

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

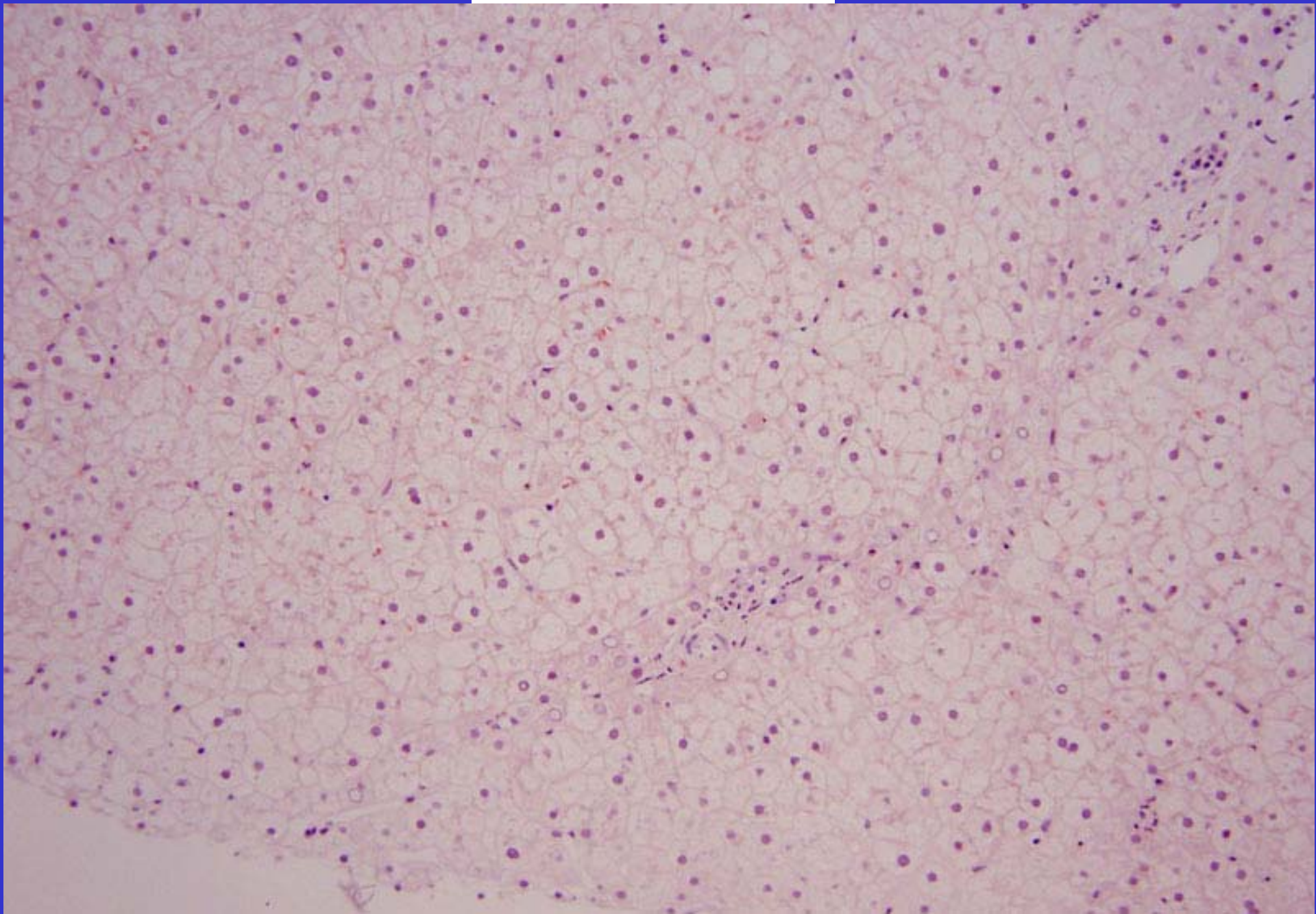
Case 1: History

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

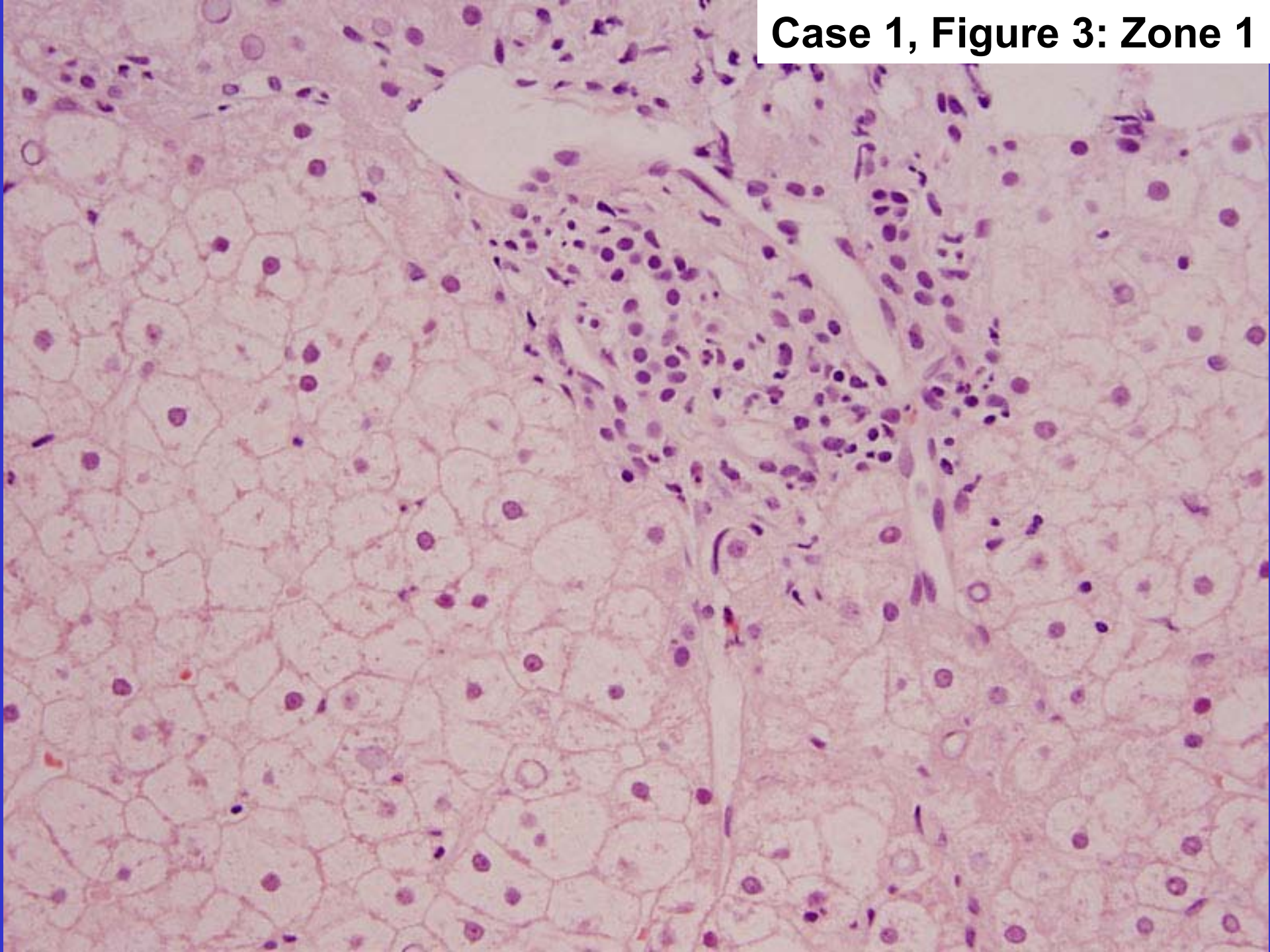
Case 1: History

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

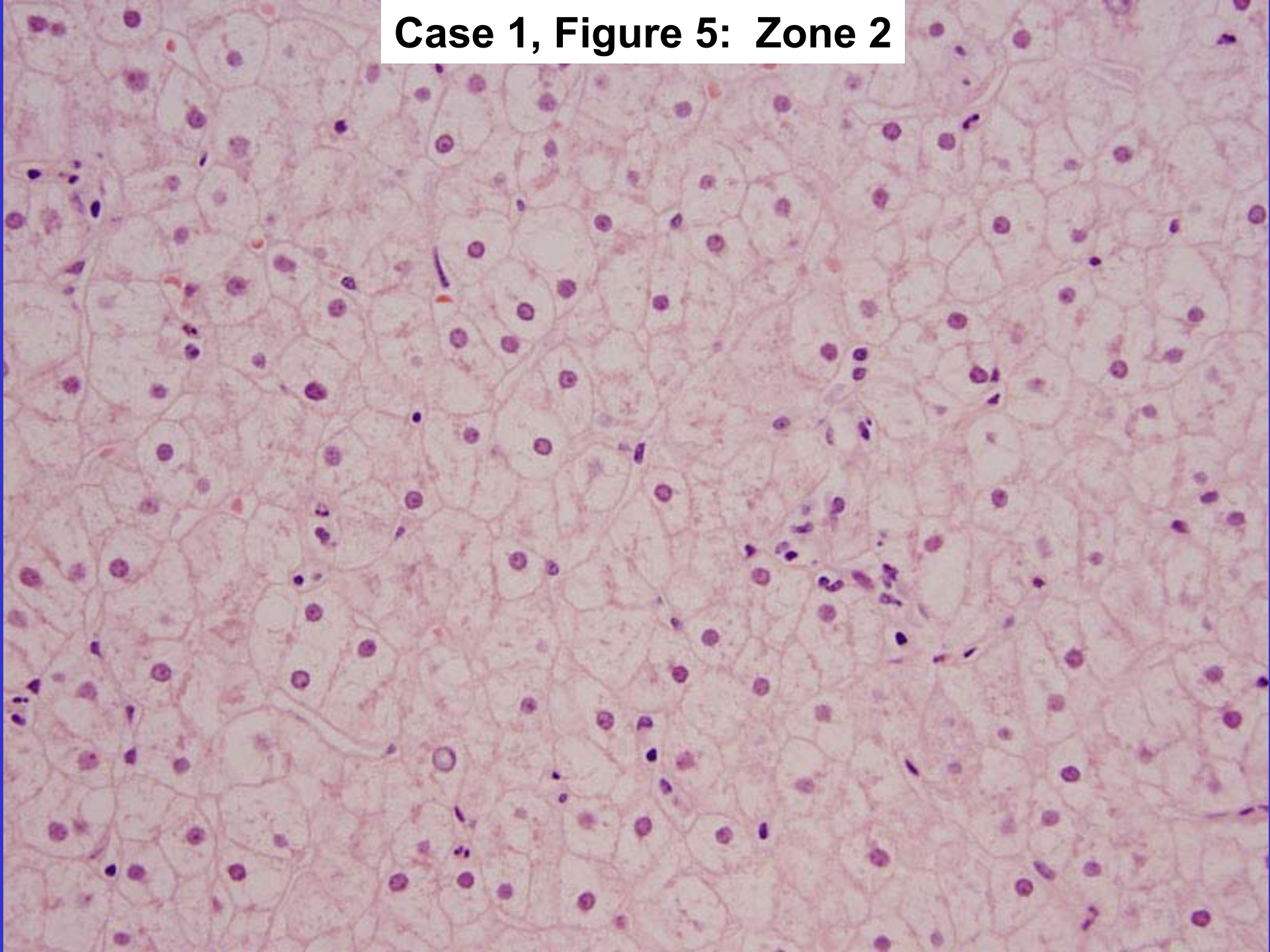
Case 1, Figure 2



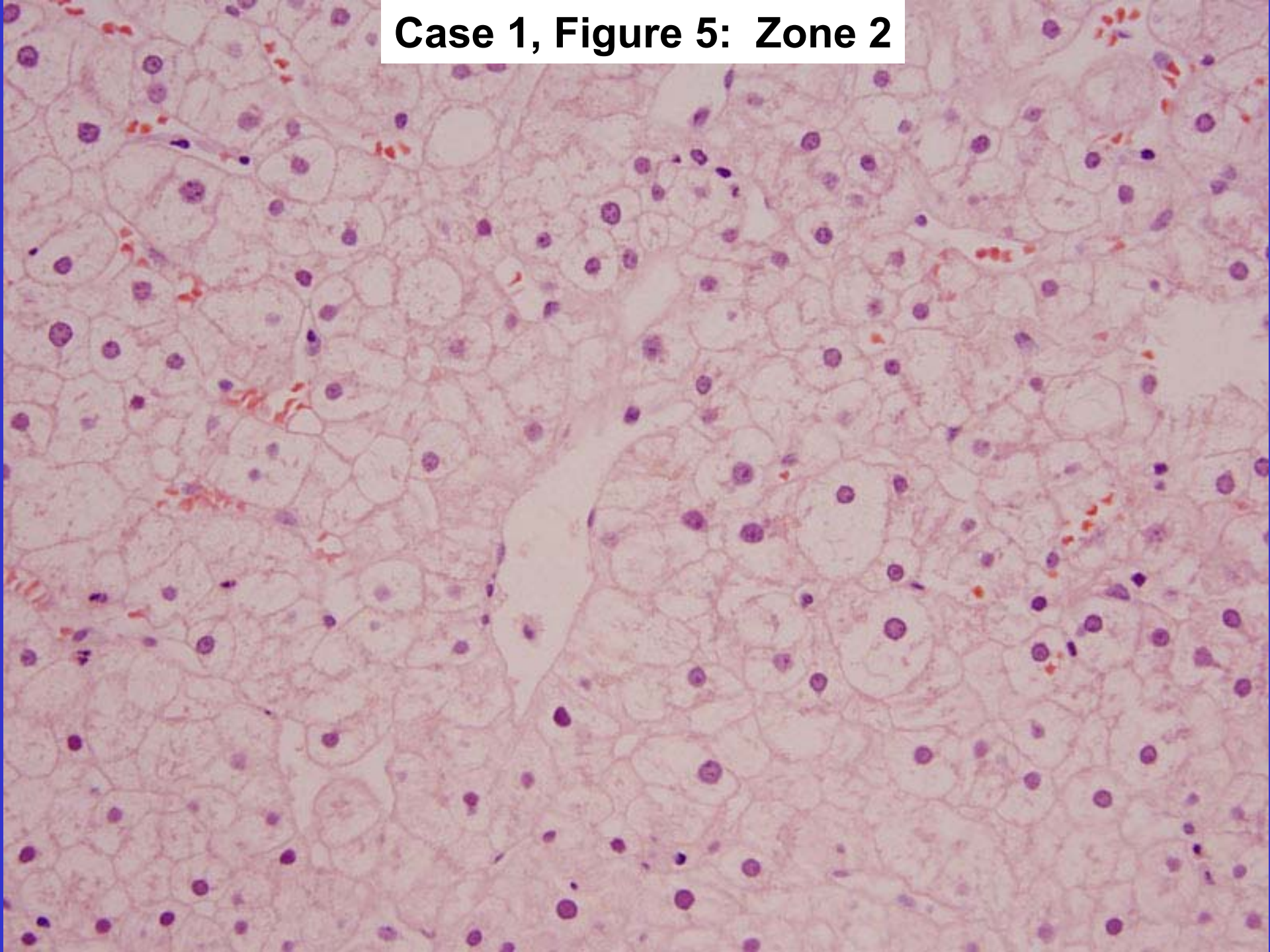
Case 1, Figure 3: Zone 1



Case 1, Figure 5: Zone 2



Case 1, Figure 5: Zone 2



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 glycogenosis³**
- **Liver glycogenosis²**
- **Liver glycogen storage^{7,21}**
- **Diabetes mellitus-associated glycogen storage hepatomegaly¹⁷**

– (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
- **Nonalcoholic 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

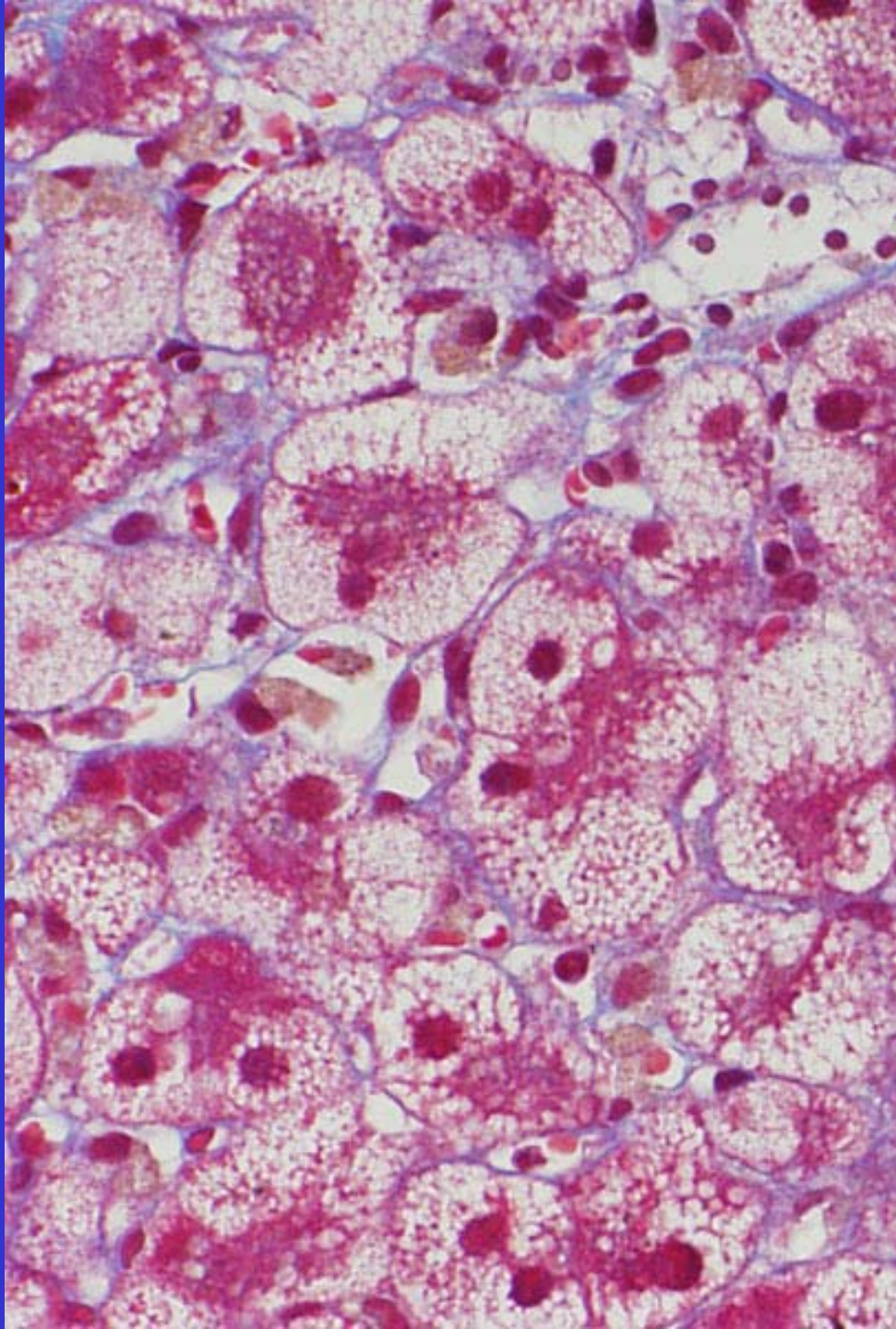
**NASH: Rare variant
'Subacute' Fatty Liver Disease
of Nonalcoholic type**

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**

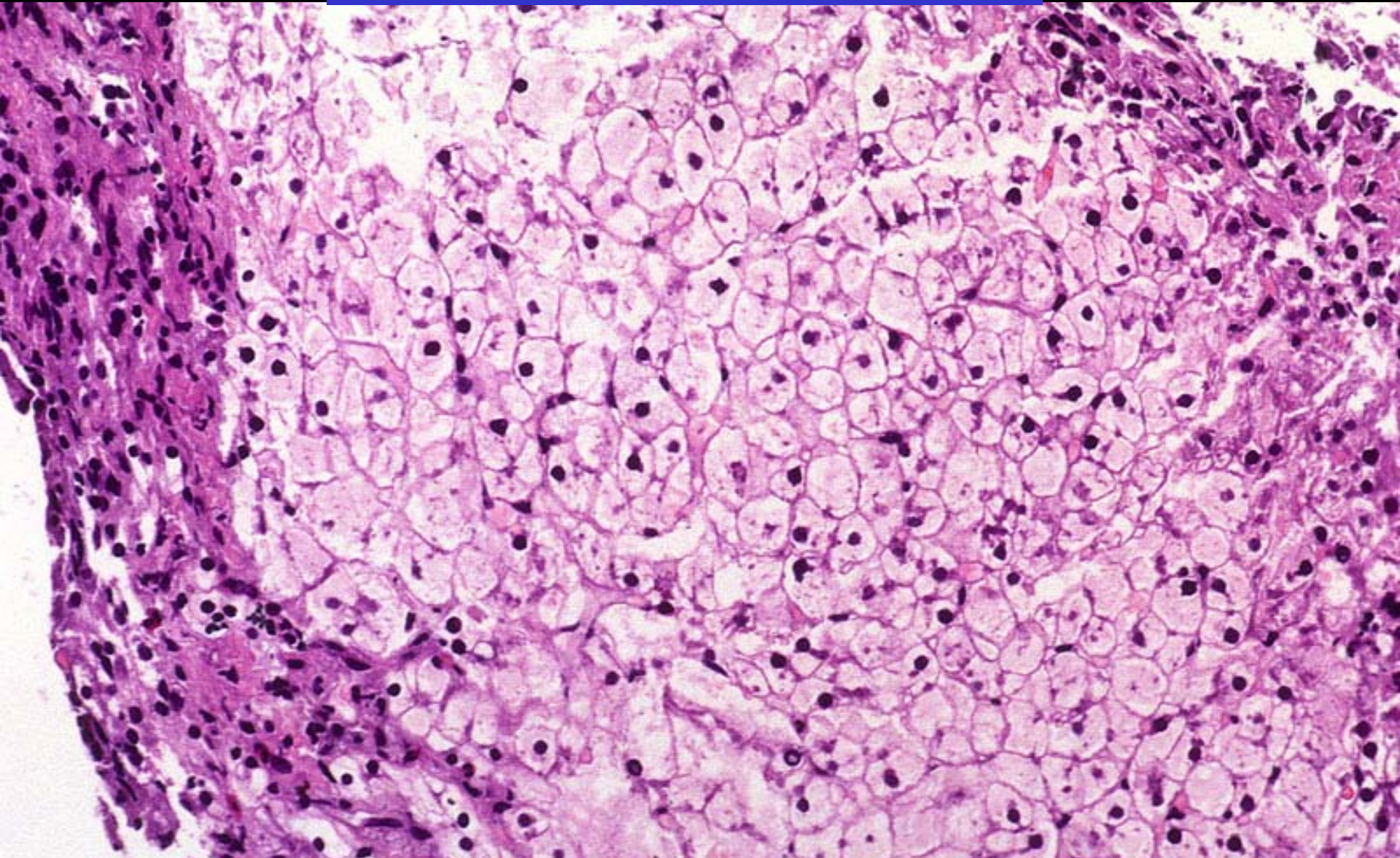
**Fatty Liver of
Pregnancy**

**Other causes:
Tetracycline
Carbon tetrachloride
Alcohol**

Glycogen Storage Disorders

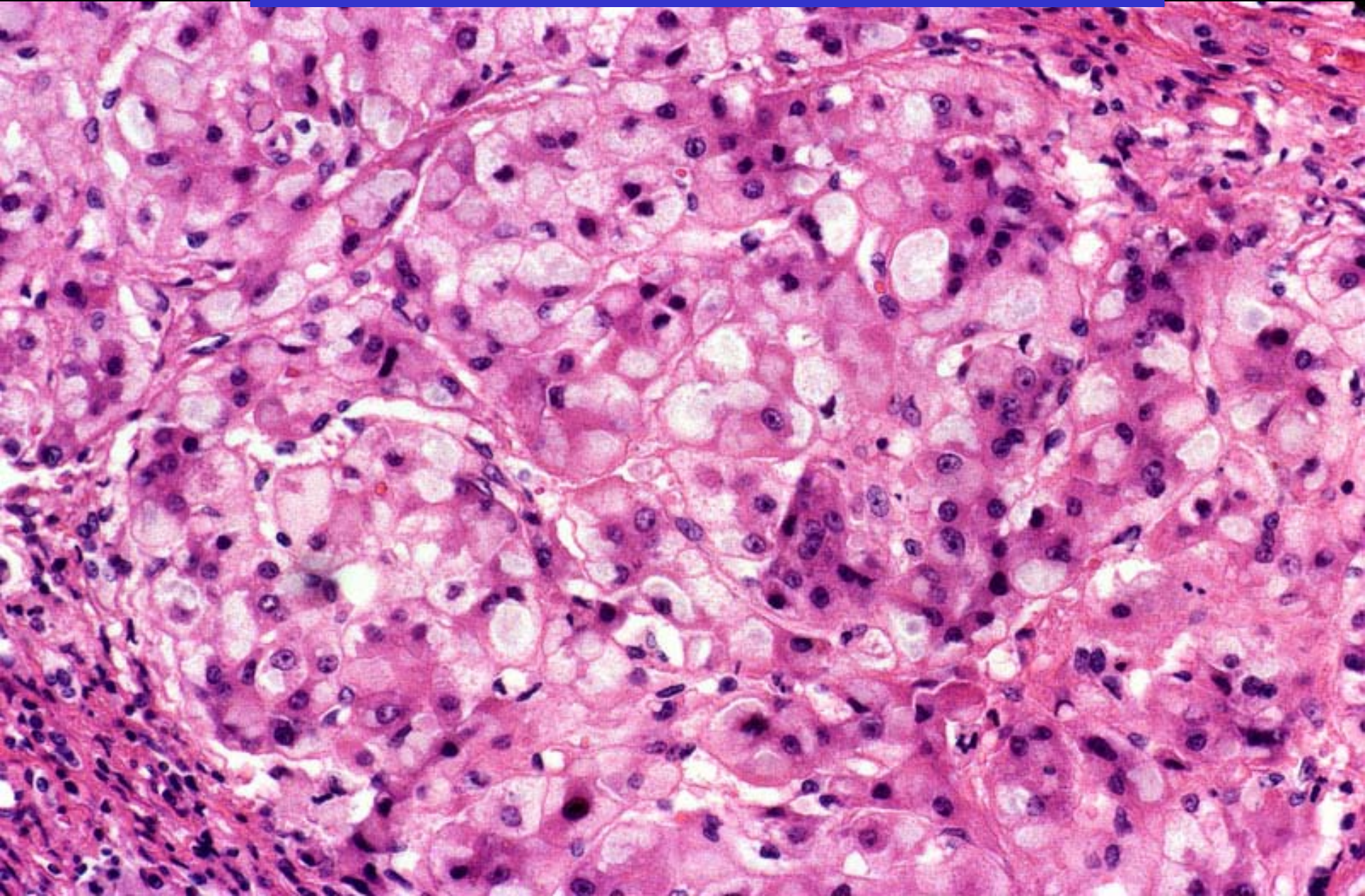
- **Overlap with GH**
 - Diffuse hepatocyte swelling due to glycogen deposits
 - May see small droplet fat
- **Clinical picture differs from GH**
 - Poorly-controlled diabetes with response to diabetic control

Glycogen Storage Disease



pink cytoplasmic changes

Glycogen Storage Disease Type IV



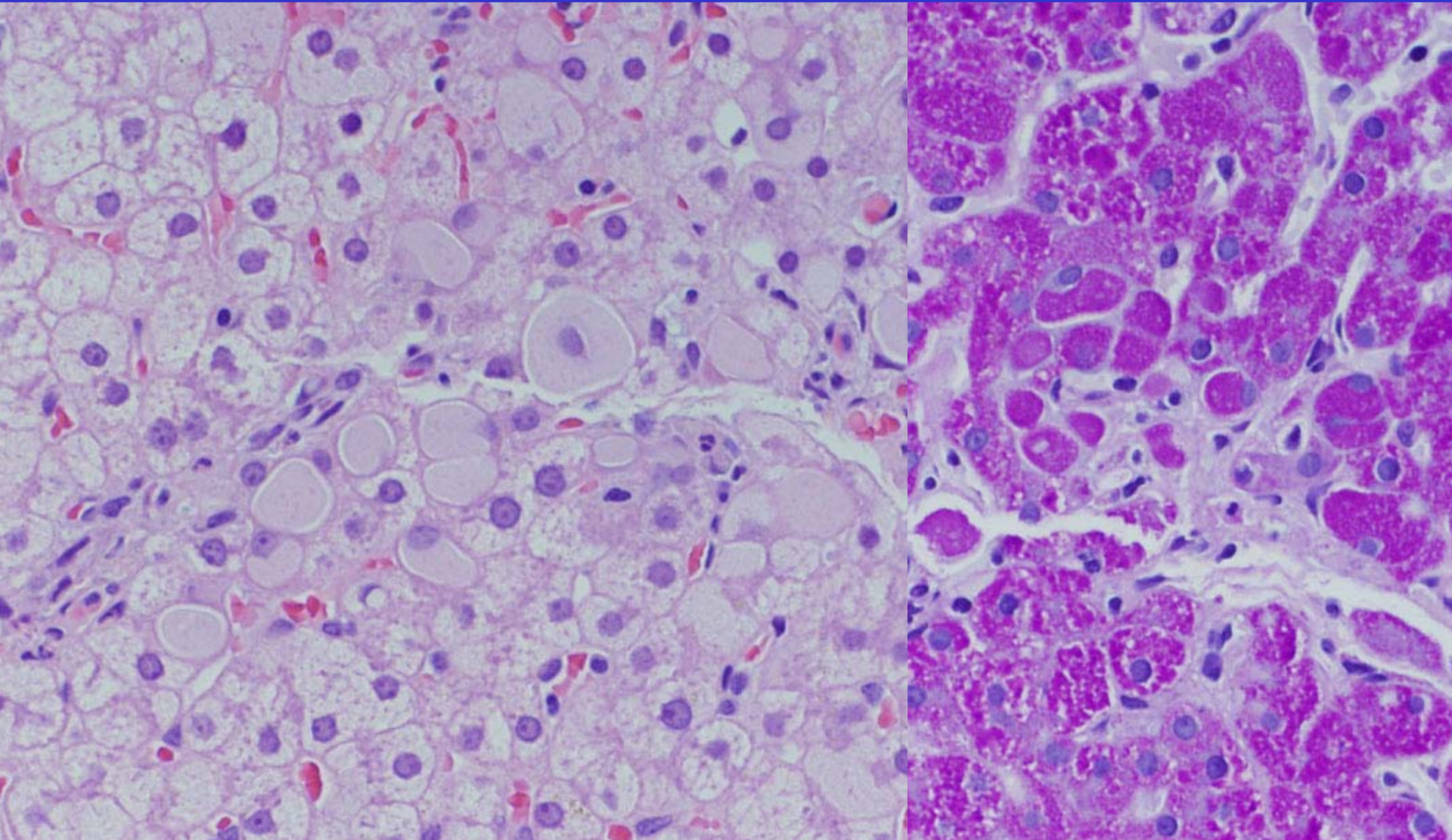
Other Glycogen Lesions

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

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**