Liver Specialty Conference

Case #1
Monday, Mar 26, 2007, 7:30 pm

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Case 1: History

- 12 year old male
- Diabetes, Type 1, poorly controlled
- Presented with ketoacidosis
- PE: Hepatomegaly, RUQ pain
- Lab: Increased ALT/AST 2x normal, Glucose 635; HbA1c 13.5 (nl<6)
- Ultrasound suggested fatty liver

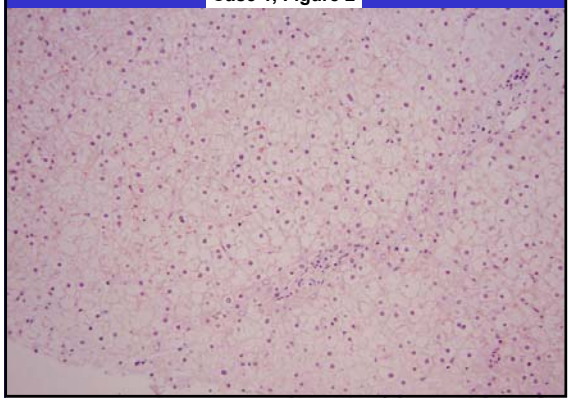
Case 1: History

- Liver biopsy performed
- Referred to UCSF to exclude glycogen storage disorder

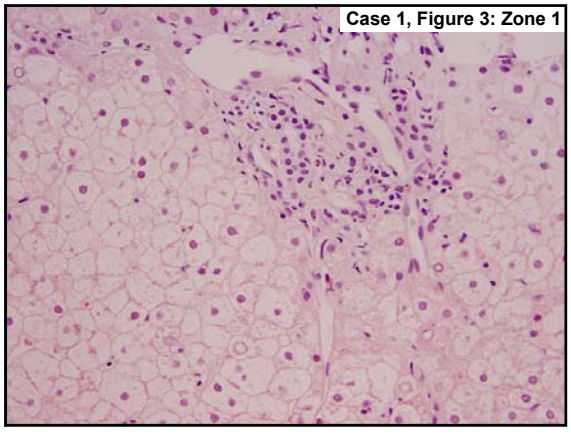
Case 1: History

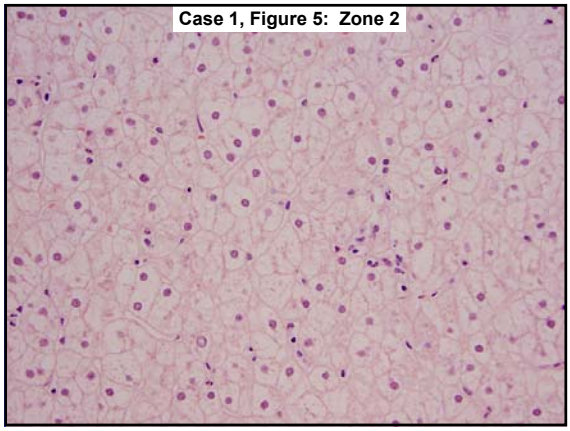
- Patient treated for ketoacidosis, hyperglycemia
- Transaminases returned to normal, and liver decreased in size
- No known long-term sequelae

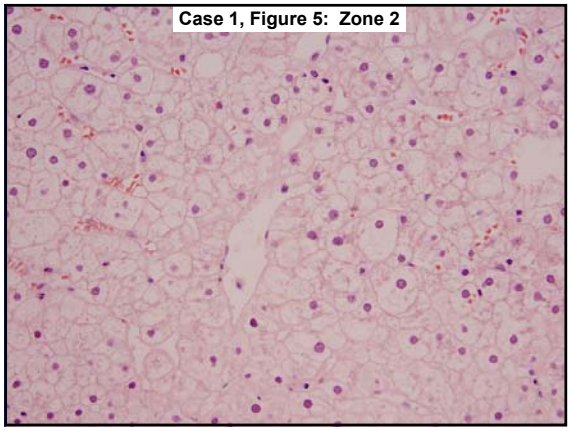
Case 1, Figure 2



Case 1, Figure 3: Zone 1







Glycogenic Hepatopathy

An under-recognized hepatic complication of Diabetes Mellitus

Torbenson, Chen, Brunt, Cummings, Gottfried, Jakate, Liu, Yeh, Ferrell. Amer J Surg Path 2006;30:508-13.

Glycogenic Hepatopathy

- 14 patients, ages 8-25
- History of type 1 poorly-controlled diabetes
- Elevated transaminases
- Hepatomegaly
- "Ballooned" hepatocytes mimicking those of NASH, PAS+, PASD-

Glycogenic Hepatopathy Background

First described: Mauriac's syndrome in 1930 (ref 13).

Glycogen loading, hepatomegaly, and abnormal liver enzymes associated with:

-growth retardation and/or dwarfism

-delayed puberty

-cushingoid features

-hypercholesterolemia

AKA….

- Hepatic glycogenosis[3]
- Liver glycogenosis[2]
- Liver glycogen storage[7,21]
- Diabetes mellitus-associated glycogen storage hepatomegaly[17]

– (References in syllabus)

Glycogenic Hepatopathy Overview

- Adults/children, usually with Type I diabetes mellitus
- CHARACTERISTIC FEATURE: Marked or prolonged hyperglycemia with poor glycemic control
- Treated with insulin

Glycogenic Hepatopathy Overview

- Elevated liver transaminases of variable degrees (ranges normal to >1000).
- Hepatomegaly
- Coincidental fatty change or NASH uncommon (<20% in combined studies)

NOTE: No evidence for development of significant fibrosis or cirrhosis as in NASH.

Glycogenic Hepatopathy Histology

- Diffuse hepatocyte swelling
  - Rarefaction of cytoplasm
  - Pale cytoplasm due to increased glycogen
  - Prominent hepatocellular membranes
  - Sinusoids appear "compressed"
- Preserved liver architecture
- Giant mitochondria commonly seen

Glycogenic Hepatopathy Histology

What you DON'T see:

- Fibrosis
- Extensive steatosis
- Apoptosis, other forms necrosis
- Inflammatory infiltrates
- Mallory hyaline

Problems Clinical Diagnosis

- Difficulty in distinguishing from fatty liver by ultrasound
- Lesion is rare, so under-recognized by clinicians
- Patients commonly do NOT have Mauriac Syndrome

Glycogenic Hepatopathy

Clinical features

- Young patients with diabetes (type 1)
- Elevated transaminases
- Hepatomegaly

Liver Lesions in DM, Type 1

- Lorenz and Bärenwald (ref 12)
- 99 cases of hepatomegaly in diabetic children
  - Fatty liver with hepatomegaly in 8%
  - Mild fatty change in nearly half of the total number of cases
  - Most related to glycogen accumulation
    - moderate glycogen 22%
    - pronounced glycogen 19%

Other Fatty Liver Lesions

- Nonalcoholic fatty liver disease (NAFLD):
  - steatosis only
- Nonalchoholic steatohepatitis (NASH):
  - Steatosis
  - Inflammation
  - Ballooned hepatocytes

NASH: Major Associated Risks

- Metabolic Diseases
  - Obesity
  - **Diabetes type 2**
  - Hyperlipidemia

NASH: Histologic Findings

- **Fat** (large and small droplet type)
- **Ballooned hepatocytes**
- **Inflammation** (mononuclears predominate)
- **Centrizonal fibrosis** (pericellular, sinusoidal)

Other:

- Glycogenated nuclei, apoptosis, pigmented macrophages, Mallory hyaline, and giant mitochondria

Glycogenic Hepatopathy
Overlapping features with NASH:

Hepatocyte swelling/ballooning (diffuse in GH)

Giant mitochondria

Pediatric NASH

- Incidence increasing
- Similar risk factors as adults (including diabetes)
- Histology: FAT but may also show:
  - Periportal Fibrosis
  - **Lack of ballooned hepatocytes**

"Type 2 NASH"

Schwimmer, Behling, et al. Hepatol 2005;42:641-9

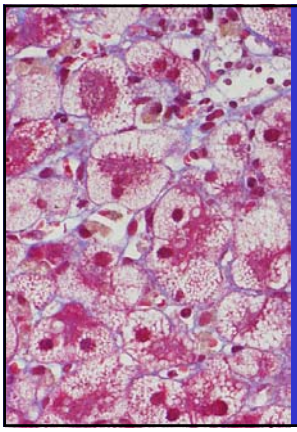
NASH: Rare variant 'Subacute' Fatty Liver Disease of Nonalcoholic type

Other Lesions in DM

- Drug effects
- Diabetic Hepatosclerosis

Diabetic Hepatosclerosis

- Longstanding diabetes with endstage multiorgan disease
- Perisinusoidal collagen in a non-zonal pattern
- Hyaline thickening of hepatic arterioles
- Elevated alkaline phosphatase
- (Steatosis rare, no ballooned hepatocytes)



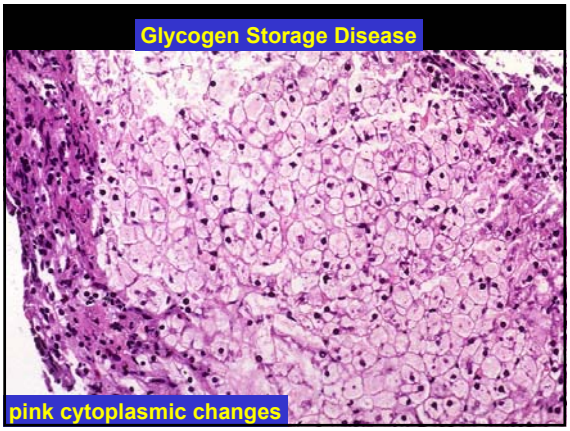
Other fatty lesions:
Microvesicular Fat

Fatty Liver of Pregnancy

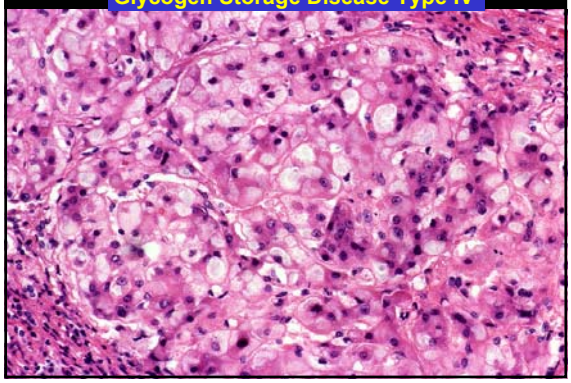
Other causes:
Tetracycline
Carbon tetrachloride
Alcohol

Glycogen Storage Disorders

- Overlap with GH
  - Diffuse hepatocyte swelling due to glycogen deposits
  - May see small droplet fat
- Clinical picture differs from GH
  - Poorly-controlled diabetes with response to diabetic control



Glycogen Storage Disease Type IV



Other Glycogen Lesions

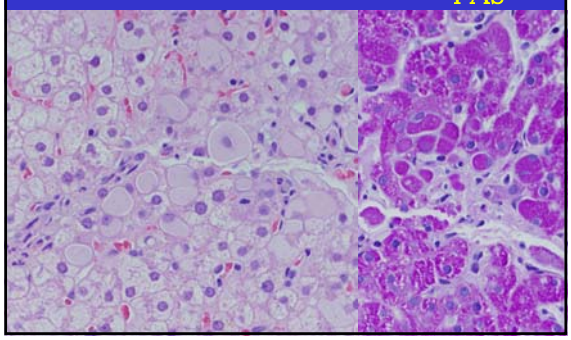
Glycogen "pseudo–ground glass" inclusions

- Tend to be periportal
- Setting: "Complex" patients typically on multiple drugs
- Possibly an abnormal form resulting from acquired defect in glycogen metabolism

Wisell J, Boitnott J, *et al*, AJSP Sep;30(9):1085-1090, 2006

Glycogen Loading: Inclusions

PAS



Wilson Disease

- Overlap in this age group
- Histology doesn't overlap

Glycogen Hepatopathy Conclusions

- Clinical setting important
  - Diabetes type 1, poorly controlled
- Histology unique
  - Diffuse hepatocyte glycogen deposits
- No known progression

Take Home Points

- Not all liver lesions in diabetic patients are due to fat
- Prognosis and therapy varies with type of lesion
- Radiographic imaging cannot reliably distinguish lesions in diabetic patients
- Liver biopsy plays an important role in establishing the correct diagnosis