

An Interesting Pathologic Finding: Fibrinogen Positive Ground-Glass Hepatocytes

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Introduction

- “‘Ground-glass’ hepatocytes are liver cells which have eosinophilic granular, glassy cytoplasm on light microscopy.” – Cohen, 1975
- Formed by accumulation of metabolic products including glycogen, fibrinogen, viral proteins, etc.
- The differential diagnosis for ground-glass hepatocytes is shown (right, above)
- Periodic acid-Schiff (PAS) staining of these inclusions are generally positive, with the exceptions of fibrinogen accumulation and oncocytic lesions
- Few cases of patients with ground-glass, fibrinogen-positive inclusions have been observed in humans and are thought to occur from acute states of metabolic stress

Case Presentation

A 64-year-old male with a history of ulcerative colitis presented with acute on chronic diffuse abdominal pain and two months of loose, bloody bowel movements occurring up to 10 times daily.

On arrival, he was afebrile and abdominal exam showed diffuse tenderness without peritonitis.

Labs:

- AST 233 U/L, ALT 486 U/L
- Serum workup for hepatitis, HSV, and varicella were unremarkable.
- EBV PCR was weakly positive and CMV PCR was positive.
- Stool studies for clostridium difficile and other pathogens were negative.
- Serum IgG, IgA, Anti-smooth muscle antibody and ANA testing were unremarkable.

Treatment Course:

- Started IV methylprednisolone
- Transaminase elevations worsened to the low 1000s
- Initiated infliximab and began surgical planning for bowel resection
- **Liver biopsy obtained (Example shown right, below)**
 - **ground-glass hepatocytes, moderate steatohepatitis, M2Z heterozygote for A1AT deficiency (serum levels normal)**
- Underwent abdominal colectomy with end ileostomy, infliximab discontinued, steroids were tapered

Clinical Impression

- Differential diagnosis contemplated (right, above)
- Relevant case considerations:
 - PAS staining negative
 - No family history of liver disease
 - Acute illness state
- **Chose to pursue immunohistochemistry staining for fibrinogen**

Differential diagnosis for ground-glass Hepatocytes

PAS Positive

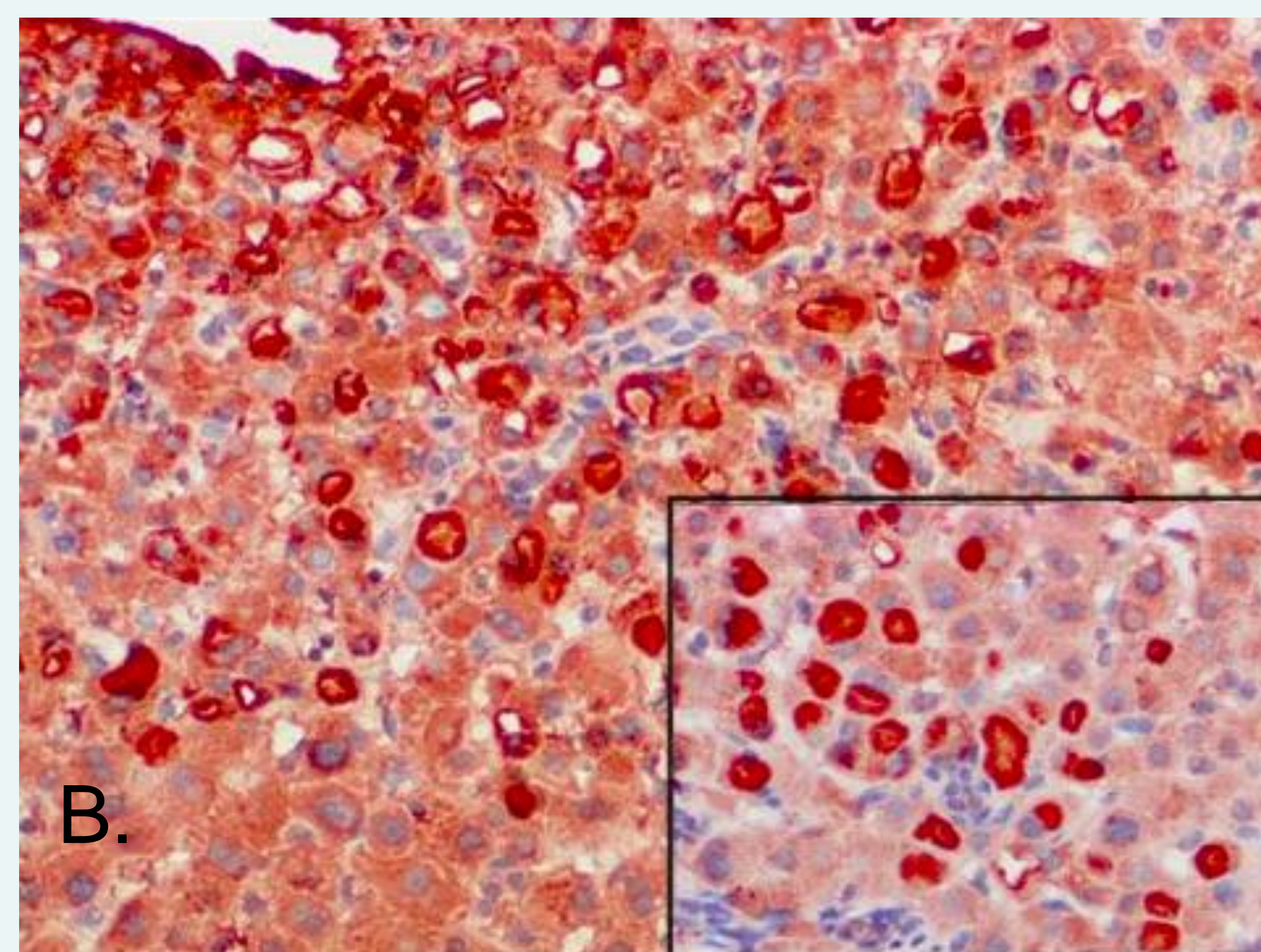
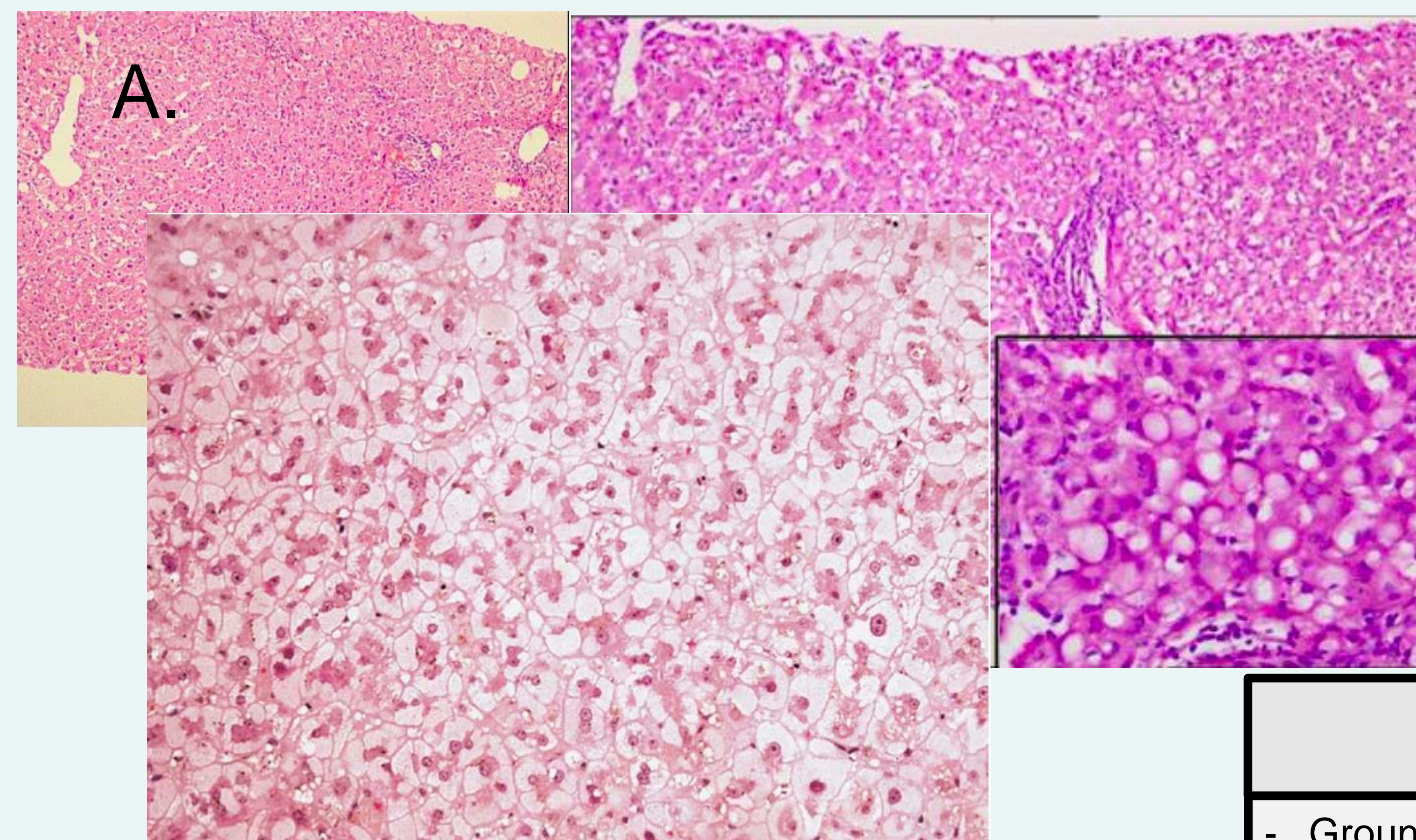
PAS Negative

- Polypharmacy (post transplant)
- Hepatitis B infection
- Alcohol use disorder and aversion therapy with cyanamide
- Lafora disease
- Glycogen Storage Disease Type IV

- Inherited fibrinogen storage diseases
- Acquired fibrinogen accumulation
- Oncocytic lesions

Diagnoses further narrowed by history

Liver Biopsy



Liver Biopsy Images

- A. Examples of H&E staining of liver specimens showing ground-glass changes within the cytoplasm of hepatocytes
- B. Examples of fibrinogen staining of a liver specimen showing diffuse positivity

– Credit: Leftkovich *et al.* 2006 and Simsek *et al.* 2005

Discussion

- Fibrinogen accumulation in hepatocytes can occur from both inherited and acquired causes.
- Pathologic analysis has identified 3 types of fibrinogen positive hepatocyte inclusions.
- **Ground-glass hepatocyte inclusions staining positive with fibrinogen (Type II inclusions) have only been associated only with the acquired causes in humans.**
- Type II fibrinogen inclusions have been demonstrated in two case reports:
 - 1) A patient being treated with estrogen replacement therapy
 - 2) Two elderly patients with sepsis
- These cases were prompted for biopsy due to persistent transaminase elevations and biopsies were reversible with correction of the underlying disease/removal of the insulting agent.

Case Follow-up

After tapering his prednisone and recovering from an acute illness state, his LFTs trended to normal 1 year later.

Take Home Points

- Ground-glass hepatocytes represent a very pointed differential diagnosis.
- A systematic approach to this differential and a good history can eliminate many of the causes.
- Fibrinogen accumulation in the liver is rare and can represent both inherited and acquired disease.
- Acquired fibrinogen hepatocyte deposits are associated with transaminase elevations and acute illness states/medications.
- Removal of the provoking illness state can lead to improvement/resolution of fibrinogen deposition and liver injury.

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