Recent publications on pathology of medical liver disease

Chris Bellamy

Edinburgh University

1. Human iron disorders

Hepcidin in human iron disorders: Therapeutic implications☆

Antonello Pietrangelo

J Hepatol 2010

Hereditary Hemochromatosis: Pathogenesis, Diagnosis, and Treatment

ANTONELLO PIETRANGELO

Gastroenterology 2010

Clinical Presentation and Molecular Pathophysiology of Autosomal Dominant Hemochromatosis Caused by a Novel Ferroportin Mutation

William J. H. Griffiths,[1] Roman Mayr,[2] Ian McFarlane,[3] Martin Hermann,[4] David J. Halsall,[3] Heinz Zoller,[2] and Timothy M. Cox[5]

Hepatology 2010

Human iron disorders

- Hepcidin
  - hormone peptide regulating plasma [iron]
  - traps iron in cells by targeting ferroportin, lowering plasma iron
  - hepatocytes (mφ, adipocytes)
    - ↓ by anaemia, hypoxia
    - ↑ by serum iron, inflammatory cytokines (IL6)
  - deficient in hereditary haemochromatosis (~endocrine)
    - unchecked iron export from macrophage & enterocytes
  - excessive in anaemia of chronic disease/inflammation, dysmetabolic iron overload
    - Iron sequestered in mφ (↑ tissue Fe, ↑ ferritin [inflam mediators])

Ferroportin diseases

- Main iron exporter from cells
  - Mφ (to distant tissues), duodenal enterocytes (to circ)
  - Interplay with hepcidin
  - Rare hepcidin resistance mutants: haemachromatosis
  - Classic (M) disease:
    - loss of export function traps iron in cells
    - High penetrance (auto Dominant: 1 parent with high ferritin)
    - various mutations: eg Griffiths WJH, Hepatology March 2010
    - Caucasian or non-caucasian 10-80years
    - Reticuloendothelial Mφ iron overload (modest iron burden, little irreversible tissue injury)
    - Mild zone 1 hepatocyte iron only
    - liver fibrosis/cirrhosis rare
    - High ferritin but *low-normal* transferrin saturation
    - Venesection precipitates anaemia (& promotes intestinal iron abs)
    - Metaanalysis : Mayr R, J Hepatol July 2010.

Dysmetabolic iron overload

- Inappropriately high hepcidin traps iron in liver [ChenLY2010]
  - ? Inflammatory cytokines
  - ?Cu deficiency in NAFLD traps iron [AignerE2008].
- N transferrin satn, mild Fe overload
- ↑ ferritin
  - common in metabolic syndrome
  - MRI confirms if & quantitates iron overload:
    - » 7/10 patients [ChenLY2010]

- Turlin B 2001 Anatomic pathology
  - 139 DMO patients vs HFE HC (C282Y homoz) histology
  - Sinusoidal cells: doesn't parallel & usually exceeds hepatocyte iron
  - Hepatocytes: heterogeneous, z1>
  - Occ portal mφ, but no biliary/vascular iron

2. Autoimmune hepatitis

J Gastroenterol
DOI 10.1007/s00535-010-0316-3

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Clinicopathological features of severe and fulminant forms of autoimmune hepatitis

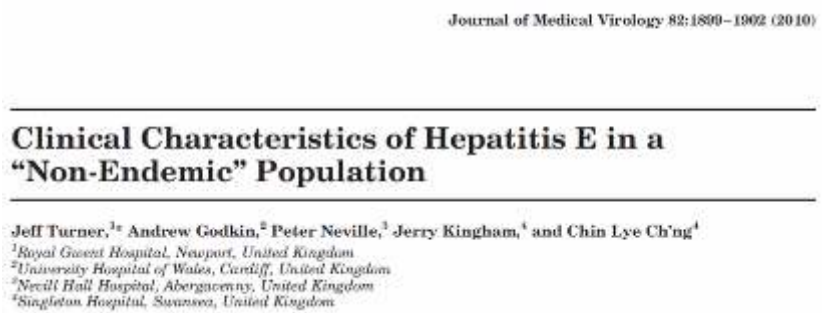
Shin Yasui · Keiichi Fujiwara · Yutaka Yonemitsu · Shigeto Oda · Masayuki Nakano · Osamu Yokosuka

Received: 28 April 2010 / Accepted: 15 August 2010

Severe/fulminant AIH

- Yasui S, *J Gastroenterol*, Sept 2010
  - 23 spec in 28 patients
  - Reminder of acute histology, especially
    - » CLNI (mod/sev in 17)
- Isolated CLNI with autoimmune features:
    - » Portal sparing
    - » Uncommon (4% of recent onset AIH, Burgart 1995)
    - » Pratt DS 1997, Hofer H 2005,
  - Zen Y 2007 Human Pathol: ? not one entity
    - » 5 cases + 17 reported
    - » Half relapsed (especially males)
    - » classic AIH (3) or persistent CLNI (3)

3. Autochthonous hepatitis E



Journal of Medical Virology 82:1899–1902 (2010)

Clinical Characteristics of Hepatitis E in a "Non-Endemic" Population

Jeff Turner,[1]* Andrew Godkin,[2] Peter Neville,[3] Jerry Kingham,[4] and Chin Lye Ch'ng[4]
[1]Royal Gwent Hospital, Newport, United Kingdom
[2]University Hospital of Wales, Cardiff, United Kingdom
[3]Nevill Hall Hospital, Abergavenny, United Kingdom
[4]Singleton Hospital, Swansea, United Kingdom

- TurnerJ 2010 JMedVirol
  - 24 non-travel HEV in South Wales over 2 years
  - male predominance (18); age 47-81
  - Jaundice 67% & anorexia
  - 2 encephalopathy, 1 death
  - Genotype 3 (12/12)
  - Keep in mind if
    - acute cholestatic hepatitis
      (cholangiolitis, mixed portal inflammation, neutrophil cholangitis, cholestasis, perivenular necroinflammation [Malcolm 2007 Histopathology]
    - unexplained decompensation of chronic liver disease [Peron 2007 Virchows Arch]

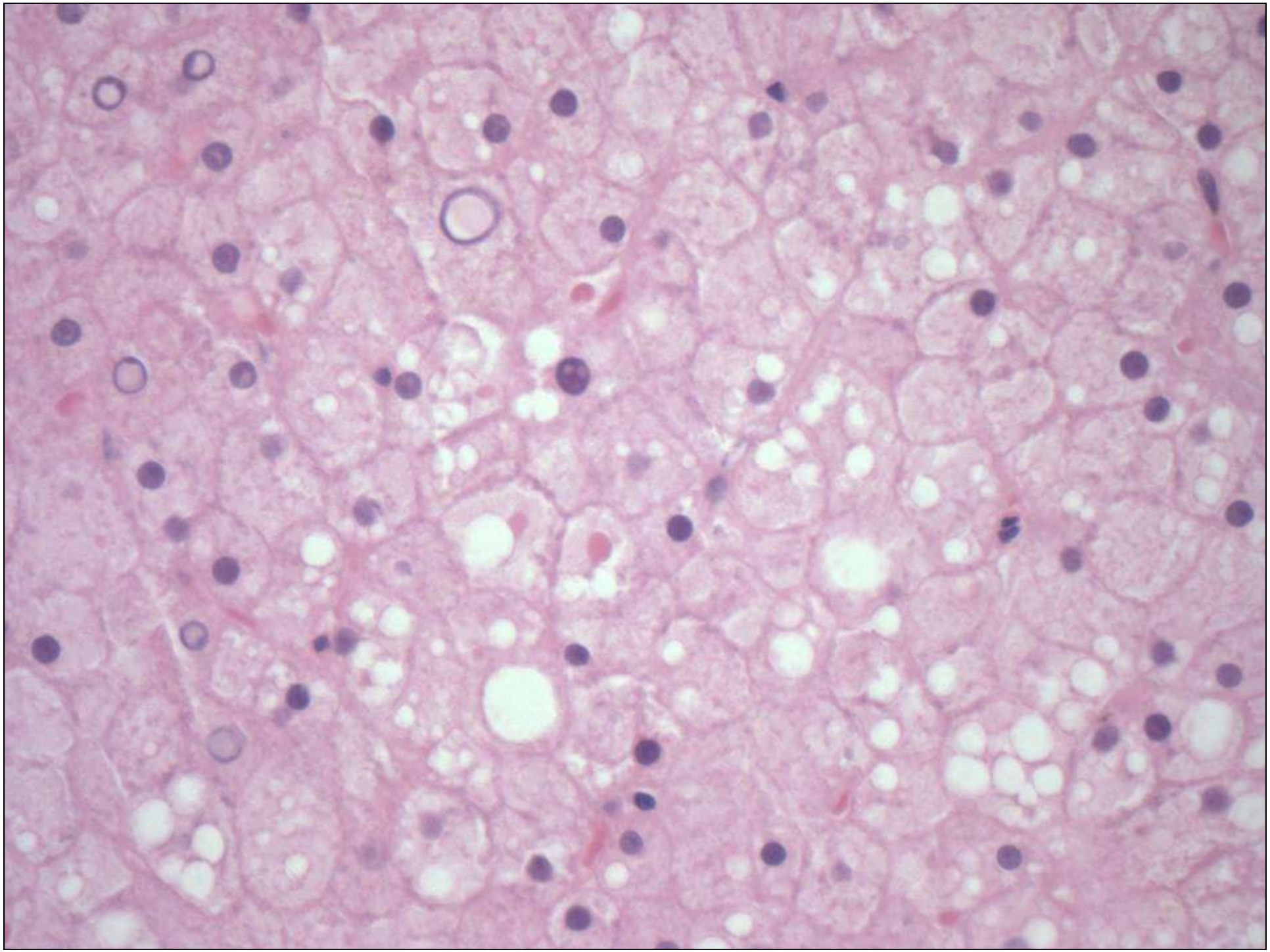
Torbenson2006

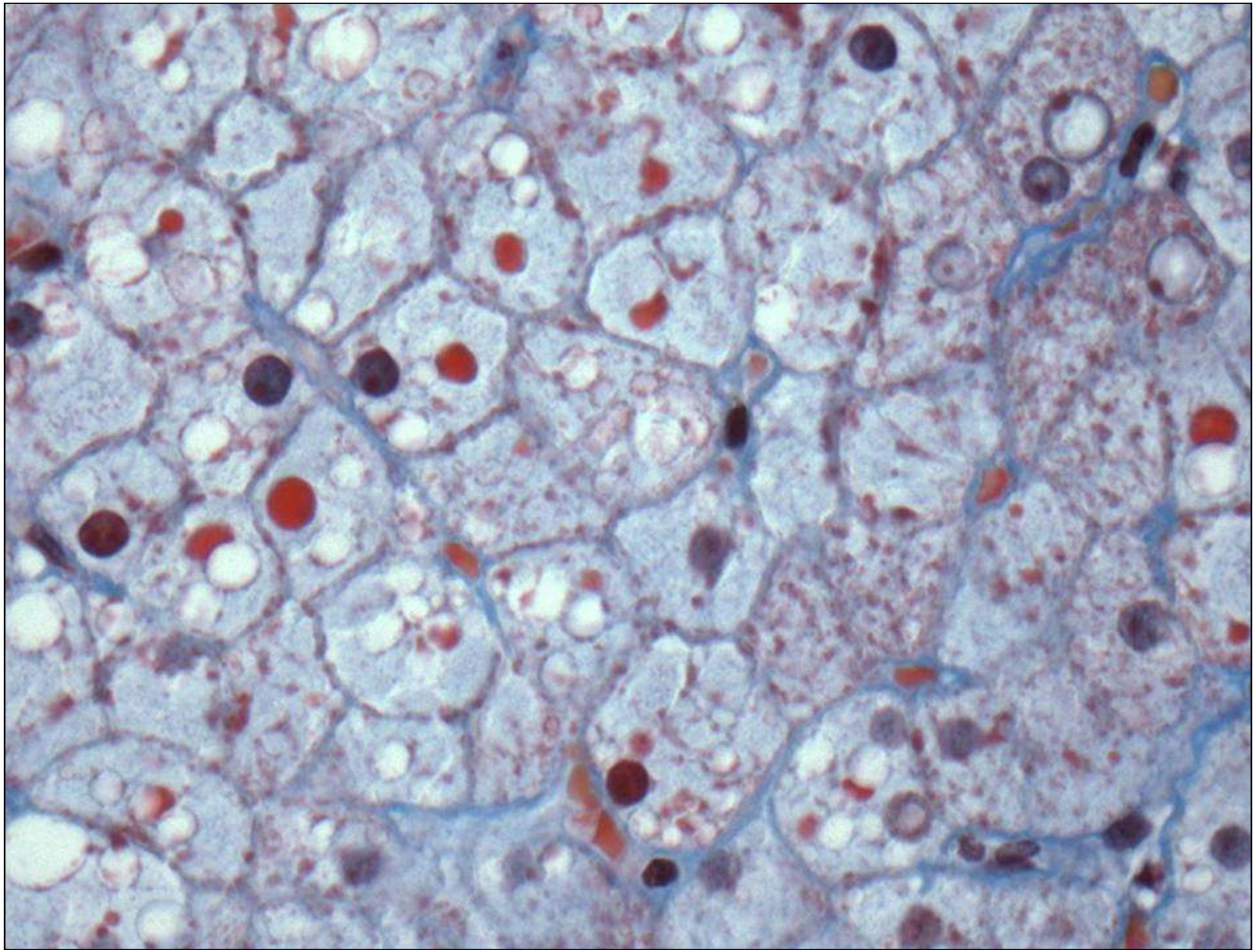
4. Metabolic diseases & liver.
- Glycogenic hepatopathy

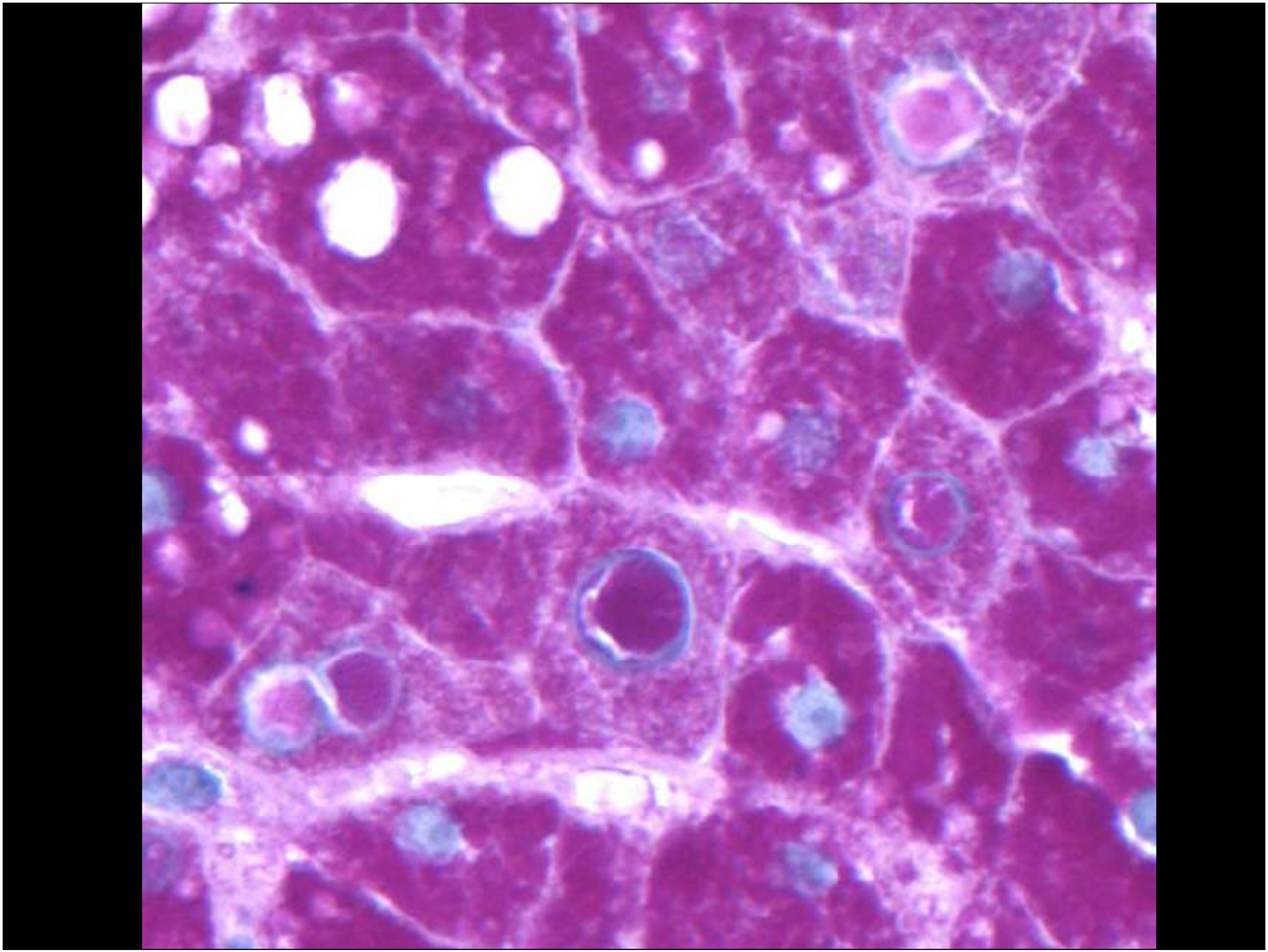
- reversible glycogen-loading
- poor diabetic control with bouts of ++ insulin
  - Short term high dose corticosteroids [Iancu1986]
- children (Mauriac1930) – adults (Evans1955)
- hepatomegaly, pain, transaminitis, ↑ALP, (occasionally ↓glc, ketoacidosis, (ascites))

- Ultrasound can't tell from fat, but bright on CT

- Pale heps with prom membs, compressed sinusoids, glycog nuc, PAS replete, giant mito
- Minimal fat/fibrosis

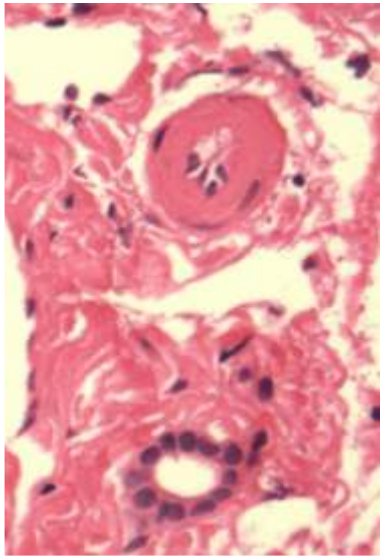






Diabetic microangiopathy of the liver

- Diabetic hepatosclerosis (Harrison2006, Chen2008)
- Dense perisinusoidal + perivenular fibrosis (laminin/coll IV) with severe portal hyaline arteriolosclerosis
  - chronic diabetes
  - Liver sinusoids site for diabetic microangiopathy like other capillary beds
- Collagenisation of space of Disse with bm components
  - Latry1987: 4/4 diabetics (I, II, retinopathy/not)
  - Bernuau1982: 6 with retinopathy, but not 6 without



  - Chen2008 Liver International: 12% (19/254) autopsied diabetics
    - » Nephropathy in 90% ($p<.05$), retinopathy 16%, ↑ALP 30%
    - » Probably most cases clinically silent/incosequential

GASTROENTEROLOGY 2008;135:840–848

Acute Liver Cell Damage in Patients With Anorexia Nervosa: A Possible Role of Starvation-Induced Hepatocyte Autophagy

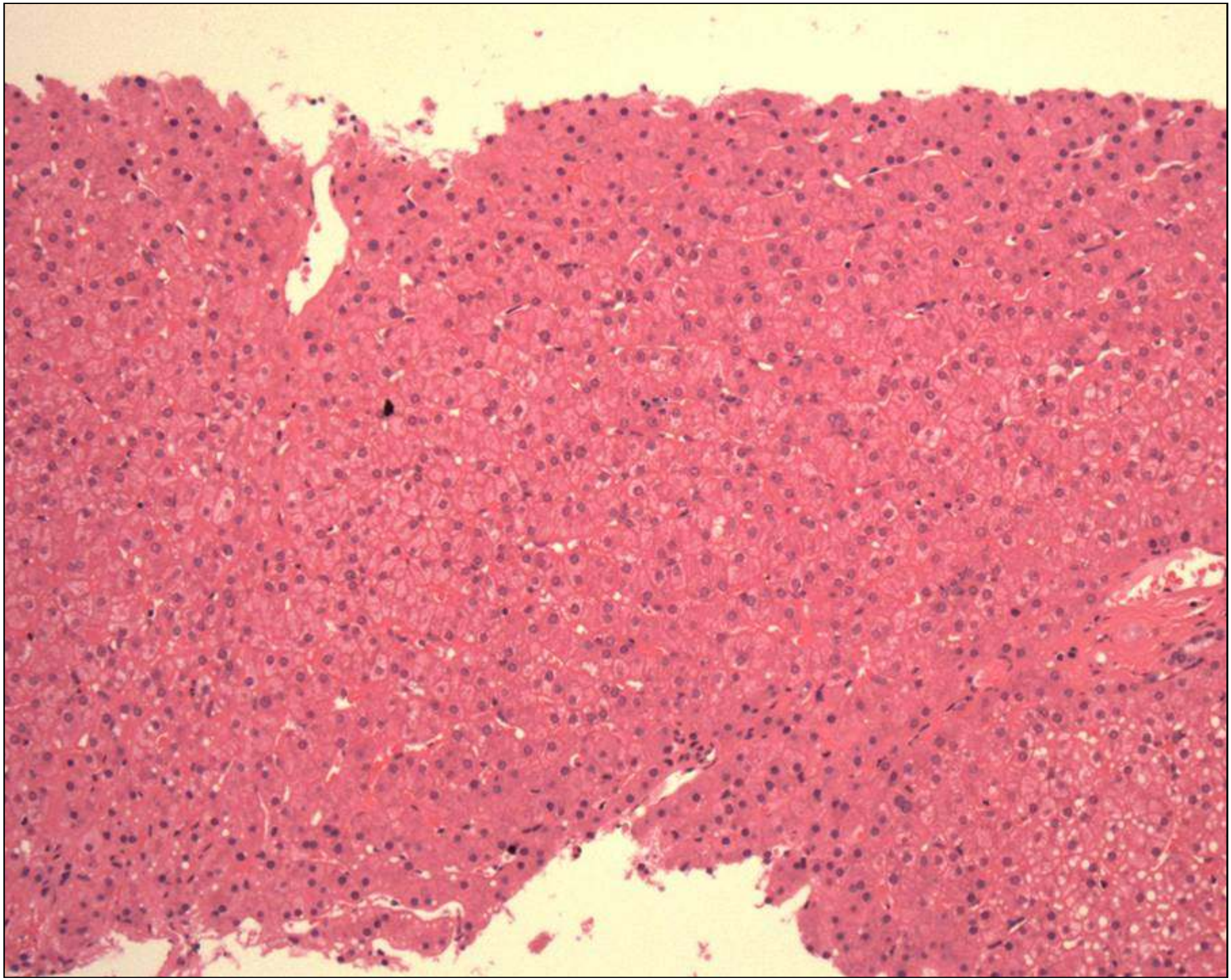
PIERRE–EMMANUEL RAUTOU,[*,‡] DOMINIQUE CAZALS–HATEM,[§] RICHARD MOREAU,[*,‡] CLAIRE FRANCOZ,[*] GÉRARD FELDMANN,[†] DIDIER LEBREC,[*,‡] ÉRIC OGIER–DENIS,[†] PIERRE BEDOSSA,[‡,§] DOMINIQUE VALLA,[*,‡] and FRANÇOIS DURAND[*,‡]

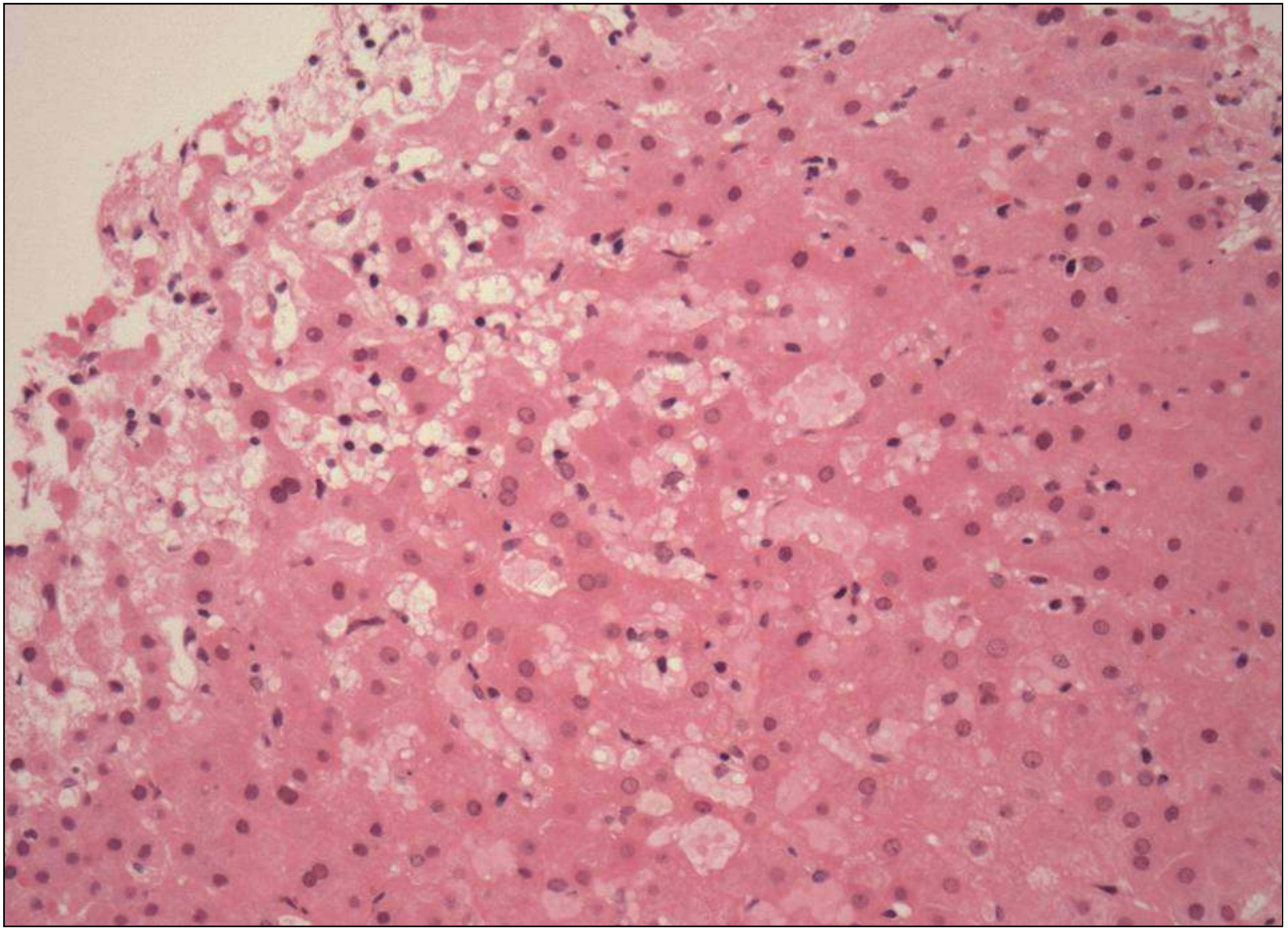
[*]Pôle des Maladies de l'Appareil Digestif, Service d'Hépatologie, Hôpital Beaujon, AP-HP, Clichy, France; [‡]INSERM U773, Centre de Recherche Biomédicale Bichat Beaujon CRB3, Université Paris 7-Denis-Diderot, Paris, France; [§]Service d'Anatomie-Pathologique, Hôpital Beaujon, Clichy, France

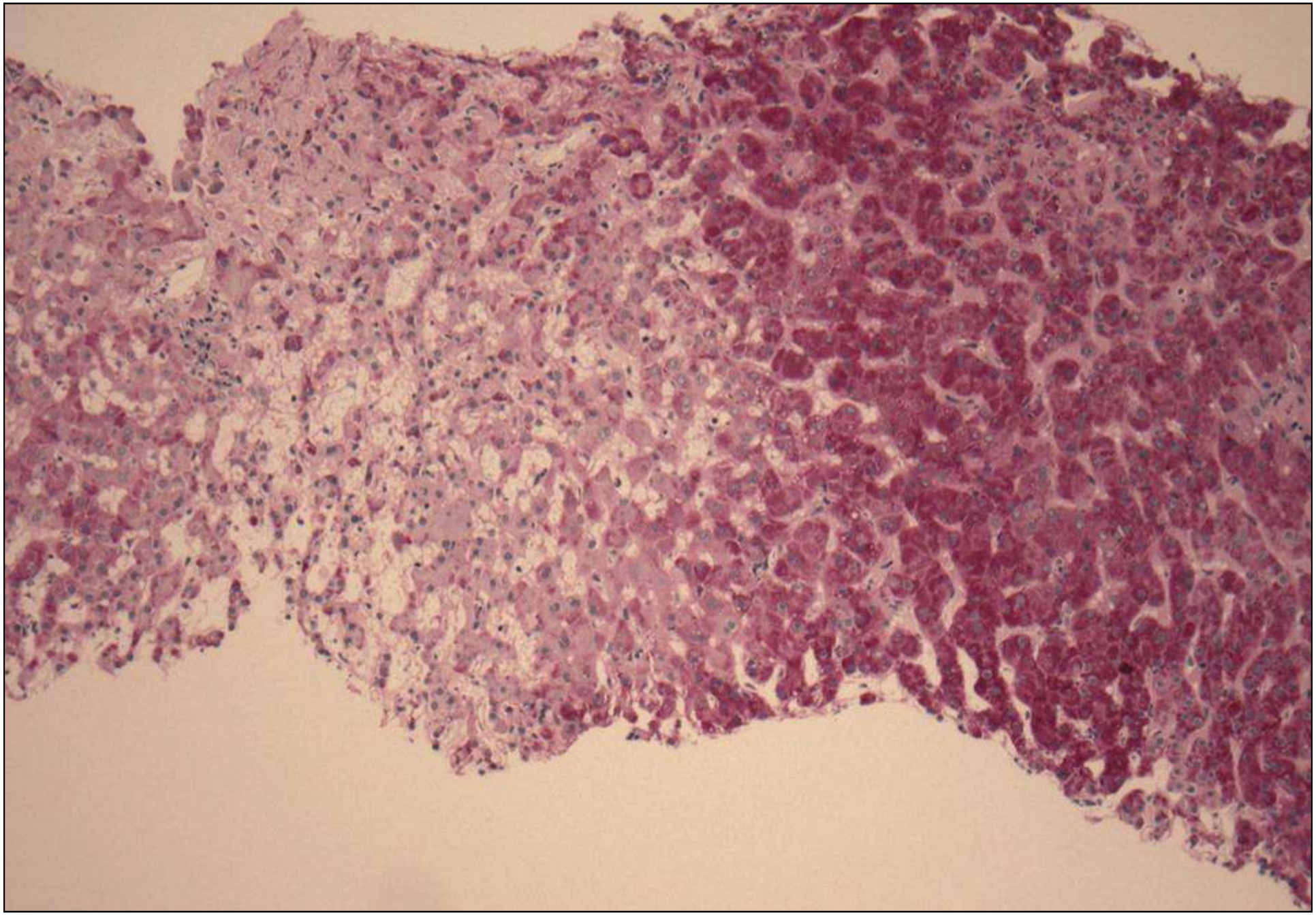
Acute liver cell damage in Anorexia

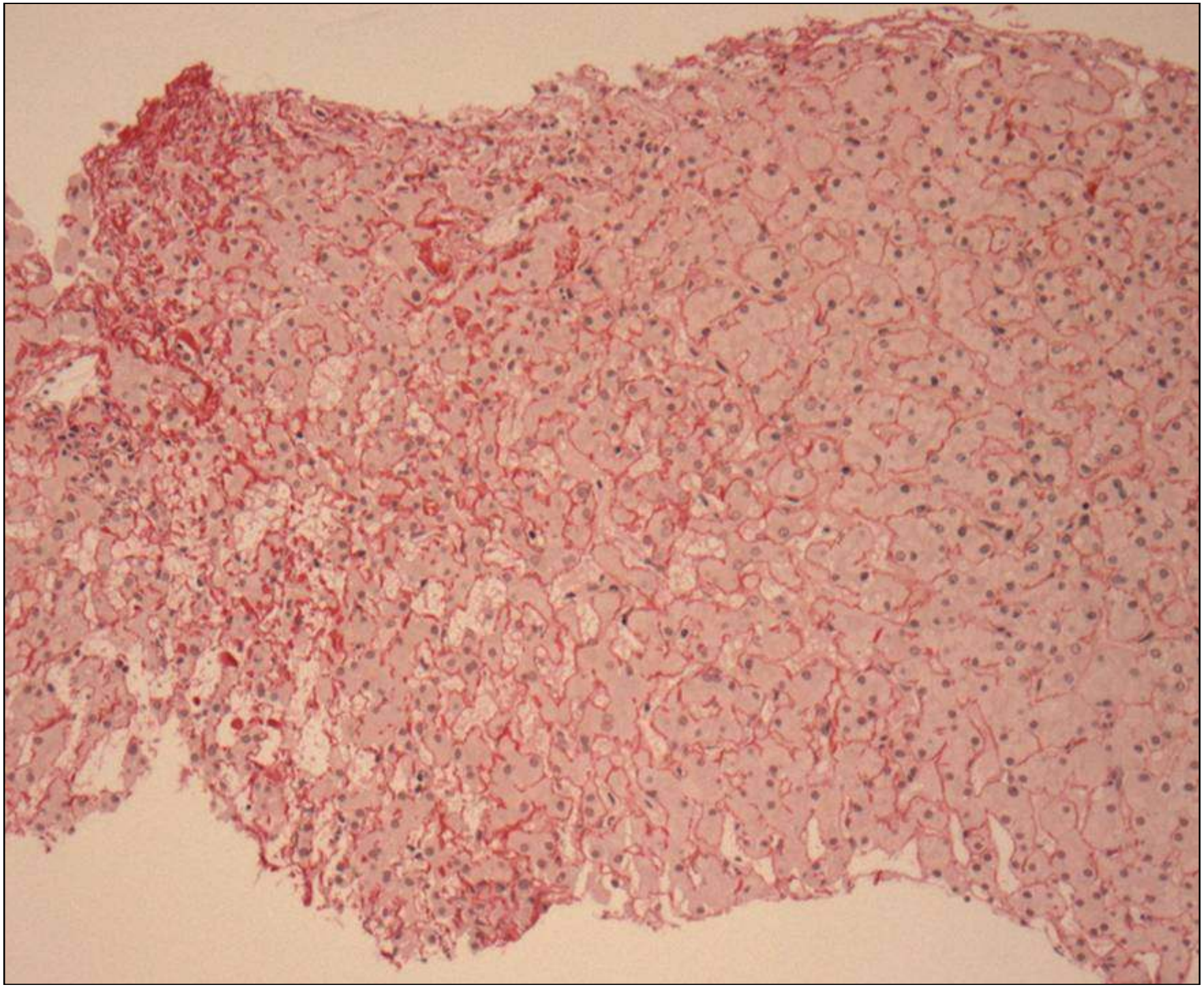
- 12 consecutive patients with acute liver failure & only anorexia as explanation. BMI 11.3 median
- 6 hypoglycaemia & coma, 4 ascites
- Median AST peak 67x ULN, ALT 56x ULN
- 8 previous transaminitis episode

- Liver biopsy (11 TJ, 1 percut)
  - Perivenular glycogen depletion
  - Perivenular atrophy & mild perisinusoidal fibrosis
  - Hepatocyte swelling & rarefaction
  - ceroid
  - Em: autophagosomes, organelle depletion (inc mitochondria)
  - No necrosis, congestion, inflammation
- Concluded acute starvation-induced autophagic liver injury









5. Sepsis & liver.

Severe Sepsis in Cirrhosis

Hepatology 2009

Thierry Gustot,[1,3,4,5] François Durand,[3,4,5] Didier Lebrec,[3,4,5] Jean-Louis Vincent,[2] and Richard Moreau[3,4,5]

Early features of acute-on-chronic alcoholic liver failure: a prospective cohort study

Katoonizadeh A, Laleman W, Verslype C, Wilmer A, Maleux G, Roskams T, Nevens F

Gut 2010

Acute-on-chronic alcoholic liver failure

- Acute deterioration in well-compensated cirrhosis
- Potentially remediable precipitant
  - High short term mortality but survivors approximate compensated cirrhosis
- 54 ACLF vs 48 chronic relentless decompensating ALD

- Infection commonest cause of mortality
  - Occult early (admission) hence value of early sepsis indicators
- Mortality predictors (multivariate)
  - SIRS <24hrs of admission
  - ductular bile plugging
  - Mallory-Denk
- Biopsy also confirms cirrhosis
  - Excluded non-cirrhotics all survived though similar otherwise

6. Drugs/toxins

Clinical Syndromes and Consequences of Antiretroviral-Related Hepatotoxicity

Marina Núñez

Hepatology Sept 2010

ELSEVIER

European Journal of Internal Medicine 17 (2006) 383

EUROPEAN JOURNAL OF INTERNAL MEDICINE

www.elsevier.com/locate/ejim

Letter to the Editor

Khat — a novel cause of drug-induced hepatitis

J.M. Brostoff *, C. Plymen, J. Birns

Department of Medicine, Central Middlesex Hospital, Acton Lane, London NW10 7NS United Kingdom

Received 17 December 2005; accepted 22 December 2005

Khat chewing (*Catha edulis*)

- Chapman, April 2010 NEJM : severe acute liver injury.
  - 6 patients, 28-36 yrs
  - 5 users for several years with prior unexplained hepatitis
  - Multiacinar necrosis (6) + chronic liver disease (2)
  - OLTx (5), death (1)
- Peevers, 2010 Liver Int
  - 7 UK Somali men, 28-41 yrs
  - 6 biopsies: z1 & z3 hepatocellular injury, 3 cholestasis, 2 cirrhotic, 1 moderate fibrosis
  - 3 SMA positive (1:40-1:160)
- Coton, 2010 Liver Int (letter)
  - UK doses low
  - Toxicity not encountered in East Africa (Djibouti)
  - ? Contaminant/associated toxin

7. Vascular

Aberrant expression of cytokeratin 7 in perivenular hepatocytes correlates with a cholestatic chemistry profile in patients with heart failure

Rish K Pai and John A Hart[1]

Department of Pathology, The University of Chicago Medical Center, Chicago, IL, USA

Modern Pathol 2010

- 22 patients
- perivenular CK7 in 20/22
  - correl with bilirubin & perisinusoidal fibrosis
- Reminder of perivenular CK7 in venous outflow obstruction & that biliary signs in venous outflow obstruction can mislead

Histologic changes mimicking biliary disease in liver biopsies with venous outflow impairment

Sanjay Kakar[1], Kenneth P Batts[2], John J Poterucha[3] and Lawrence J Burgart[4]

Modern Pathol 2004

8. Systemic IgG_4 disease.
IgG4-related sclerosing cholangitis

- Steroid-responsive
- Autoimmune pancreatitis
- IgG4 serology useful (75%)(but 9% PSC [Mendes2006])
- vs. PSC
  - Older (45-75 vs 12-65), not UC, not cholangiocarcinoma
  - Multiorgan disease
  - Segmental/distal cbd strictures vs beaded
  - Obstructive Jaundice

Small bile duct involvement in IgG4-related sclerosing cholangitis: liver biopsy and cholangiography correlation

Itaru Naitoh · Yoh Zen · Takahiro Nakazawa · Tomoaki Ando · Kazuki Hayashi · Fumihiro Okumura · Katsuyuki Miyabe · Michihiro Yoshida · Shunsuke Nojiri · Takayoshi Kanematsu · Hirotaka Ohara · Takashi Joh

J Gastroenterol 2010 ePub

- How useful is liver bx to tell IgG_4-SC (19) from PSC (22)?
  - 26% (5) diagnoseable on liver bx
  - Best yield if proximal strictures
    - intrahepatic (57% diagnosed;4) or at least hilar (5^{th})

- Criteria
  - 10 IgG_4 plasma cells/hpf (average of 3hpf, ?portal tracts)
  - Bile duct damage

Intrahepatic IgG_4-SC on *biopsy*

Like PSC but:

- More than sparse IgG_4 plasma cells
  - heterogeneity problematic
  - IgG_4/IgG_1 ratio > 1
- ↑ portal inflammation
  - Plasma cells, neutrophils, eosinophils
- Portal fibroinflammatory nodules
- No ductopenia

PSC hepatectomies

- 35%: abundant hilar IgG_4 plasma cells (?aggressive)
  - Not in portal tracts or parenchyma
- Hilar fibrosis lamellar bundles, not storiform cellular

Umemura2007, Zhang2010, Koyabu2010, Deshpande2010, Naitoh2010

“Autoimmune hepatitis” with IgG_4 plasma cells

Umemura 2010 J Gastroenterol

- 60 type I AIH vs. 22 AIP
- Two: ↑serum IgG_4 + >10 IgG_4 plasma cells/hpf
  - Steroid sensitive
  - IgG_4-SC 5yrs later (1)

- Argue
  - these are hepatic manifestation of systemic IgG_4 disease, ie: “IgG_4 hepatopathy”, not AIH
  - Chung 2010 cases are different (no serum ↑ IgG_4)
    - IgG_4 plasma cells in 9/26 AIH
    - More steroid sensitive, no relapsers

Patterns of liver involvement in systemic IgG_4-related disease

- AIP patients with liver dysfunction
- "IgG_4 hepatopathy:"
  - Portal hepatitis +/- interface hepatitis
  - Large duct obstructive
  - Lobular hepatitis
  - Centrilobular canalicular cholestasis
  - Portal fibrosis (pauci-inflammatory)

Umemura 2007 Hepatology