - 5.5 gr/dL		**3.1**	**2.4**	**2.4**	**2.3**	
UREA	10 - 50 mg/dL	40	37	23	23	19	
CREATININE	0.7 - 1.4 mg/dL	0.9	0.8	0.8	0.8	0.8	
CALCIUM	8.5 - 10.5 mg/dL		9.2	9.0			
PHOSPHORUS	2.5 - 5.0 mg/dL		3.6	3.0			
ALK. PHOSPHATASE	30 - 120 U/L	**264**	**514**	**1135**	**1497**	**770**	
GOT (AST)	7 - 37 U/L	24	27	22	29	29	
GPT (ALT)	0 - 40 U/L	14	14	10	16	31	
GGT	7 - 49 U/L	**584**	**1101**	**1638**	**1789**	**918**	
LDH	230 - 460 U/L	424	**467**	**546**	**661**	**541**	
CHOLESTEROL	200 - מרצוי קטן mg/dL		166	156			
BILIRUBIN-TOTAL	0.2 - 1.5 mg/dL	0.8	0.7	0.7	0.9	0.9	
HEMOGLOBIN A1C %	4.8 - 6.0 %						**12.2**

	טווח ויחידות / תאריך	03/05/2010 10:26	14/04/2010 10:38	06/04/2010 10:46	29/03/2010 09:47
C-REACTIVE PROTEIN	0 - 0.5 mg/dL	**1.12**	**2.32**	**11.57**	**17.69**

D-DIMER	0 - 500 ng/mL						**1517**
PROTEIN- URINE 24	28 - 140 mg/24h	**1214**					







2nd abdominal contrast CT (3 phases)

Hepatic AVM!
Hepatic collection, 11X12 cm!

Summary

- HHT patient. RUQ pain. Elevated cholestatic enz., fever, Rt heart failure
- DX: Pyogenic abscess, Staph. Aureus
  Hepatic AVMs
  No portal HTN.

- Questions:
  - Staph Aureus seeding?
  - Related to HHT?
  - Why Rt heart failure?


Thank You!

HHT

- Autosomal dominant. Varying penetrance and expression.
- Mutations in at least five genes can cause HHT. ~600 different HHT-causing mutations
- Wide geographic distribution
- Common: epistaxis, GI bleeding, iron deficiency anemia, mucocutaneous telangiectasia.
- Visceral AVM - pulmonary, hepatic, cerebral.

Govani FS, Eur J Hum Genet. 2009
Alan, NEJM 1995

HHT DIAGNOSIS

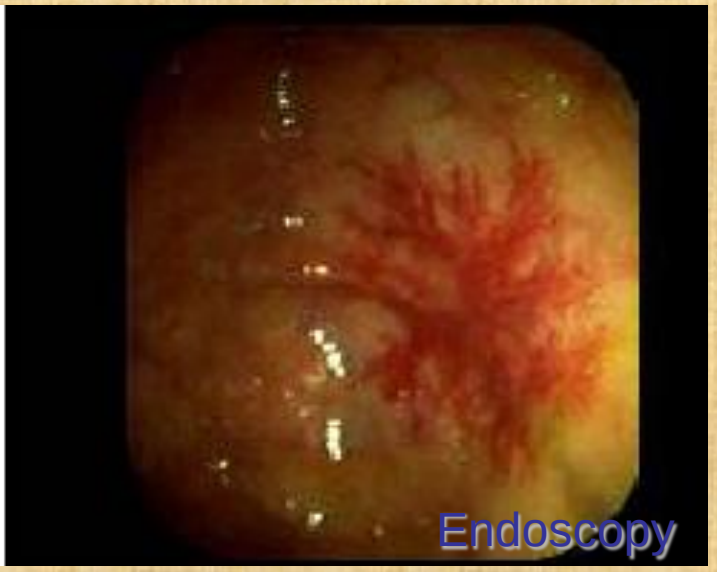
International consensus diagnostic criteria, Curacao

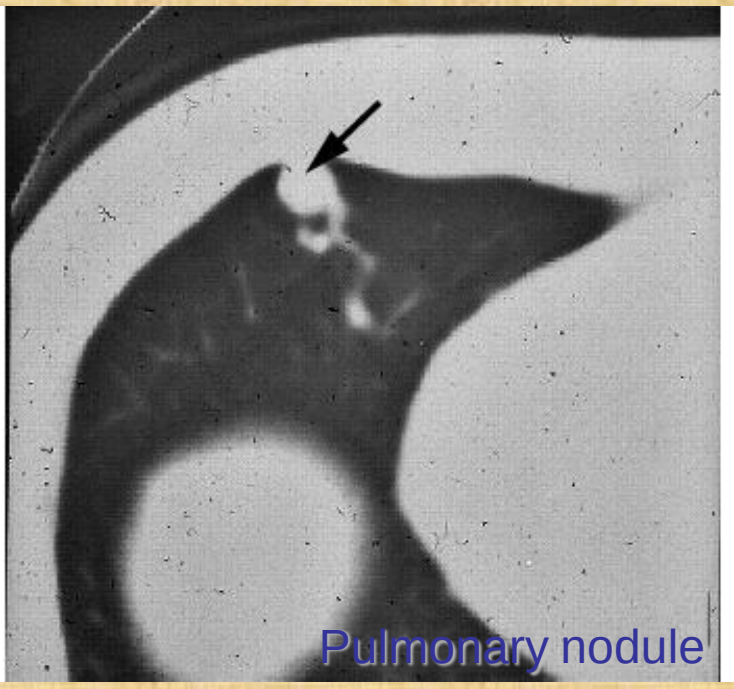
- 4 findings:
  - Spontaneous and recurrent epistaxis
  - Multiple mucocutaneous telangiectasias
  - Visceral involvement - gastrointestinal, pulmonary, cerebral, hepatic AVMs
  - A first-degree relative with HHT

HHT Clinical Manifestations

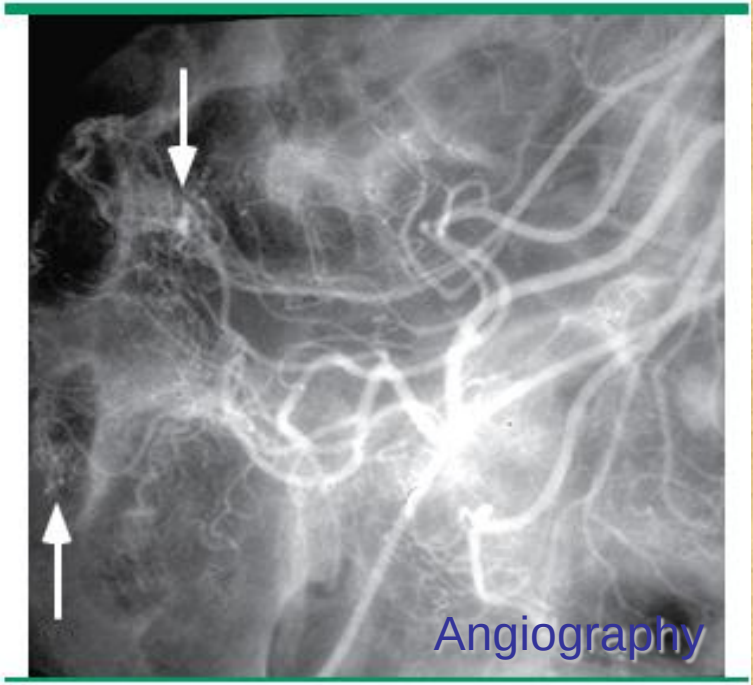
Nasal Telangiectasia(TE)	**> 90%**
Mucocutaneous TE	50-80%
GI TE	11-40%
Pulmonary AVMs	11-30%
Cerebral AVMs	10-15%
Hepatic AVMs	<75%
Conjunctive TE	35%

Ianora AA, Radiology 2004

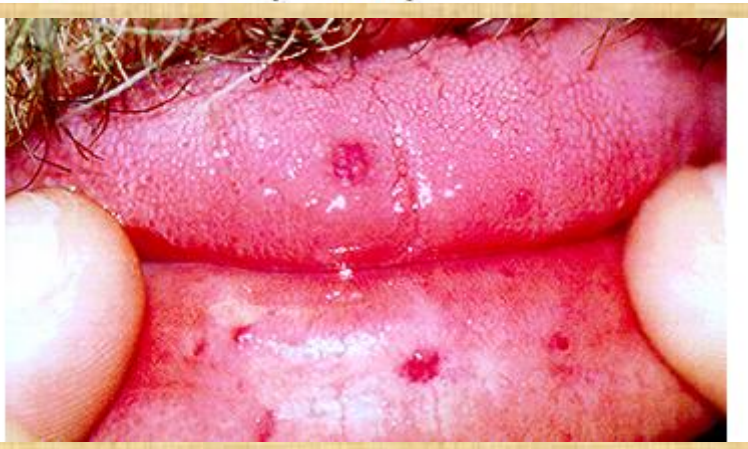




Angiodysplasia of the colon



A superior mesenteric arteriogram demonstrates puddling of contrast material in tortuous distended vessels in the cecal wall (arrows).

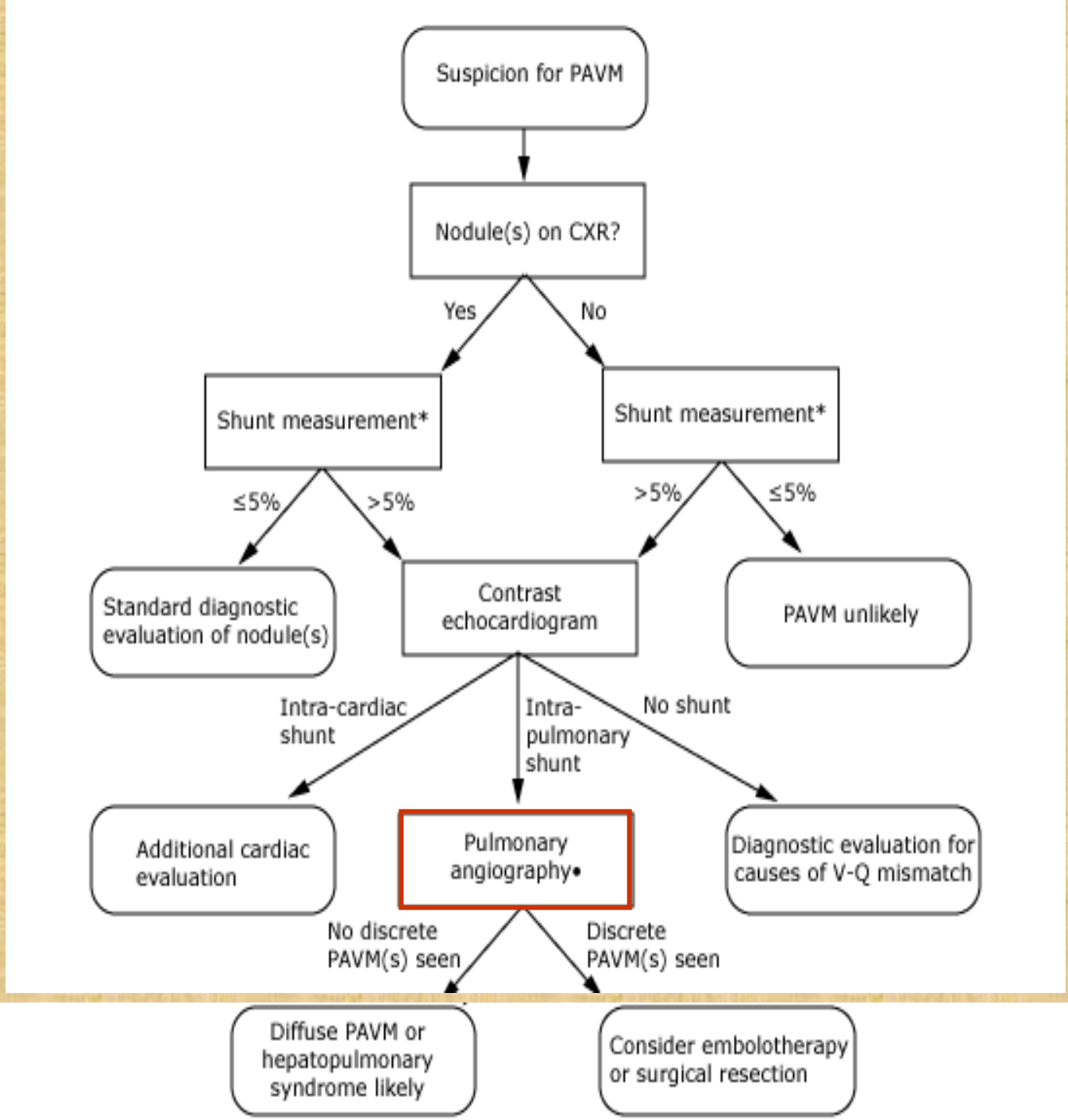


Pulmonary AVMs

Arterio-Venous Malformations

- Abnormal communications between pulmonary arteries and veins 11-30% in HHT pts
- Important DD in common pulmonary problems
- Usually no respiratory symptoms

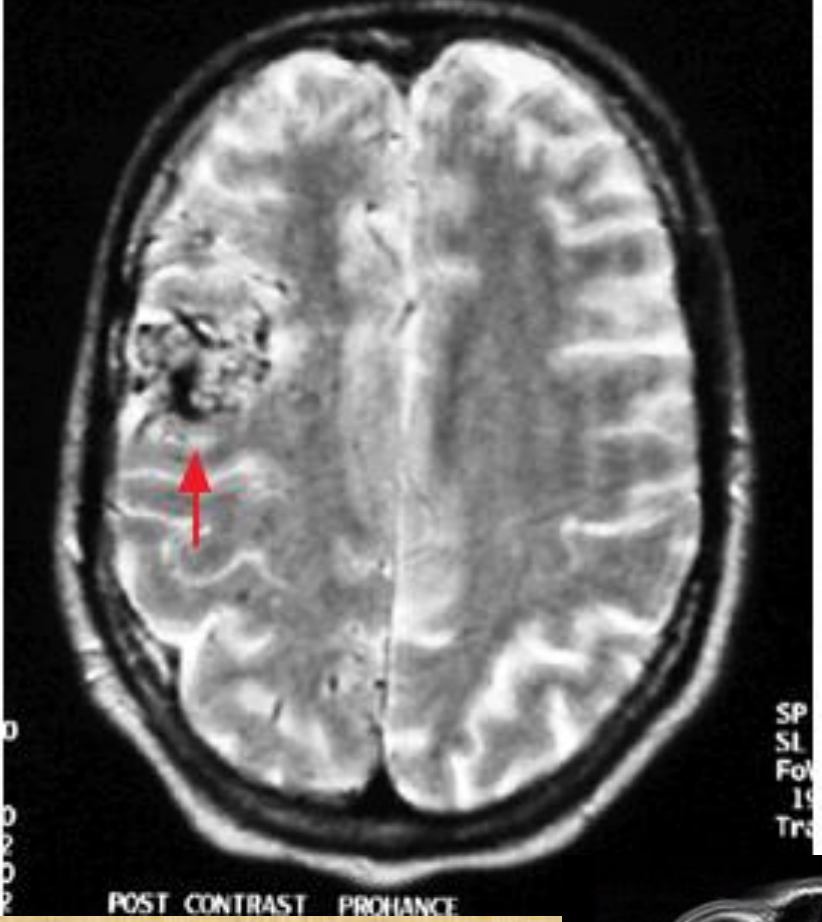
- Suspected patients:
  - CXR/CT -pulmonary nodule/s
  - Mucocutaneous telangiectases
  - Hemoptysis
  - Stigmata of right-to-left shunting: dyspnea, hypoxemia, polycythemia, clubbing, cyanosis, cerebral embolism, or brain abscess
  - A relative with HHT

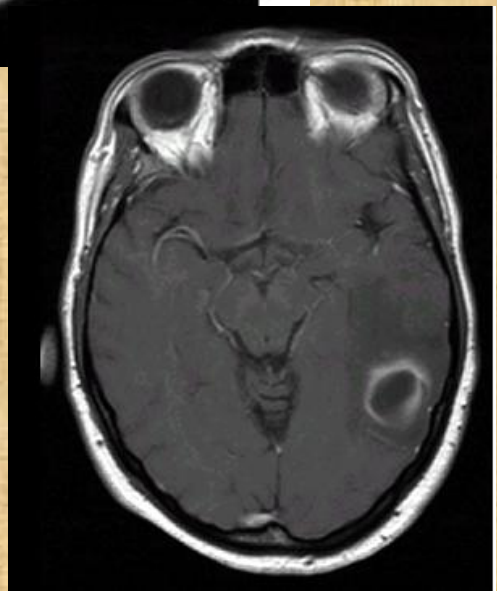

Suspicion for PAVM
Nodule(s) on CXR?
Yes
No
Shunt measurement*
Shunt measurement*
≤5%
>5%
>5%
≤5%
Standard diagnostic evaluation of nodule(s)
Contrast echocardiogram
PAVM unlikely
Intra-cardiac shunt
Intra-pulmonary shunt
No shunt
Additional cardiac evaluation
Pulmonary angiography•
Diagnostic evaluation for causes of V-Q mismatch
No discrete PAVM(s) seen
Discrete PAVM(s) seen
Diffuse PAVM or hepatopulmonary syndrome likely
Consider embolotherapy or surgical resection

Pulmonary AVM

- Even while asymptomatic - pending neurologic complications (common):
  - Catastrophic embolic cerebral strokes and abscesses
  - Hemorrhages into bronchial or pleural cavity (usually pregnancy).
- Early diagnosis and intervention
  - Embolization (preferable)- indicated according to VM size
  - Antibiotic prophylaxis for interventional procedures, especially dental

Cerebral AVM in HHT





- cerebral or spinal cord involvement (10-15%).
- Presentation:
  Headache, seizures
  Ischemia (“steal effect”)
  Hemorrhage.
- Dx: MRI
- Tx: Embolothrapy

HHT Screening

- Family members of HHT Pts:
  - Physical examination
  - Pulmonary AVM screening
  - Pts with family history of cerebral hemorrhage, or personal history for cerebral symptoms → MRI

HHT Hepatic Involvement

- Silent hepatic involvement occurs in up to 30% of HHT patients
- If symptomatic-3 different patterns of vascular involvement:
  - High-output heart failure
  - Portal hypertension
  - Biliary disease

The NEW ENGLAND JOURNAL of MEDICINE

Liver Disease in Patients with Hereditary Hemorrhagic Telangiectasia

- *19 patients*
- *From 1994 to 1998 (700 referrals), 19 HHT patients*
- *Clinical features: heart failure, ascites, pain in the right upper quadrant, a liver bruit, abnormal results of liver tests*
- *Liver involvement was confirmed by the presence of disseminated intrahepatic telangiectases or AVM on angiograms or CT scans.*

Guadalupe Garcia-Tsao, NEJM 2000

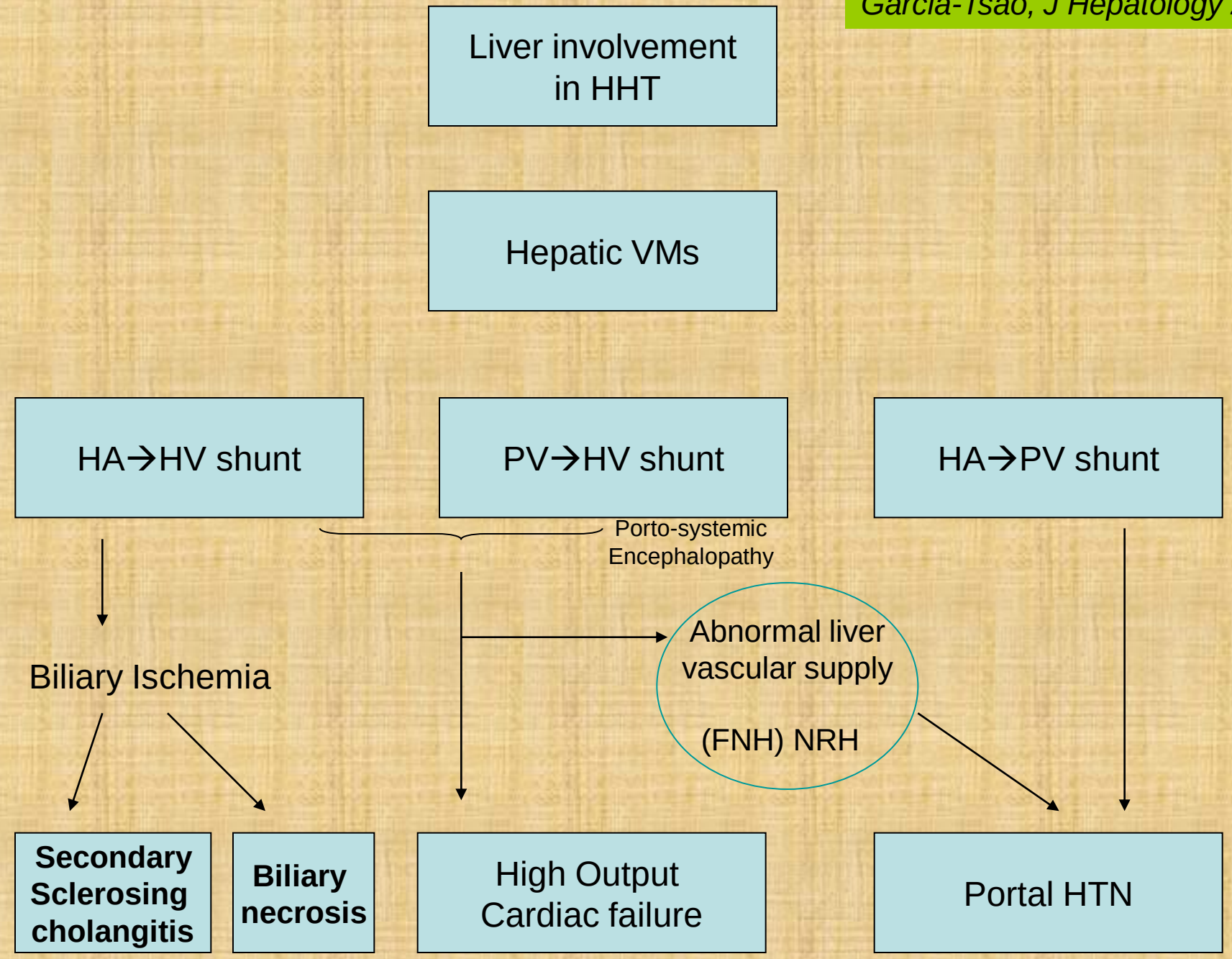
TABLE 1. CHARACTERISTICS OF 19 PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA AND LIVER DISEASE, ACCORDING TO THE CLINICAL PRESENTATION.

Three distinct clinical patterns of hepatic involvement
Occasionally with spontaneous resolution

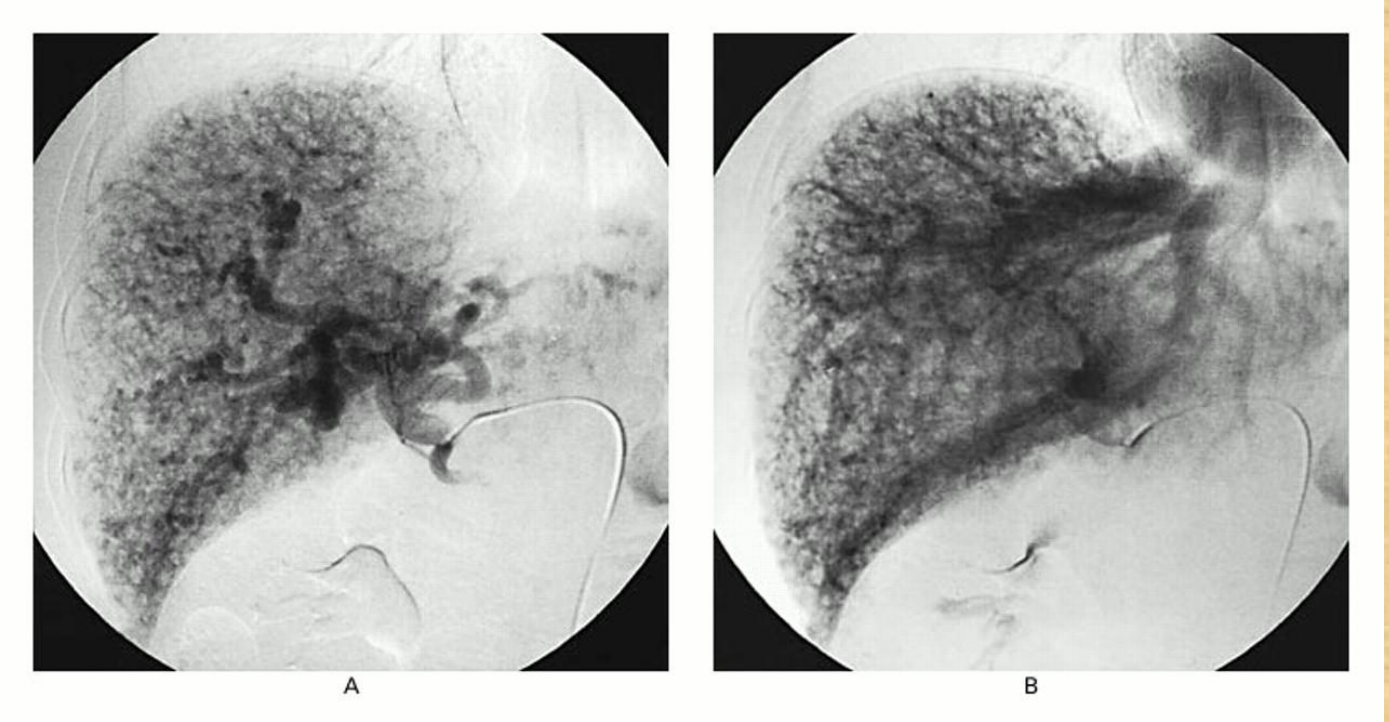
	Heart failure No=8	Portal Hypertension No=6	Biliary Disease No=5
symp. And signs at presentation			
Shortness of breath	8		
Intractabale GI bleeding		3	
Liver bruit	7	1	2
Ascites		4	
ALP median	100	100	355 (1066)
Pulmonary wedge preesure	17	9	11
Hepatic venous pressure gradient	2	20	2.5

Guadalupe Garcia-Tsao, NEJM 2000

Garcia-Tsao, J Hepatology 2007

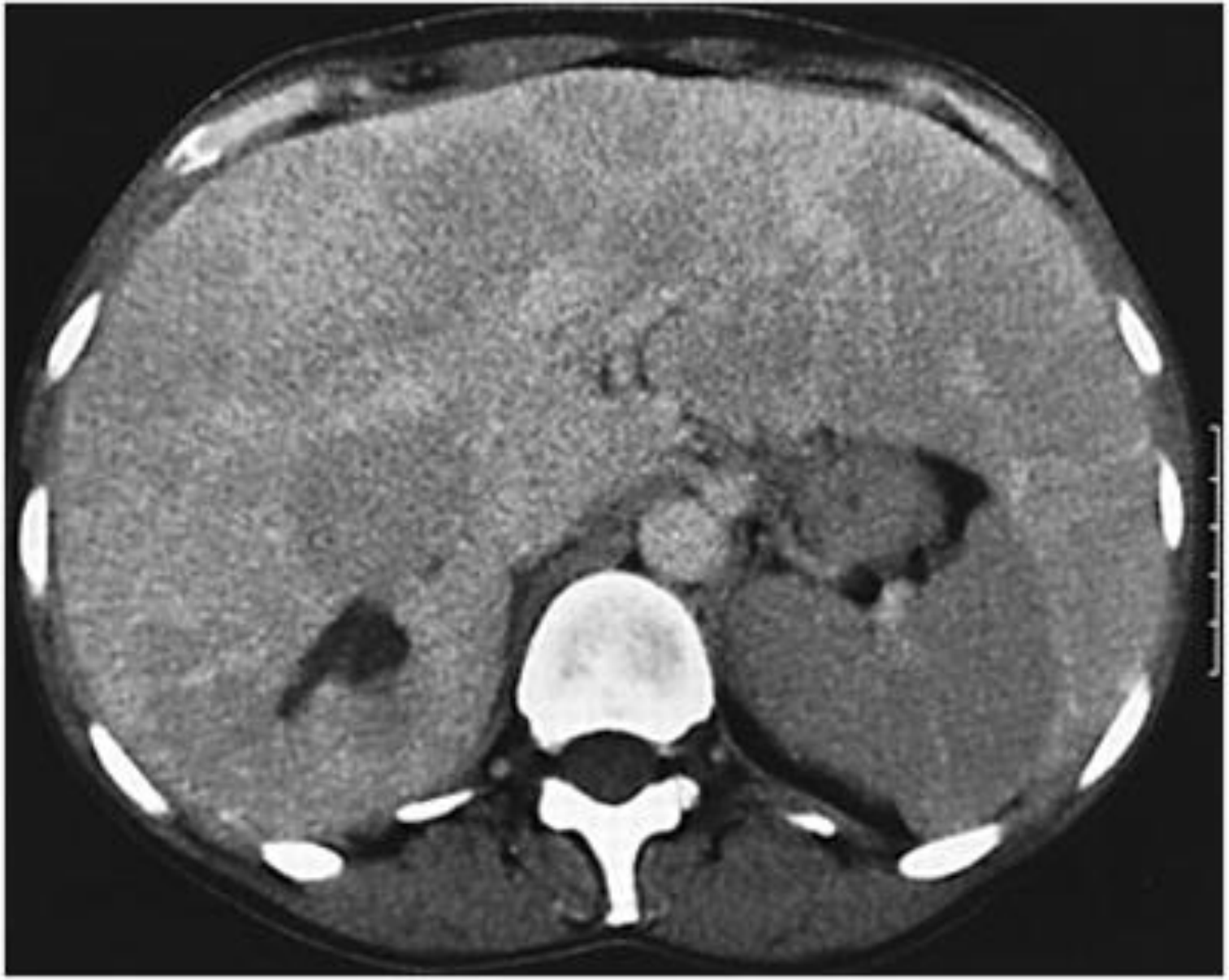


Hepatic Angiogram



- HHT patient with HO Cardiac failure, Cardiac Index of 7.0 Liters/M2
- The liver parenchyma has a hypervascular pattern (Panel A), with early opacification of the hepatic veins (Panel B).

Guadalupe Garcia-Tsao, NEJM 2000



Guadalupe Garcia-Tsao, NEJM 2000

HHT Hepatic Involvement

- Liver biopsy is not recommended
- No embolization of hepatic AVM- several cases of fatal hepatic necrosis.
- Liver transplantation program :
  - acute hepatic failure
  - intractable heart failure
  - portal hypertension

HHT Treatment

- No RCTs
- Symptomatic relief:
  - Endoscopic ablation
  - 2 Antihemorrhagic therapies (based on RCT)
    - Female hormones
    - Anti-estrogens , tamoxifen
  - Angiogenesis inhibitors — Bevacizumab, thalidomide, case reports
  - immunosuppressive agents (eg, sirolimus, interferon)
- Potential beneficial effects vs prothrombotic effect of antifibrinolytic therapy

HHT Management

- Pulmonary AVMs→ embolotherapy is recommended
- Cerebral AVMs → embolectomy, surgical removal, or stereotactic radiotherapy.
- Hepatic AVMs→ if medical management fails, liver transplantation (~30)
- Major complications of pregnancy in women with HHT.

Garcia-Tsao . J Hepatology 2007


תודה

HHT Clinical Manifestations

Site	Incidence	Presentation patterns	Treatment regimens
Nasal telangiectasia	>90 percent	Nose bleeds are usually the first manifestation of HHT, frequently commencing in childhood	1) **Routine therapy:** Packing, humidification, iron, and transfusions when needed. Estrogen/progesterone therapy proposed (in view of possible induction of squamous metaplasia) but no benefit in only controlled trial
			2) **Laser treatment** successful. Argon and KTP lasers which use wavelengths maximally absorbed by hemoglobin often preferred to Nd-YAG which carries a higher risk of cartilage absorption and septal perforation.
			3) **Surgery,** such as septal dermoplasty to replace thin nasal mucosa with a tougher skin graft, is successful in expert hands, though vessels regrow
			4) **Other:** Therapeutic embolization may be difficult because of extensive anastamoses; cauterization has only a limited role.
Mucucutaneous telangiectasia	50 to 80 percent	Increase in size and number with age. Main concerns are cosmetic. May hemorrhage	Generally not indicated, but laser therapy can be used

Ianora AA, Radiology 2004

HHT Clinical Manifestations

Gastrointestinal telangiectasia	11 to 40 percent	Onset generally over 30 years: iron deficiency anemia, occasionally acute gastrointestinal hemorrhage	Flexible endoscopy, endoscopy angiogram, capsule endoscopy	Iron supplementation and transfusion are the mainstays of treatment. Estrogen-progesterone, and laser therapy beneficial. The role of antifibrinolytics is unclear
Pulmonary AVMs	11 to 30 percent	Cyanosis, clubbing, bruit, dyspnea, paradoxical embolis, cerebral absess Many are asymptomaatic	Chest radiography, blood gas measurement, helical CT, angiography, chest echocardiography	Therapeutic embolization, surgical resection, ligation of arterial supply (artery ligation is only of historical interest).
Cerebral AVMs	10 to 15 percent	Headache, epilepsy, ischemia, intracerebral hemorrhage	CT, MRI, Doppler Sonography, angiography	Therapeutic embolization, neurovascular surgery, stereotactic radiosurgery
Hepatic AVMs	Up to 74 percent*	Usually silent. Hepatic artery-hepatic vein AVMS: hyperdynamic circulation. Portasystemic shunts: ascites and encephalopathy.		Therapeutic embolization, liver transplantation
Conjuctive telangiectasia	35 percent	Usually silent. May have "bloody tears"		

Ianora AA, Radiology 2004

TABLE 1. CHARACTERISTICS OF 19 PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA AND LIVER DISEASE, ACCORDING TO THE CLINICAL PRESENTATION.

CHARACTERISTIC	HEART FAILURE (N=8)	PORTAL HYPERTENSION (N=6)	BILIARY DISEASE (N=5)
Age			
Median	59	67	48
Range	34–72	56–74	36–55
Female sex	6	3	5
Symptoms and signs at presentation (no. of patients)			
Shortness of breath	8	0	0
Abdominal pain	1	0	2
Intractable chronic gastrointestinal bleeding	0	3	0
Liver bruit	7	1	2
Ascites	0	4	0
Alkaline phosphatase (U/liter)			
Median	94	100	355
Range	47–142	87–369	153–1066
Bilirubin (mg/dl)*			
Median	4.1	4.0	4.1
Range	3.7–4.5	2.7–4.4	3.4–4.8
Prothrombin time (sec)			
Median	12.6	12.6	11.7
Range	12.1–12.8	12.0–13.3	10.9–13.2
Cardiac index (liters/min/m²)			
Median	6.8	4.6	5.5
Range	5.8–7.3	4.2–5.5	2.9–6.6
Pulmonary-capillary wedge pressure			
No. of patients	6	4	4
Median (mm Hg)	17.0	9.0	11.3
Range (mm Hg)	14.0–22.0	7.0–16.0	5.0–15.5
Hepatic-artery-to-hepatic-vein shunting (no	6/6	0/4	1/2
Hepatic ven			
No. of pa			
Median (r			
Range (m			

*To conve

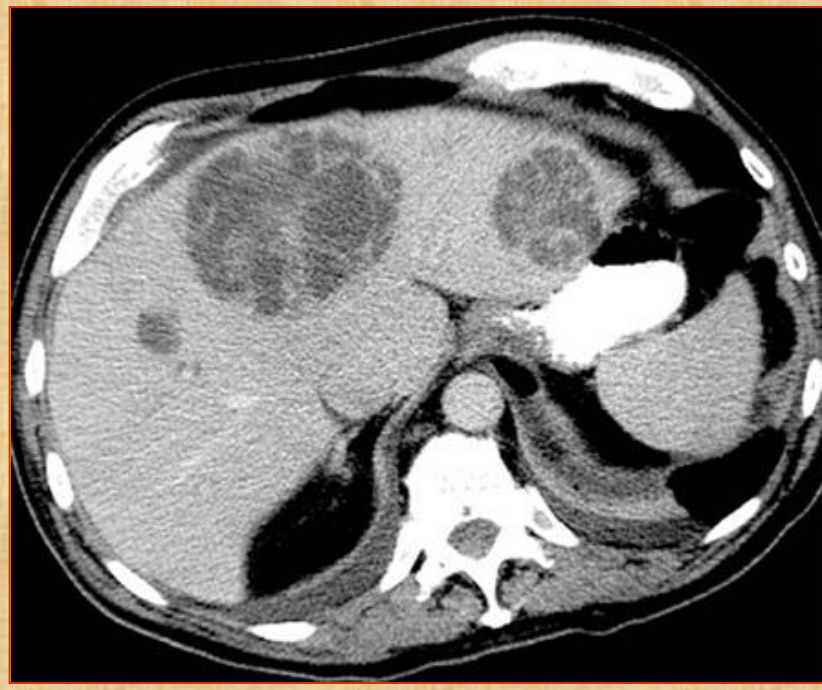
†Three of

Three distinct clinical patterns of hepatic involvement
Occasionally with spontaneous resolution

	Heart failure No=8	Portal No=6
Shortness of breath	8	
Intractabale GI bleeding		3

Pyogenic Liver Abscess

- Clinical manifestations: fever (90%), abdominal pain 50-75%, nausea, vomiting, anorexia, weight loss, and malaise.
- Lab: elevated ALP in 67-90%, leukocytosis, 50% Bacteremia
- Portal vein pyemia (bowel leakage and peritonitis), direct spread from biliary infection (40-60%)
- Polymicrobial: mixed enteric facultative and anaerobic species



Pyogenic Liver Abscess-TX

- No RCT.
- **Drainage and antibiotic therapy**.
- Emprical TX – enteric gram negative and anaerobes. (pending cultures)
- Clinical follow up: temperature, WBC, CRP
- Resolution on imaging is slower
  Nepal: 102 pyogenic liver abscess pts. Mean time to ultrasonographic resolution of abscesses <10 cm was 16W; for abscesses >10 cm was 22W. *Sharma D. Eur J Radiol 2009*
- Usually 4-8 week course of treatment, depends on pathogen.

Pyogenic Liver Abscess

- Typical clinical manifestations:
  fever (90%), abdominal pain 50-75%
  nausea, vomiting, anorexia, weight loss, and malaise.
- PE-
  pain, guarding, rocking tenderness, even rebound tenderness.
  The absence of right upper quadrant findings does not exclude liver abscess. Half of patients have no symptoms or signs indicating liver involvement

Pyogenic Liver Abscess

- Laboratory findings:
  - may include elevated bilirubin and/or liver enzymes (~50%). Serum alkaline phosphatase is elevated in 67-90% .
  - Leukocytosis
  - Hypoalbuminemia
  - Anemia (normochromic, normocytic).
  - 50% Bacteremia
- CXR- new elevation of the right hemidiaphragm is seen, right basilar infiltrate and a right pleural effusion.

Liver Abscess- Pathogenesis

- Portal vein pyemia: bowel leakage and peritonitis.
- Direct spread from biliary infection d/t underlying biliary disease- gallstones or malignant obstruction (40-60%)
- Iatrogenic- Surgical or penetrating wounds
- Systemic hematogenous seeding: A monomicrobial liver abscess due to a streptococcal or staphylococcal species should prompt evaluation for an additional source of infection.

- Liver abscesses usually involve the right lobe of the liver: it is larger and has greater blood supply than the left and caudate lobes.

Huang. Ann Surg 1996
Rahimian. Clin Infect Dis 2004

Bacteremia is Documented in ~50%

Polymicrobial: mixed enteric facultative and anaerobic species are the most common pathogens	Most cases, most common - ECOLI
Streptococcus milleri or S. anginosus group	search for simultaneous metastatic infections at other locations
S. aureus, S. pyogenes, and other Gram positive cocci	transarterial embolization for hepatocellular carcinoma (1%), accounted for 60%, SBE indwelling catheter
candida	chemotherapy and presents with recovery of neutrophil counts
Klebsiella pneumoniae	Monomicrobial, no previous hepatobiliary disease, Diabetes mellitus is a major RF
Tuberculous liver abscesses	uncommon but should be considered when typical pyogenic organisms are not recovered
Amebiasis	Traveling to endemic areas within 6M
Burkholderia pseudomallei (Melioidosis)	endemic areas: Southeast Asia and Northern Australia

Pyogenic liver abscess (Schwart'z)

- Aspiration and placement of a drainage catheter is beneficial for only a minority of pyogenic abscesses, because most are quite viscous and drainage is ineffective.
- Antibiotic therapy must be continued for at least 8 weeks. Effective in 80 to 90% of patients. If this initial mode of therapy fails, the patients should undergo surgical drainage (Lap/open)
- Early surgical resection for patients who do not respond to initial antibiotic therapy- necrotic hepatic malignancy.