

Grand Rounds: A rare liver disease in a patient with Ehlers-Danlos

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Objective

- Present case study
- Describe the disease found in the patient
- Ehlers-Danlos and GI disease
- On going evaluation of case
- Conclusion

Case study

- 25 yr old male referred to GI AIM with new diagnosis of ascites found on CT done to evaluate a hernia repair
- CT had been ordered by urology to evaluate scrotal swelling

Case study: Past medical history and medications

- Ehlers-Danlos syndrome type unknown
- S/p hernia repair (inguinal canal); no other surgeries
- According to mother normal birth, growth and development
- Patient denies any medication use; no regular use of tylenol; no previous exposure to unusual meds

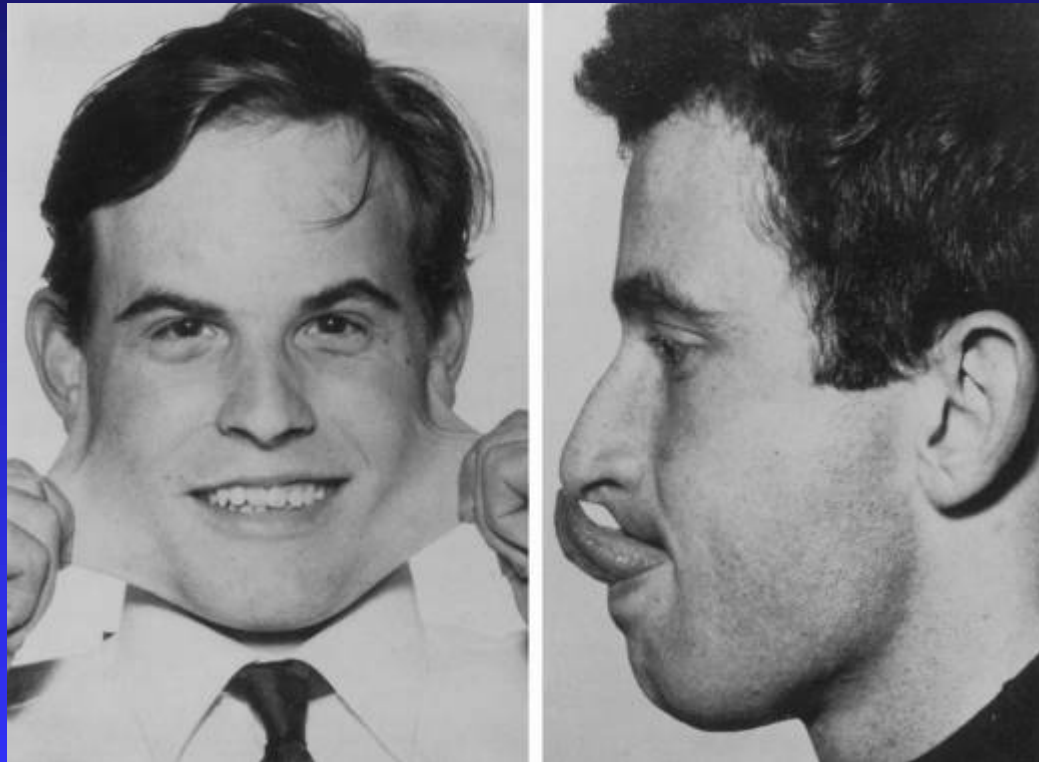
Case study: Social Hx and Family Hx

■ Social Hx:

- ◆ Does not use alcohol or tobacco
- ◆ Graduated from high school; Janitor; lives with parents; denies unusual chemical exposure; has never traveled outside the continental US
- ◆ No pets; City water;

■ Family Hx: No liver disease; CAD

Ehlers Danlos



Case study: Review of systems

- No fever, chills
- Heent: no lymph nodes; patient able to pull skin;
- CV: no chest pain; no doe
- Chest: mild cough
- Abd: no n/v; some increased bloating; BM normal
- Skin: some easy bruising

Case study: Physical Exam

- T=97 BP 110/50; P 64
- Gen: pleasant; nad
- CV: rr; no murmur
- Chest: decreased at base but otherwise clear
- Abd: Mild distended, fluid wave, nt, +bs, no hsm
- Ext: no lower extremity edema
- GU: right scrotal swelling, thinned skin, healing excoriation

Case study: Lab evaluation

- Urinalysis: Negative protein; Negative bilirubin; Negative blood or wbc
- Lipid panel: Cholesterol 142, TG 50; HDL 39; LDL 93
- WBC 3.7; Hgb 13.9; Hct 40.5; MCV 85; platelet 280; differential normal

Lab	Aug 3	Aug 5	Sept 15
Protein (g/dL)	7.8	7.9	8.0
Albumin (g/dL)	4.6	4.5	4.6
T Bil (mg/dL)	1.4	2.1	1.3
D Bil (mg/dL)	0.1	0.65	0.47
Alk Phos (U/L)	127	151	168
AST (U/L)	39	33	35
ALT (U/L)	35	29	31

Lab	Aug 3	Aug 5	Aug 10	Sept 15
PT (9.4- 11.6)	12.7	11.8	13.2	16.5
PTT (26.8- 35.2)	32.9	41	32.8	43.1
INR (0.9- 1.2)	1.2	1.1	1.3	1.2

Case study: Lab evaluation

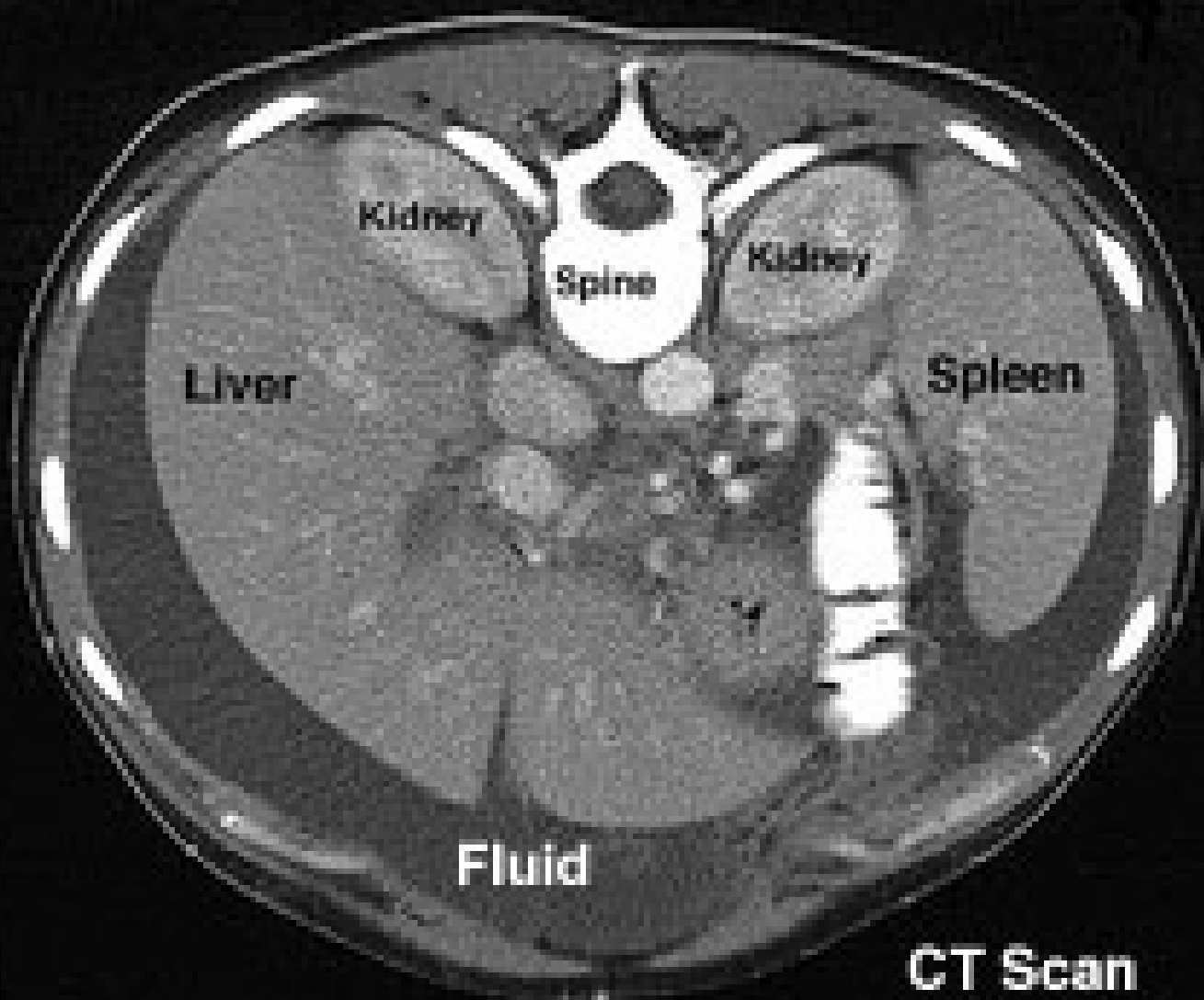
- Alpha 1-antitrypsin: 188 (90-200 mg/dL)
- Ceruloplasmin 31.3 (16.2-35.6 mg/dL)
- Hep C Ab < 1.0 (neg);
- Hep B surface Ab < 3.0 mIU/mL (neg)
- Hep B surface AG negative
- Hep A total Ab negative
- TIBC 315; Iron saturation 17%; Ferritin 114 ng/mL
- ANA 30 U/mL (0-99)
- Quantitative immunoglobulins: wnl

Case study: CT July 19, 2005

- Massive ascites and large left pleural fluid collection. The heterogeneous appearance of the liver and lack of visualization of the hepatic veins would favor a Budd-Chiari syndrome. Passive congestion of the liver could have a similar appearance but the hepatic veins should be visualized.

Case Study: CT

- The large left pleural fluid collection and compressive atelectasis at the left base is presumed to be secondary to massive ascites. But recommend CT of chest
- Massive ascites collecting in the pelvis extending into the right inguinal canal and right hemiscrotum
- Pelvic vascular congestion is nonspecific and could be seen with either Budd Chiari or passive congestion of the liver



Note the layer of ascitic fluid between the abdominal wall and liver.

Case study: Ultrasound 8/10/05

- Ultrasound guided paracentesis done: 700 cc of dark yellow fluid obtained
- Normal venous doppler of right upper quadrant except for increased caliber of the IVC and several of the hepatic veins which could represent right heart failure with passive congestion.

Case study: Ultrasound 8/10/05

- Hepatosplenomegaly with no focal hepatic nor splenic abnormality
- Bilateral small pleural effusions with ascites in the upper abdomen
- Pancreas not well seen secondary to overlying bowel gas obscuring tail and portion of the body

Case study: Fluid studies

- Albumin (g/dL) = 2.3
- Serum albumin (g/dL) = 4.6
- SAAG: $4.6 - 2.3 = 2.3$
- Total protein in fluid = 4.9
- RBC 2243; WBC 168
- 64% segs; 35% lymphs; 0 % mono; 1 % eo

With suggestion of Budd-Chiari

- Checked for hypercoagulability
- Hexagonal phase phospholipid 4.9 (0.0-8.0)
- PTT-LA 43.1(0-52)
- dRVVT 30.4 (0-42.8)
- If the patient had Lupus anticoagulant these would all be abnormally high
- Factor II DNA (prothrombin gene) mutation: negative

More labs

- Homocysteine 18.4 umol/L (4.3-11.4)
- RPR: non reactive
- Factor V activity 56% (60-140)
- Antithrombin activity 91% (75-135)
- Protein C Antigen 66% (>70%)
- Protein S Antigen
 - ◆ Protein S, Total 100% (58-150)
 - ◆ Protein S, Free 42% (56-124)

2D Echocardiography

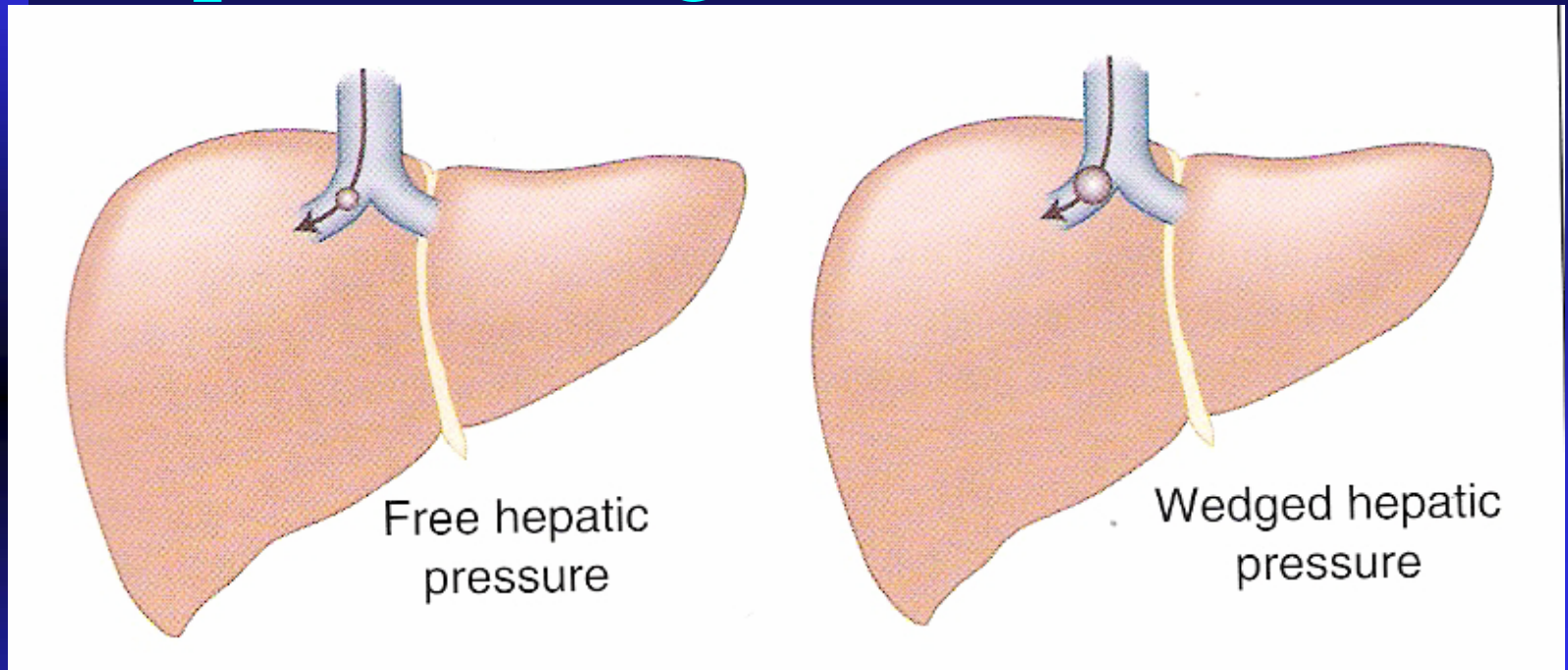
- LV systolic fxn nl
- Normal LV, RV, RA size
- EF 50%
- NI ascending aorta
- NI descending aorta
- Plethoric IVC consistent with RA pressure 15-20 mmHg (0-6)



Color Flow and Doppler

- Normal aortic valve velocities
- No aortic insufficiency
- Normal mitral valve velocities
- Mild mitral regurgitation with frequency vibrations on doppler consistent with pliable mitral valve
- Normal tricuspid valve velocities
- Mild tricuspid regurgitation
- Normal pulmonic valve velocities
- Mild pulmonic insufficiency

Hepatic venogram

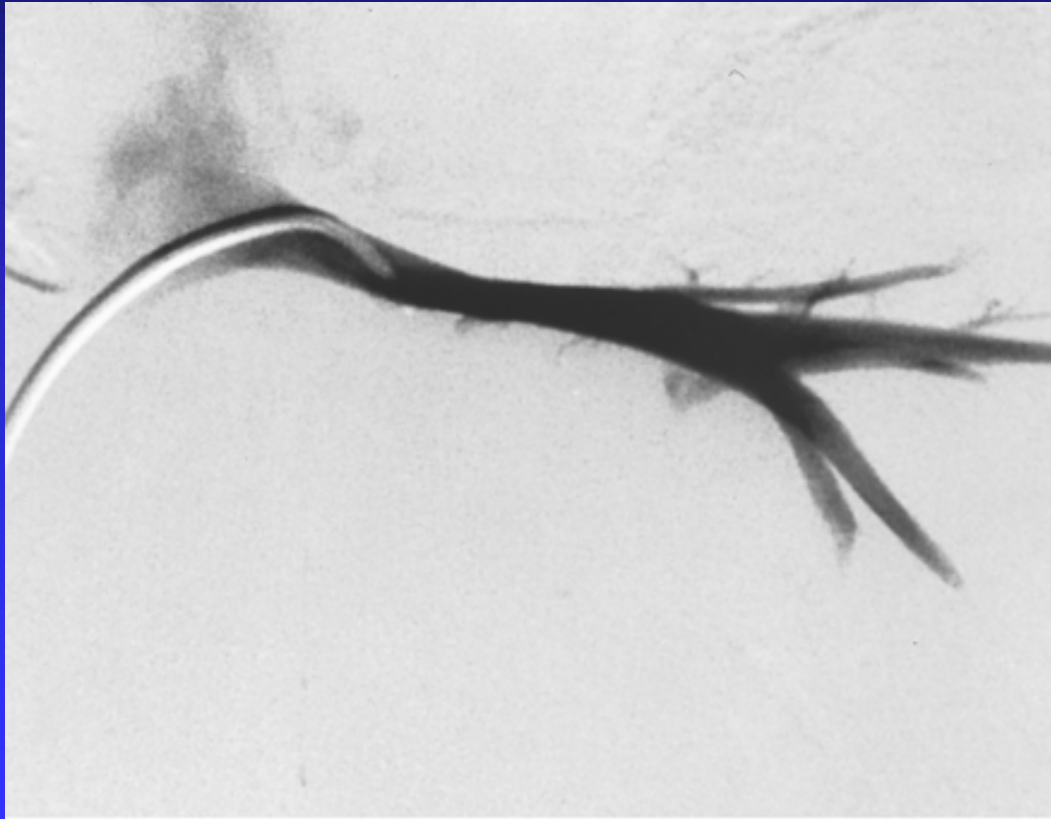


Hepatic venous pressure gradient (HVPG) =
Wedged hepatic pressure – Free hepatic pressure
(normal does not exceed 5 mm Hg)

Hepatic venogram

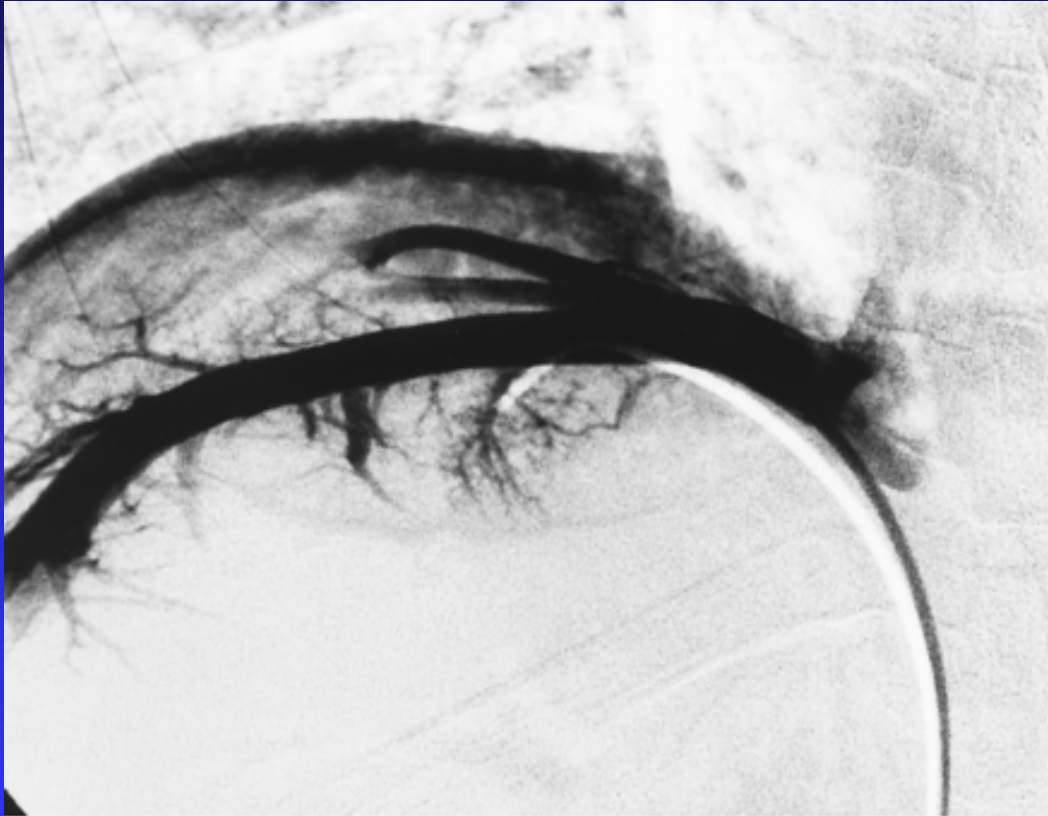
- Free hepatic vein pressure was 30-27 mmHg (mean 28 mm Hg)
- Another free hepatic vein pressure 23 mmHg
- Wedge pressure 25 mmHg
- HVPG < 5 mm Hg (portal htn usually exists if the HVPG is greater than 5)

Left hepatic venogram



5.3.

Right hepatic venogram



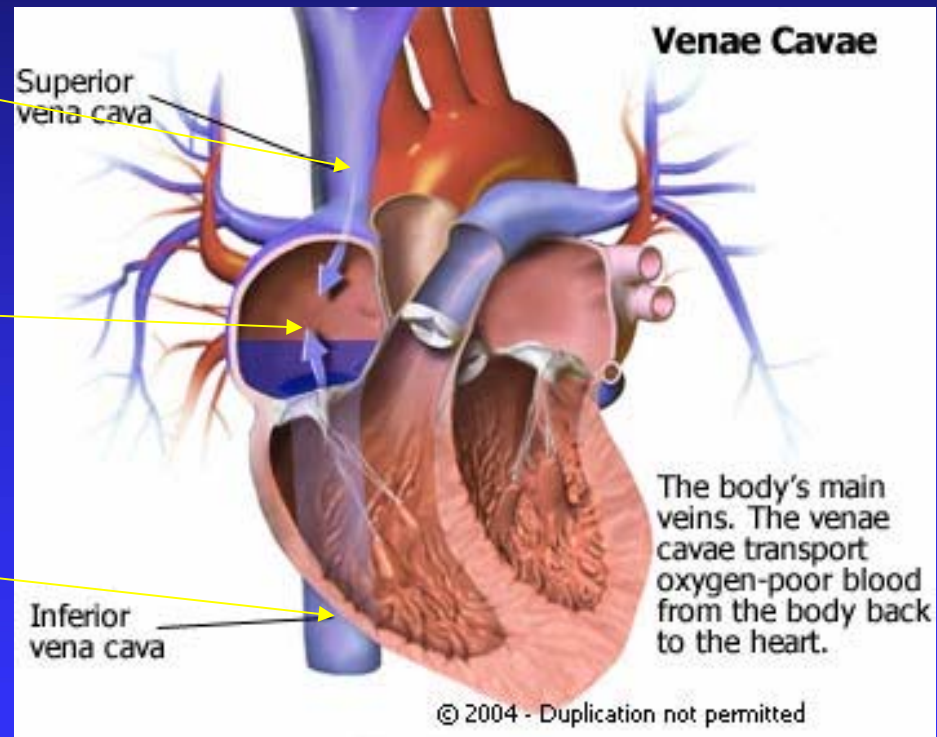
5.4.

Hepatic venogram

SVC = 25-28 mmHg

RA = 26-28 mmHg

IVC = 29-31 mm Hg



Hepatic venogram

- Impression: High pressure in the SVC, IVC, RA, and hepatic veins. Rec: cardiology consultation
- No evidence of hepatic vein thrombosis, but does not exclude the fact that some other hepatic veins may be obstructed

What does this mean? He still has ascites.

- Presinusoidal portal hypertension
- Caused by increased resistance to portal venous flow **before** the blood reaches the hepatic sinusoids
- Therefore, measurements of sinusoidal pressure by way of wedged hepatic venous catheter will be normal despite the presence of significant portal hypertension

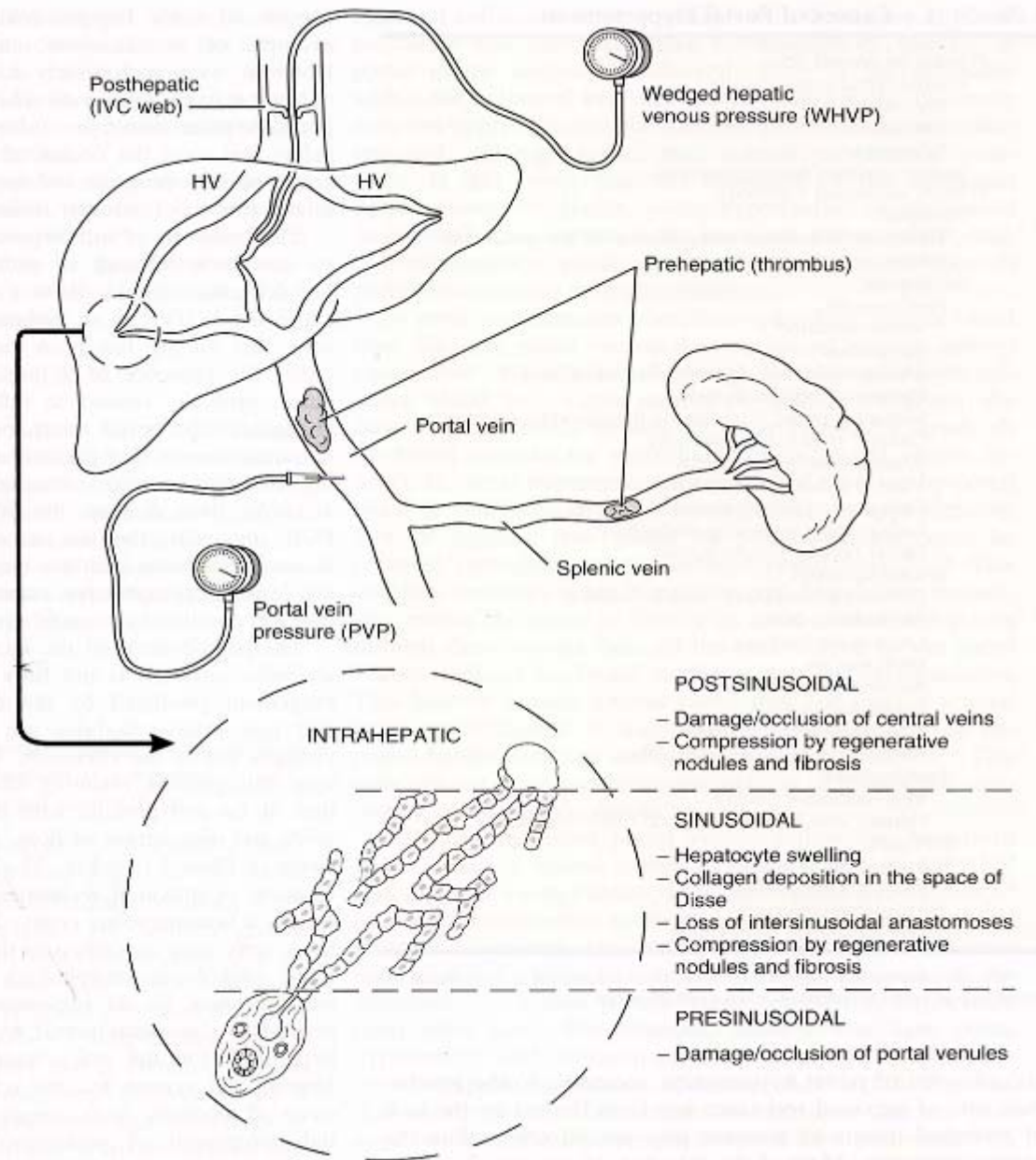
Liver vasculature

■ Efferent

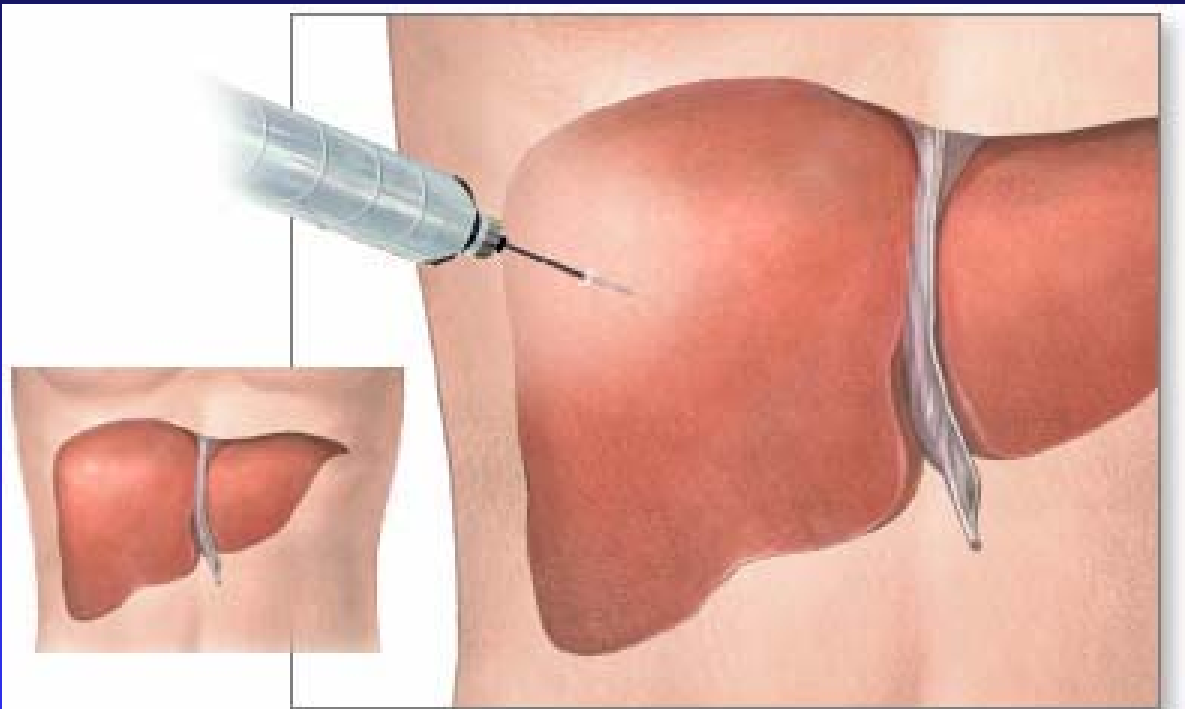
- ◆ Sinusoids to central vein to hepatic vein to IVC

■ Afferent

- ◆ (1/3) Hepatic artery branch to arteriosinusoidal branches to sinusoids
- ◆ (2/3) Hepatic portal vein to inlet venules to sinusoids

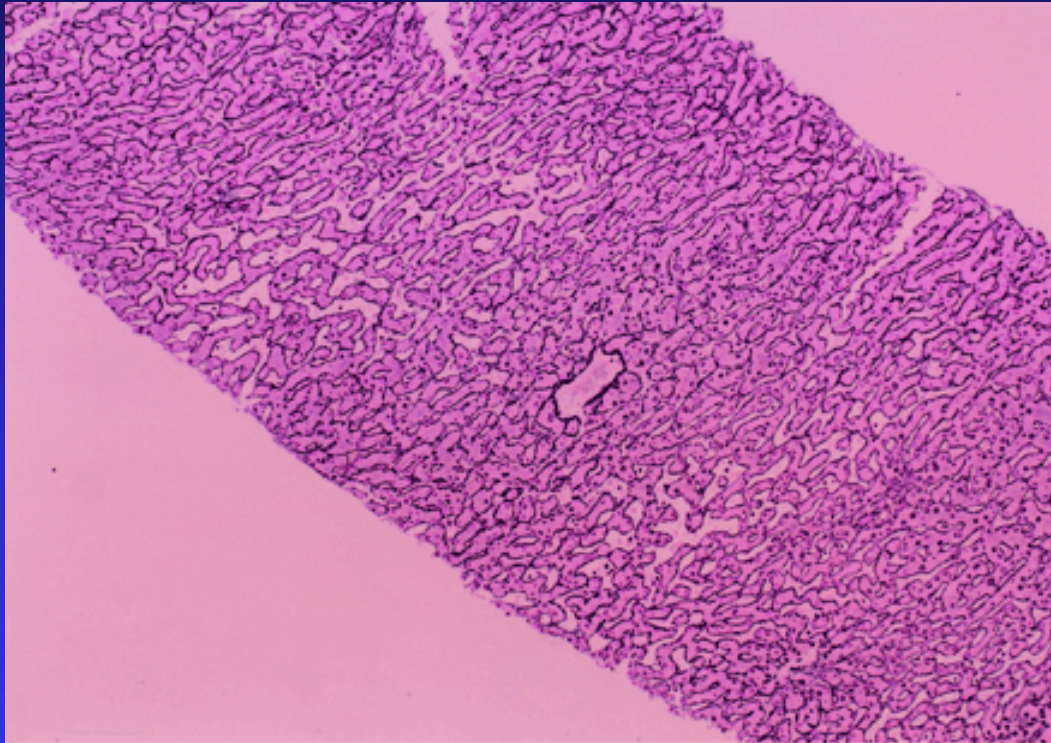


What caused this? Pop the liver



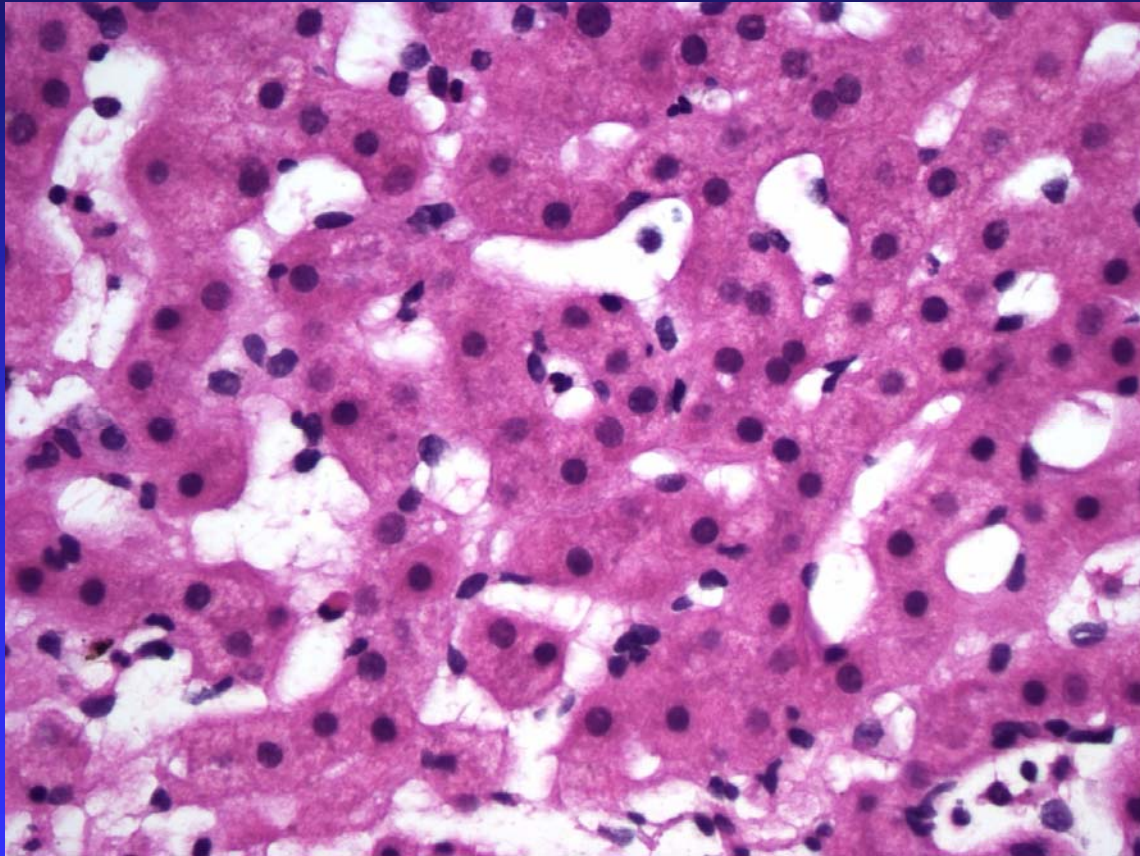
Biopsy needle is inserted and a sample of the liver is removed

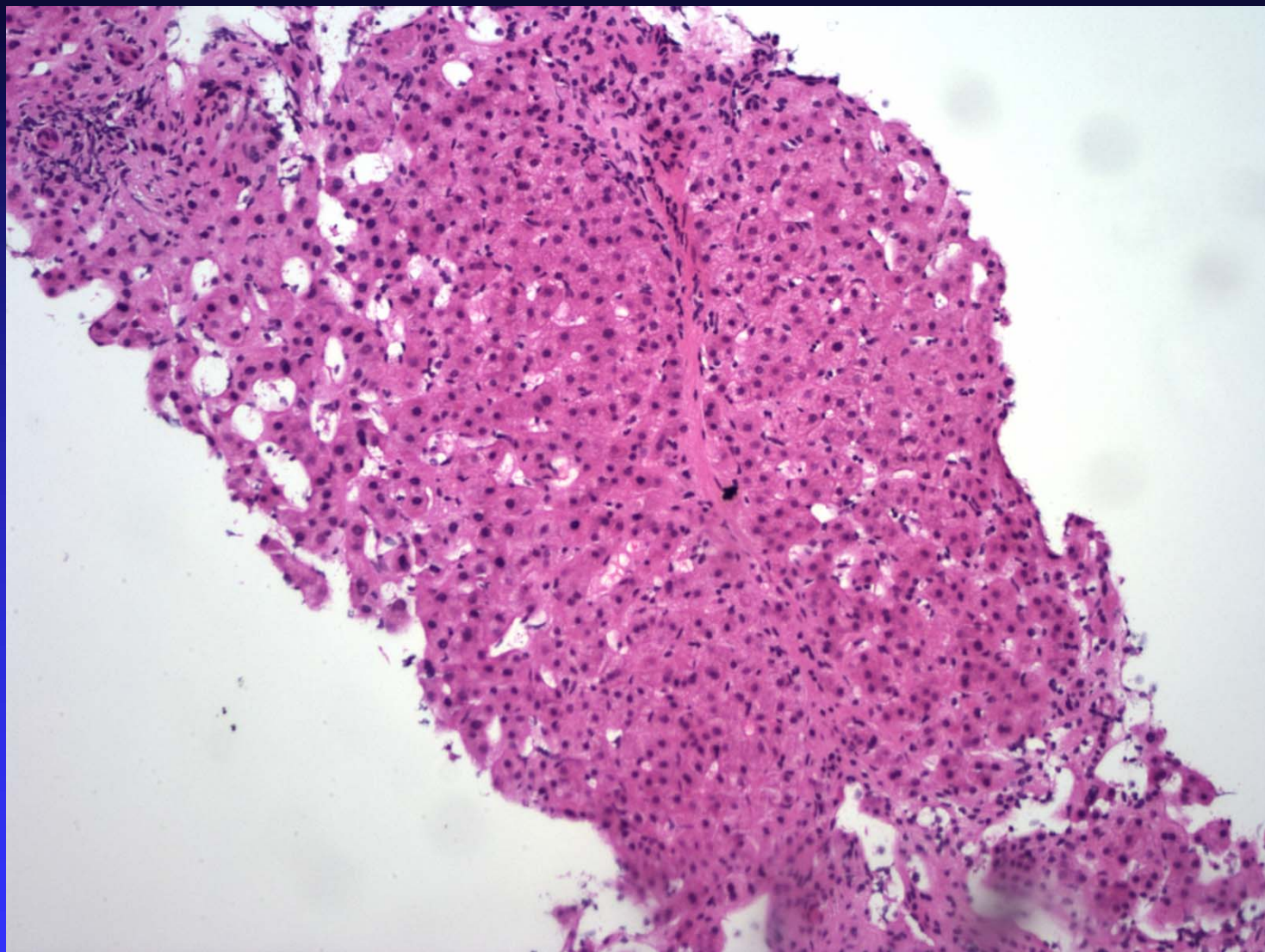
What did the pathologist see?



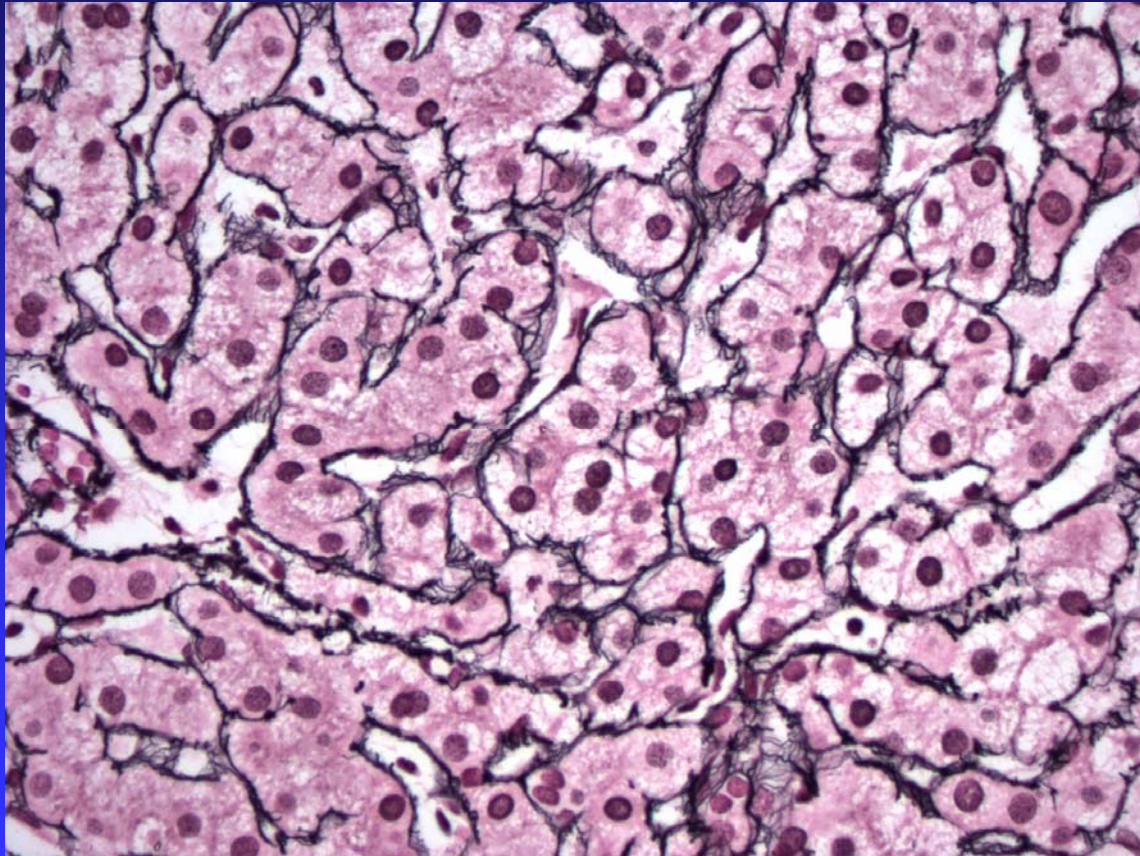
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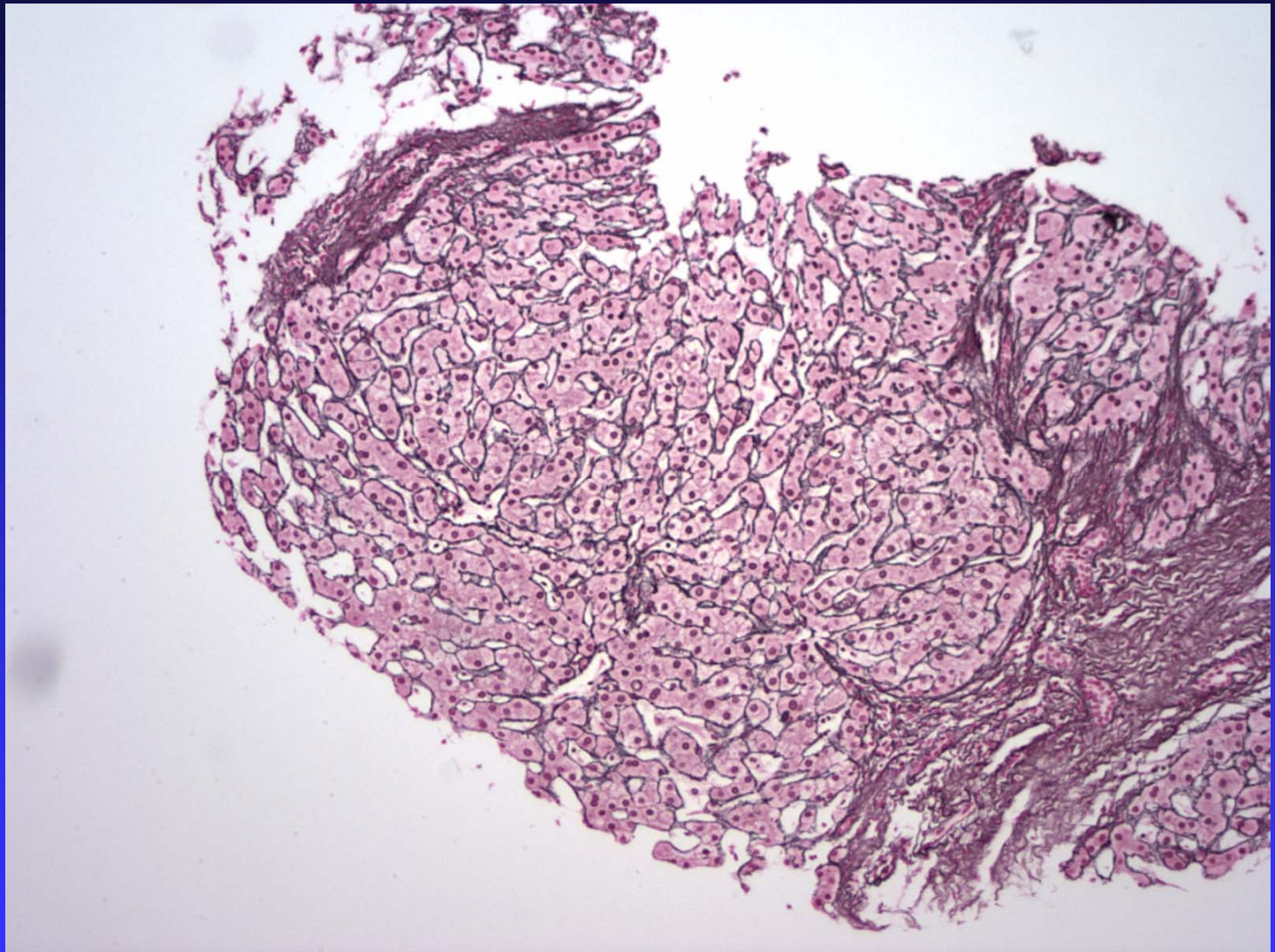
Dilated sinusoids

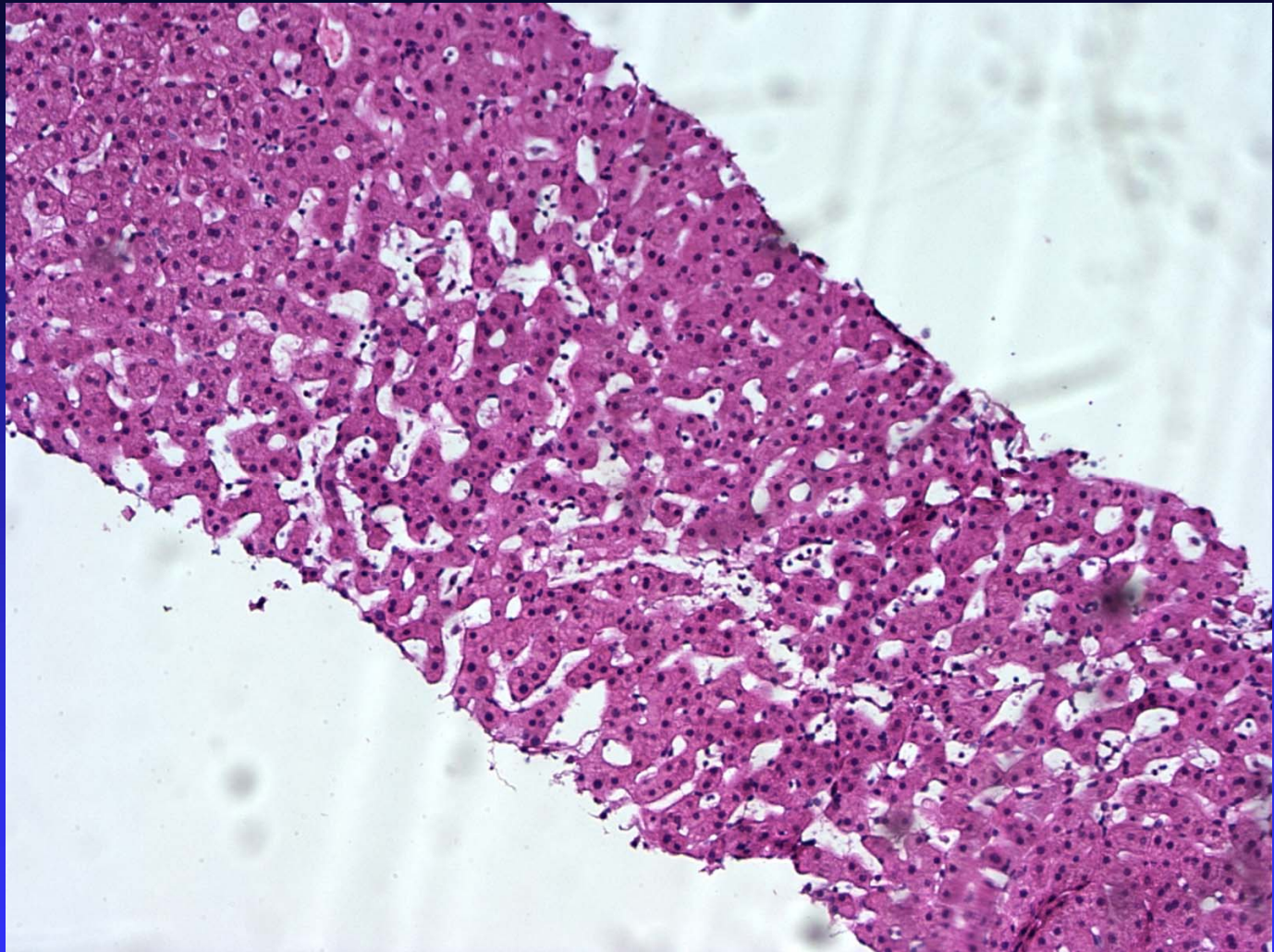


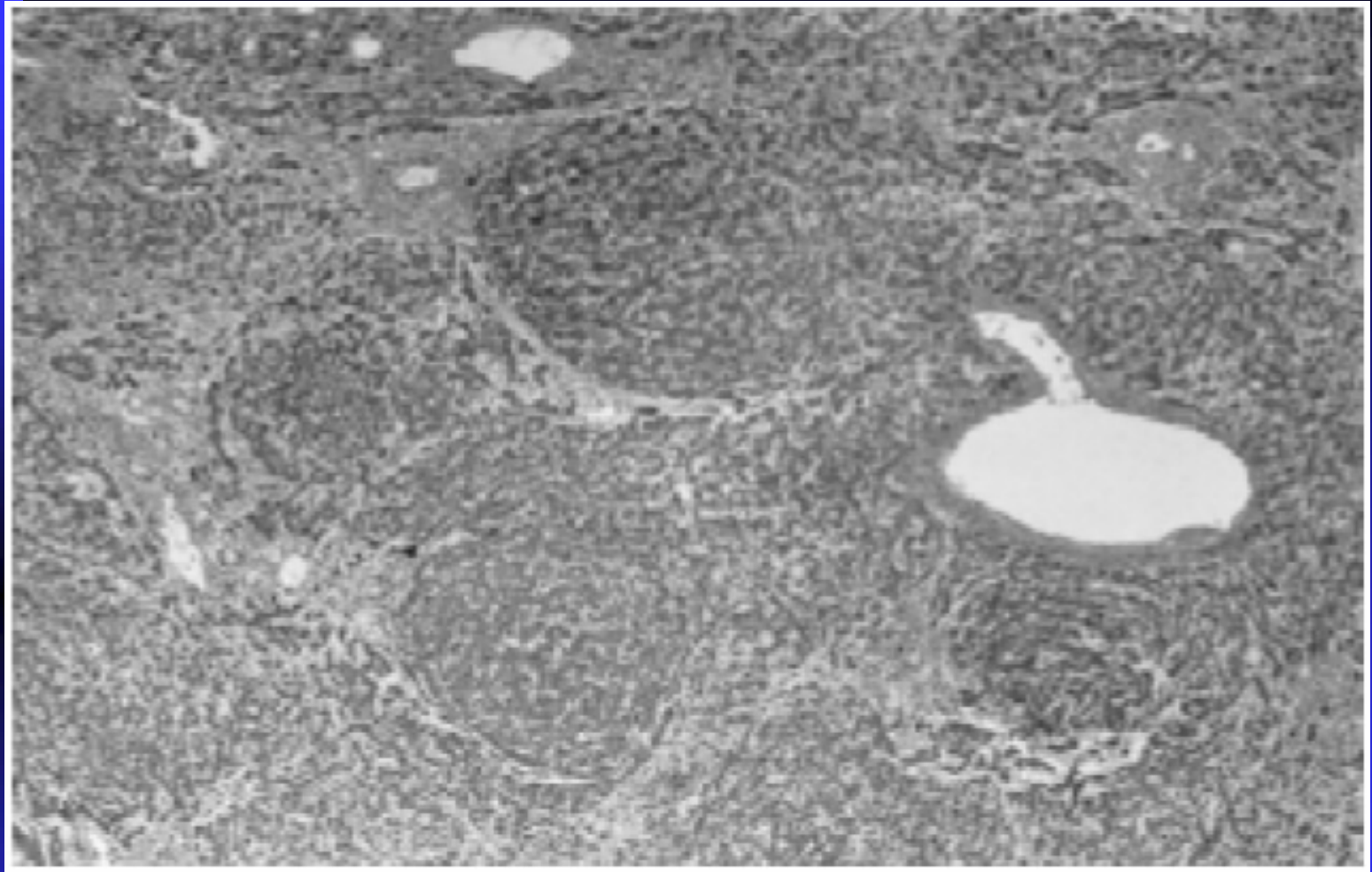


High powered reticulin stain



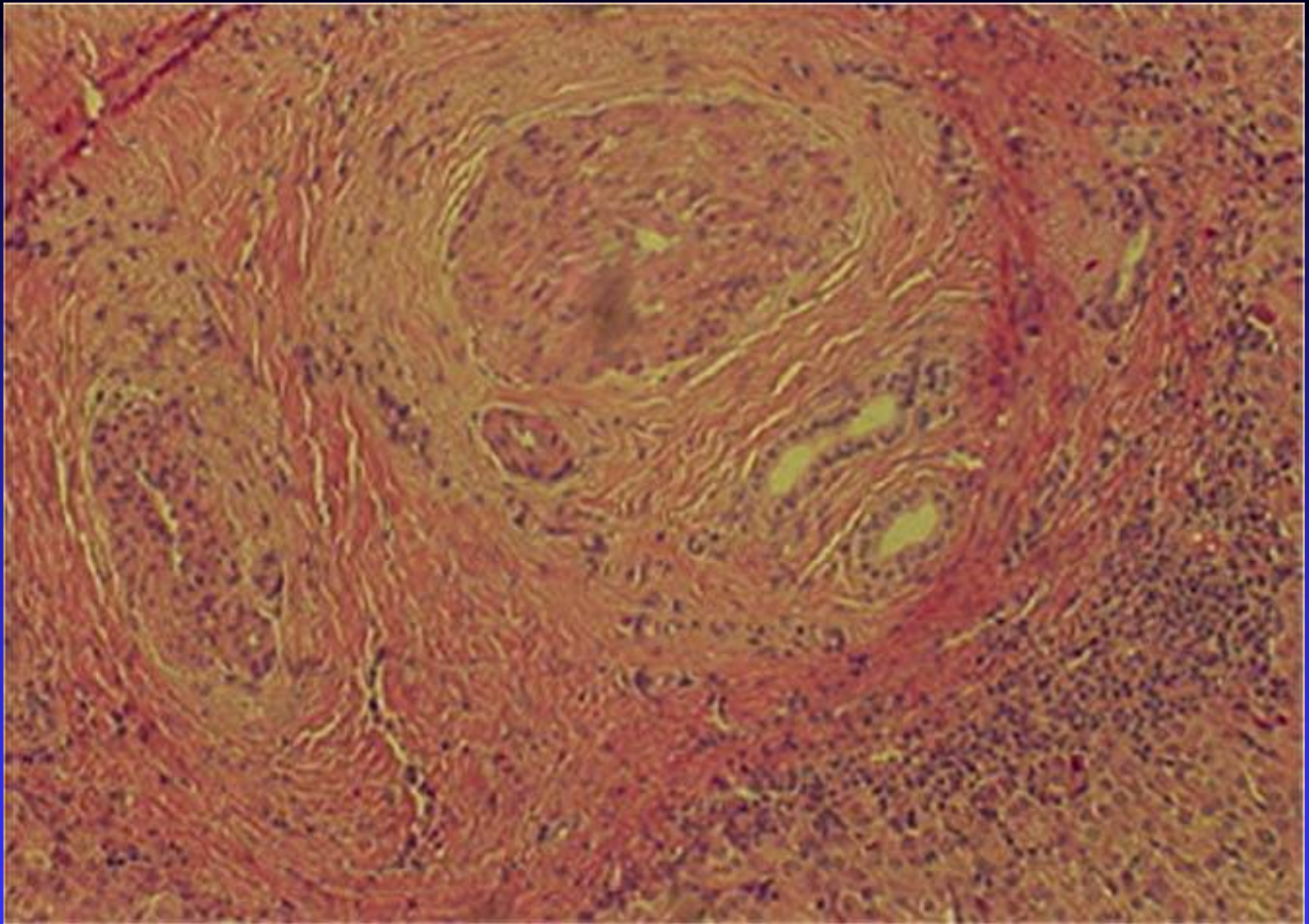






Nodules of hyperplastic hepatocytes surrounded by atrophied
Parenchyma without fibrosis and with pericentral and periportal areas
Of ischemia changes (hematoxylin and eosin staining)

Riestra et al J Clin Gastro 2001;33 (4):323



Hyperplastic nodular formation displacing the normal liver parenchyma

Kiyuna, et al Dig Dis and Sci 50 (2):314

Case study: Liver biopsy report

- **Nodular Regenerative Hyperplasia**
- Moderate dilation of hepatic sinusoids without evidence of centrilobular necrosis
- Trichrome stain confirms the presence of stage III fibrosis with focal pericellular fibrosis
- No steatosis, no significant portal or lobular inflammation, no increase iron or copper binding protein, No PAS positive hepatic inclusions or cholestasis, No granulomatous inflammation

Nodular Regenerative Hyperplasia

What is it?

Nodular diseases of the liver

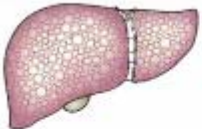
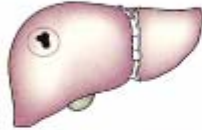
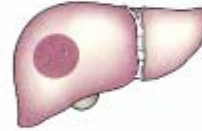
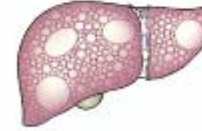

Lesion	Size	Single/ Multiple	Common underlying causes	Comment
Nodular regenerative hyperplasia 	Usually < 1 cm	Multiple	Immunologic disorders (eg, rheumatoid arthritis) Myeloproliferative disorders	Pathogenesis related to portal venopathy and decreased blood flow; usually presents with portal hypertension
Focal nodular hyperplasia 	Usually < 5 cm	Single	None recognized	Often an incidental finding
Hepatocellular adenoma 	May be very large	Usually single; occasionally multiple	Estrogen use	Requires resection because of risk of rupture or hemorrhage
Hepatocellular carcinoma 	May be very large	Often multiple	Cirrhosis Chronic viral hepatitis	Probably arises from within dysplastic nodules
Partial nodular transformation 	1-5 cm	Multiple but localized to perihilar area	None recognized	Rare entity; presents with portal hypertension

FIGURE 13-7.

Nodular diseases of the liver.

Nodular regenerative hyperplasia: other names for it

- Nodular transforatmion
- Non-cirrhotic nodulation
- Hepatocellular adenomatosis
- Adenomatous hyperplasia

Nodular regenerative hyperplasia (NRH): Definition

- Hepatocellular nodules distributed throughout the liver in the absence of fibrous septa between the nodules

Description of liver with NRH

- Diffuse fine nodularity (nodules 0.5-3mm)
- Microscope: normal architecture replaces with monoacinar regenerative nodules that contain portal tracts
- Usually not associated by fibrosis
- Nodules surrounded by compressed liver cell plates (reticulin)
- Dilated sinusoid

NRH: Epidemiology

- RARE
- 27% of cases in Europe among a series (Naber et al 1990)
- 14% in Japan (Nakanuma et al 1996)
- In 1989, Colina et al reported 24 cases over 9 years (prevalence 31/100,000 and incidence 0.34/100,000)

NRH: Pathogenesis

- Unknown but related to disturbance in liver blood flow
- Insufficient blood supply to portions of the liver leads to atrophy of the parenchyma with compensatory hyperplasia occurring in areas with adequate blood supply

NRH pathogenesis

- Another potential etiology is a direct immunological attack on sinusoidal endothelial cells
- Ziolkowski et al observed CD 8+ cytotoxic T cells in 14/44 patients with NRH
- Kiyuna et al suggest that IL-6 mediated intrahepatic vascular effect
- Site of elevated resistance NOT clear some say sinusoidal (Sleisenger & Fordtrans) but may also be mixed (presinusoidal); one small series found it to be post sinusoidal?

NRH Pathogenesis

- Austin et al described NRH in patients with celiac and IgA anticardiolipin antibody
- Hypothesis was that the apoptotic enterocytes during active celiac disease also lead to generation of anticariolin antibody
- This antibody would then lead to abnormal thrombosis, abnormal flow, and NRH
- Of note: 9% of patients with cryptogenic elevated transaminases have celiac disease (?connection)

NRH: Associated conditions

- Up to 50% of patients have a prothrombotic disorder
- Vascular disease
 - ◆ Budd-Chiari syndrome
 - ◆ Portal venous thrombosis

NRH: Associated conditions

■ Drugs and toxins

- ◆ Azathioprine (?incidence, no relation to dose or duration, but if later onset or delayed dx poorer prognosis)
- ◆ Thorotrast
- ◆ Toxic oil syndrome
- ◆ Thioguanine

NRH: Associated conditions

- Collagen vascular disease
 - ◆ SLE
 - ◆ Mixed connective tissue disease
 - ◆ Rheumatoid arthritis
 - ◆ Felty syndrome (RA, splenomegaly, low WBC)
 - ◆ Polymyalgia rheumatica

NRH: Associated conditions

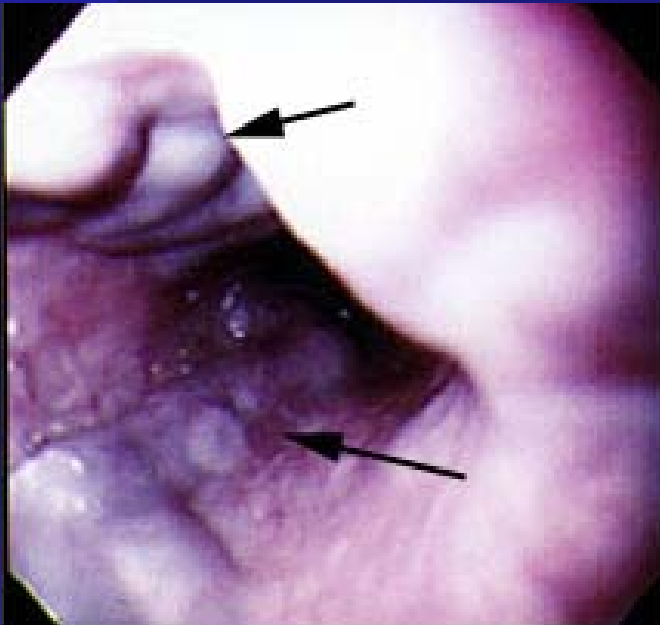
- Other liver disease: PBC, post transplant, Mets from pancreatic dz; HCC
- Neoplastic conditions: Castleman's disease (angiofollicular lymph node hyperplasia)
- Celiac disease
- Immunodeficiency syndromes: HIV, Common variable immunodeficiency

NRH: Associated conditions

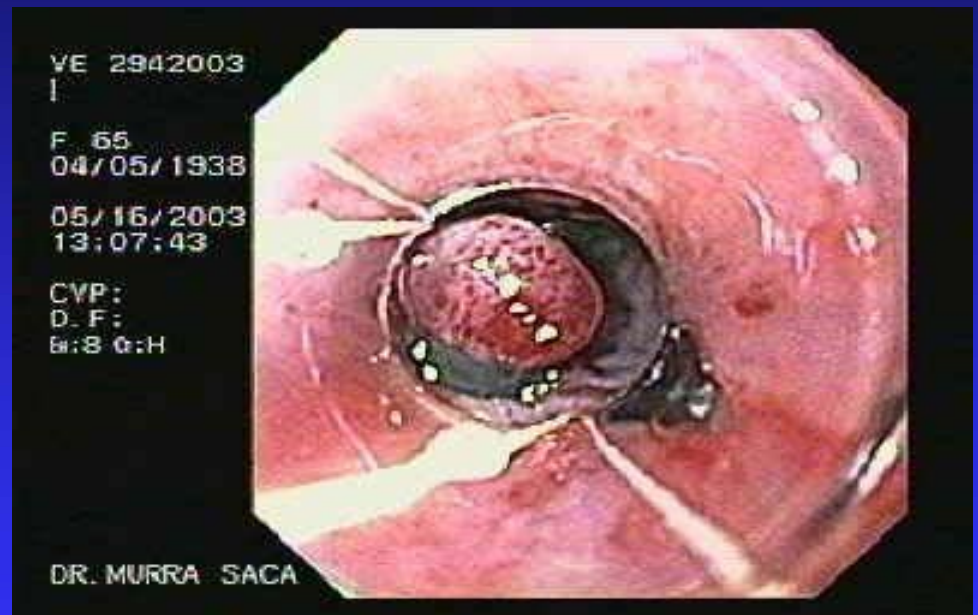
■ Misc

- ◆ Primary pulmonary hypertension
- ◆ Glomerulonephritis
- ◆ Behcet's
- ◆ Schnitzler syndrome (chronic uricaria with IgM gammopathy)
- ◆ Diabetes
- ◆ Heart failure

Clinical presentation



Esophageal Varices



NRH: Clinical presentation

- Variable
- Main clinical problem is portal hypertension (about 50% of patients will develop)
- Ascites uncommon
- Aminotransferase levels normal
- Alkaline phosphatase moderately elevated
- Familial form (based on case study) without associated disease demonstrated poor clinical course and progressive renal failure (Gut 1999;45:289)

NRH: clinical presentation

- Non-specific pathologic manifestation of several disorders
- Most frequent presentation is with variceal bleeding and/or symptoms of hypersplenism
- Prognosis is felt to be good overall, but some reports hepatic decompensation requiring OLT

Diagnosis

- For the most part histological (but adequate sample needed)
- Based on case reports MRI better

Management

- Remove causative agent if possible
- Control portal hypertension
- TIPS rarely indicated
- Splenectomy should be avoided because of high incidence of ensuing portal vein thrombosis
- ?Life long anticoagulation may be indicated

Results of Liver transplantation



Liver transplant: a retrospective review of four cases

- All did well; no acute rejection (4 years post)
- NRH difficult to diagnose with needle biopsy
- May be an option in patients presenting with complications of liver failure

Radomski, et al The Amer Surg 2000; 66: 1067

Ehlers-Danlos Syndrome (EDS)

Cases involving the GI tract

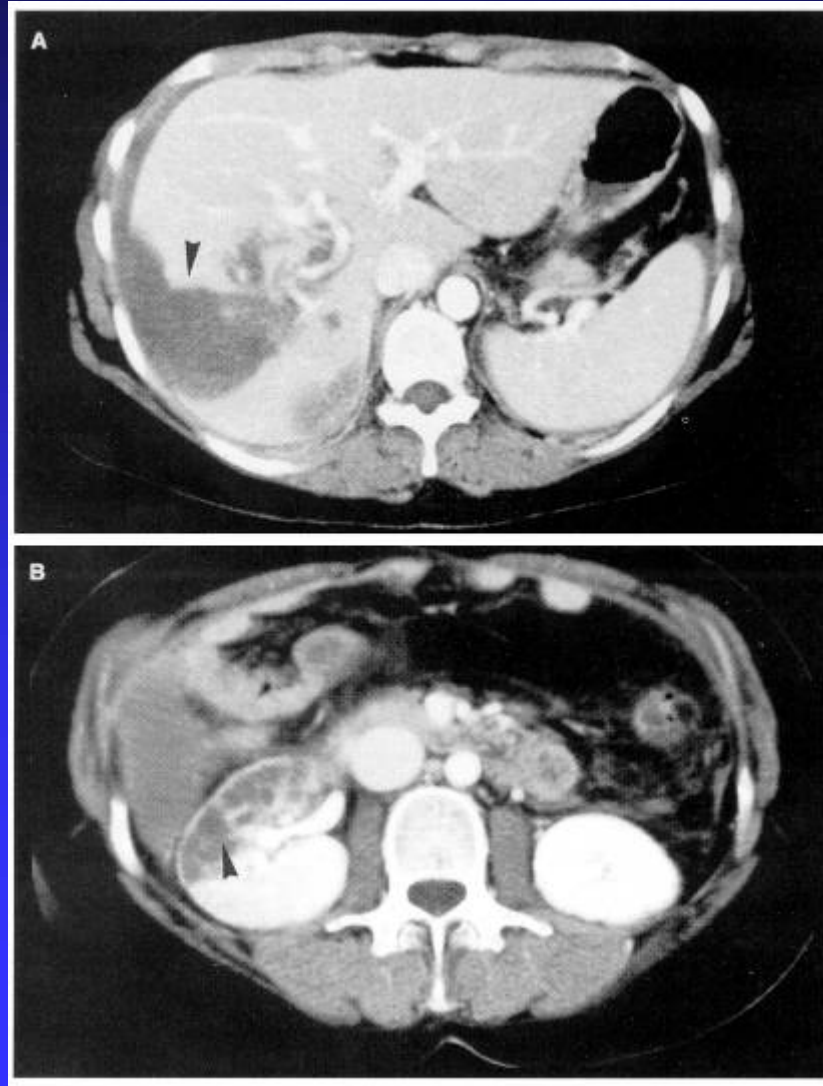
Ehlers-Danlos

- Rare heterogeneous group of inheritable connective tissue disorder resulting in skin fragility, joint laxity, and ligamentous fragility or shortening, some have easy bruising
- Several types
- Type IV (defect or reduction in collagen III) the vascular type causes most GI troubles

Ehlers-Danlos type IV

- Mutation in type III collagen (COL3A1) gene
- No or only mild hyperextensibility and joint laxity limited to hands
- High risk for rupture of large intestine, gravid uterus, medium sized arteries
- May mimic mesenteric vasculitis (case study Bloch et al. JVIR 2001;12: 527)
- Death usually from vascular complications

Ehlers Danlos patient with abdominal pain had CT



Ehlers Danlos Case in 1997

- 33 yo with abdominal pain with spontaneous rupture of the liver and right renal infarction
- Not a common feature of EDS
- Pt's past history: easy bruising; hx of uterine rupture; hx of prominent varices in legs, difficult healing from left hemicolectomy (ischemia from uterine rupture)

Gerlbmann, et al Diges Dis & Sci 1997; 42(8): 1724

Ehlers Danlos: Another ruptured liver

- 54 yo ESLD from HCV transplanted
- The donor was a 38 yo brain death secondary to subarachnoid hemorrhage
- After completing the caval and portal anastomoses, the liver was revascularized. Within seconds the liver developed multiple large subcapsular hematomas that spontaneously ruptured with extrusion of the liver parenchyma
- Patient then had this liver removed, was placed in ICU with continuous venovenous hemofiltration, placed on venous bypass, and successfully transplanted 40 hours later

Why did the donor liver explode?

- Donor liver biopsy did not reveal abnormalities
- Initial suprahepatic caval anastomosis was satisfactory
- At the time of revascularization the pulmonary arterial pressures were not high

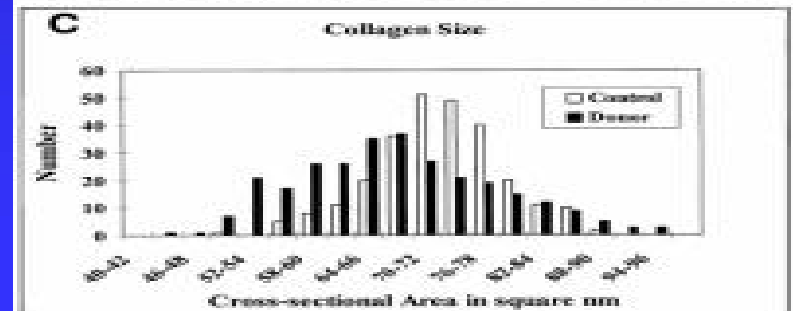
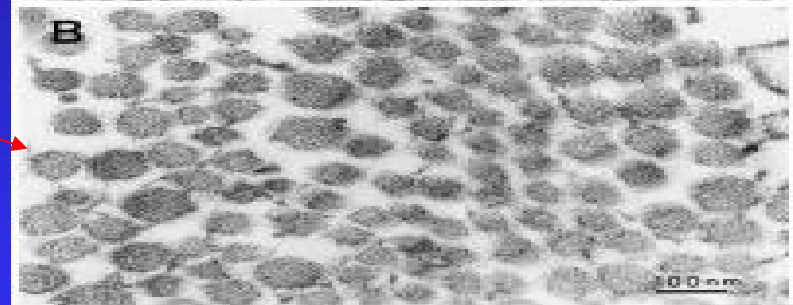
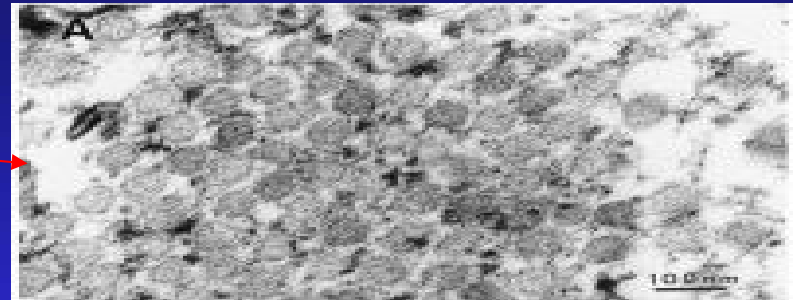
Why did the donor liver explode?

- Clues: The procurement agency made an attempt to obtain the donor heart valves but they were too fragile and discarded
- Donor's cousin had an aneurysm and before the donor's death she had undergone evaluation for a connective tissue disease but this was inconclusive

Why did the donor liver explode?

Normal collagen in arterial wall

Donor liver

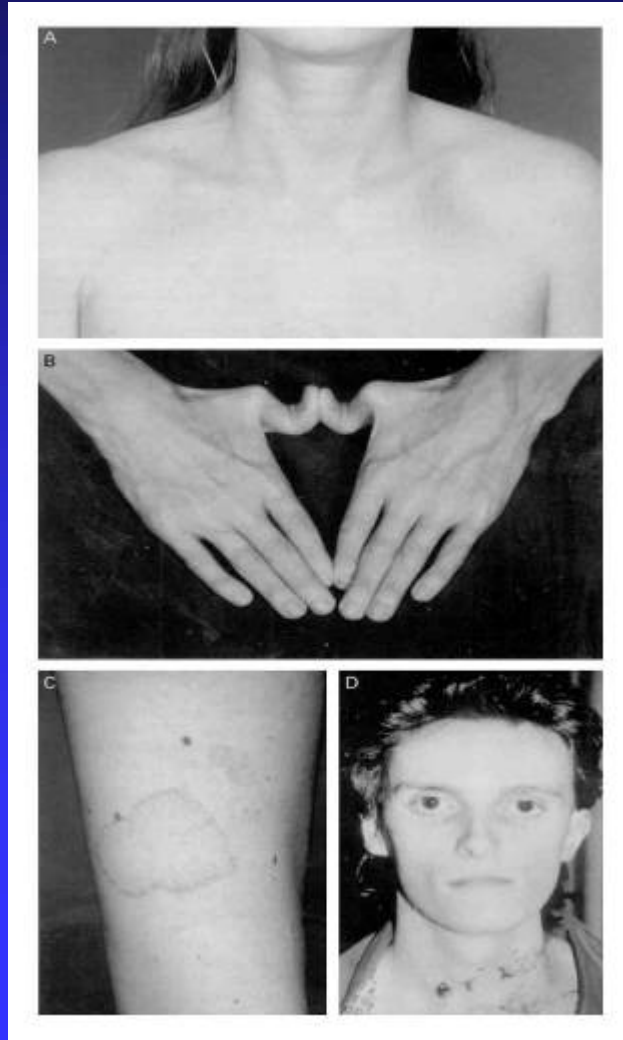


Mistry, B et al Transplantation 2000;69 (10):2214

Electron micrographs revealed

- Donor liver revealed collagen fibers of irregular diameter and packing
- Donor liver arteries thinner (68 vs 72 μm $p < 0.001$)
- The variability in the collagen in the liver arteries are consistent with the abnormalities found in Ehlers-Danlos type IV
- Bottom line: The associated friability of tissues, especially the vessels making repair or anastomosis difficult contributed to this case

Caution when using livers from donors with Connective tissue disease



Intestinal Perforation

- Described in case study with Type IV EDS
- Chronic constipation along with sudden increase in colonic volume after enema with an inherently weak bowel wall in undiagnosed EDS were likely to have been factors leading to the perforation
- Enema therapy should be avoided in patients with EDS

Case study: Ongoing evaluation

- EGD is pending to evaluate for any varices
- Cardiology consult noting the increased pressures on hepatic venogram
- Will need to evaluate for celiac disease
- Will probably need treatment for mild hyperhomocytinemia (has 3.4 fold increase in MI in the US Physician's Study)
- Start diuretics and low sodium diet
- Follow up with urology

Case study: Questions

- Can the patient's Ehlers-Danlos contribute to abnormal hepatic arteries leading to ischemia prompting a mechanism for nodular regenerative hyperplasia (NRH)?

Ohbu et al described aberrant vessels in cases of noncirrhotic portal hypertension 83% of cases of nodular hyperplasia

Hepatology 1994; 20(2): 302-308

Case study: Questions

- Does the patient have a mild hypercoagulable state (increased homocysteine) with abnormal arteries that contribute to ischemia leading to NRH?
- Does the patient have another underlying pulmonary disease superimposed (noted pleural effusion) from a hypercoagulable state (ie chronic pulmonary emboli) leading to right heart failure?

Case study: tests to consider

- CT of the chest
- Pulmonary function tests
- Right heart cath
- Confirm diagnosis of Ehlers Danlos with RNA analysis, skin biopsies, and try to culture the fibroblast

Conclusions

- Nodular regenerative hyperplasia is hepatocellular nodules distributed throughout the liver without fibrous septa between them
- Associated with many diseases
- Variable clinical features, but may present with GI bleed
- Overall prognosis is good

A real mystery: Norton

