

LIVER PATHOLOGY

Thursday 28th November 2013



Coffee Reduces Risk for Hepatocellular Carcinoma

- From a meta-analysis, the risk of HCC is reduced by 40% for any coffee consumption vs no consumption.
- The relative risk was 0.80 for an increment of 1 cup of coffee per day.
- The inverse association might partly or largely exist because patients with liver and digestive diseases reduce their coffee intake.
- Coffee has been shown to affect liver enzymes and development of cirrhosis, and therefore could protect against liver carcinogenesis.

Autoimmune / Biliary Liver Disease

Clinical characteristics of autoimmune hepatitis with IgG4-positive plasma cell infiltration in liver

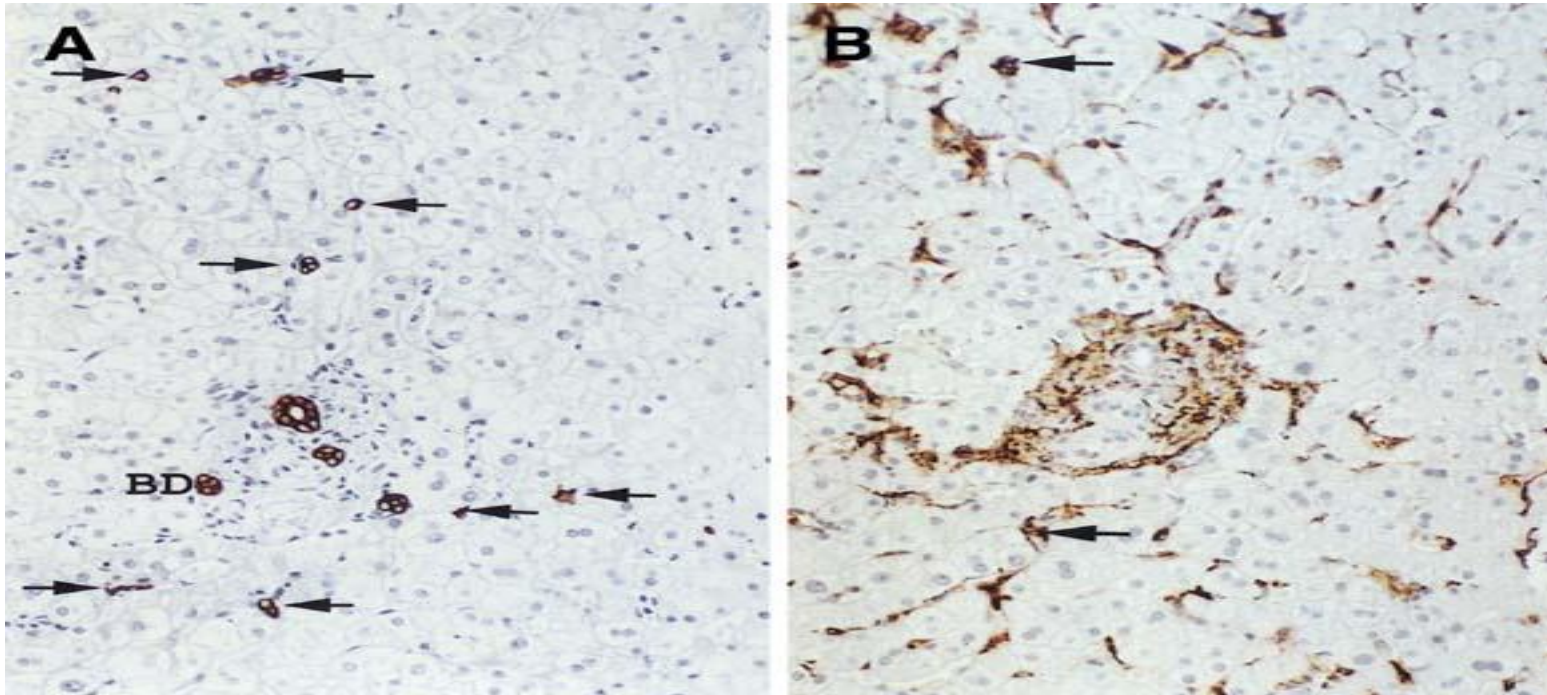
- The number of IgG- and IgG4-plasma cells was immunohistochemically counted in at least 3 portal tracts.
- Patients with 3 or more IgG4-plasma cells per portal tract on average were defined as IgG4-related AIH, and their clinical characteristics were compared to the remaining patients (classical-AIH).

- Serum IgG4 was significantly greater in IgG4-AIH.
- None of the IgG4-AIH patients revealed any abnormal findings in pancreas and bile ducts suggestive of IgG4-related diseases.

- The IgG4-AIH patients had more active inflammation and more advanced fibrosis.
- Their prognosis was not poor compared to classical AIH.
- IgG4-AIH may have a phenotype distinct from c-AIH.

Correlation of destruction of canals
of Hering with the progression of
the primary biliary cirrhosis stage

- Canals of Hering (CoH) are the most peripherally located bile drainage pathway and are considered to be a niche of hepatic progenitor cells.
- Khan et al ([Hepatology. 2013 Feb;57\(2\):700-7.](#)) and their previous study ([Saxena R, Hytioglou P, Thung SN, Theise ND. Destruction of canals of Hering in primary biliary cirrhosis. Hum Pathol 2002;33:983–988](#)) reported that destruction of CoH is a feature of primary biliary cirrhosis (PBC).
- The ratio of the number of CoH to the number of portal tracts (c/p ratio) was calculated according to the method of Saxena et al.
- We analyzed the correlation with histological parameters according to a new grading and staging system proposed by us ([Nakanuma et al. Pathology International Volume 60, Issue 3, pages 167–174, March 2010](#))



Biopsy from a patient with PBC. (A) Immunohistochemical staining for CK19 in a patient highlights CoH, which appear as clusters and strings of cuboidal cells within the hepatic lobule (arrows). Bile ductules (BD) have a circumferential lining of cholangiocytes and lie at the edges of portal tracts

Romil Saxena , Prodromos Hytioglou , Swan N. Thung , Neil D. Theise

Destruction of canals of hering in primary biliary cirrhosis

Human Pathology Volume 33, Issue 10 2002 983 - 988

<http://dx.doi.org/10.1053/hupa.2002.128060>

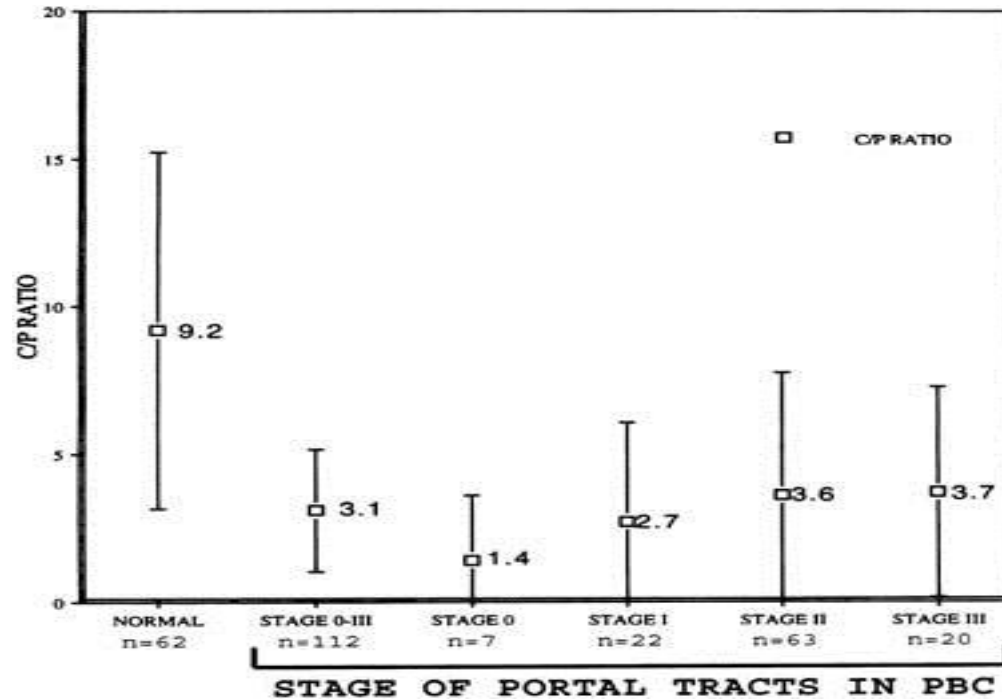


Fig. 2 Comparison of c/p ratios in various stages of PBC.

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Staging of PBC

- Scoring of fibrosis +
- Scoring of bile duct loss +
- Scoring of deposition of orcein-positive granules

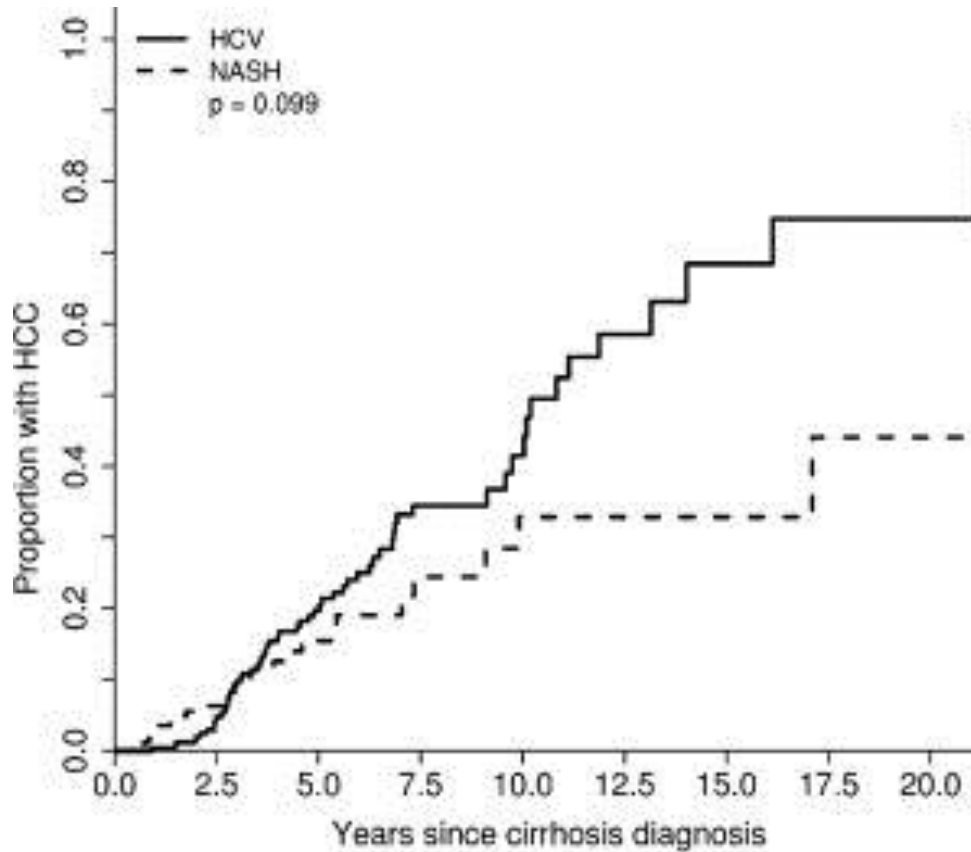
Grading of PBC

- Cholangitis activity
- Hepatitis activity

- In PBC patients, destruction of CoH was correlated with histological parameters and clinical features, particularly with stage progression.

Liver cancer

The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis



Systemic Metabolic
Derangements or Histologic
Features on Liver Biopsy are not
Associated with Increased Risk of
HCC in NASH

- Epidemiological studies have suggested an association between nonalcoholic steatohepatitis (NASH) and increased risk of developing hepatocellular carcinoma (HCC).
- HCC occurred in NASH patients in the absence of cirrhosis although NASH patients with HCC were older and more likely to exhibit advanced fibrosis/cirrhosis compared with NASH patients without HCC.
- However NAS scores on liver biopsy were not associated with increased risk of HCC in NASH patients.

Clinicopathological features of HCC derived from steatohepatitis

- Steatohepatitis is one of the important aetiologies of hepatocellular carcinoma (HCC) and the incidence is increasing.
- We analyzed the clinicopathological features of HCC derived from steatohepatitis related with non-alcohol and alcohol consumption to characterize HCC risks in these groups.

- We classified into two groups according to the amount of alcohol consumption (less than 20g/day (non-alcoholic fatty liver disease; NAFLD) and over 70g/day (alcohol liver disease; ALD)).
- The expression status of 4-hydroxy-2'-noneal (HNE) and 8-hydroxydeoxyguanosine (8-OHdG), the markers of the oxidative DNA damage and Nanog a pluripotent gene involving in the regulating self-renewal of cancer-stem cells, were determined by immunohistochemistry

- HCCs in NAFLD cases were diagnosed in older and more obese patients with lifestyle-related diseases than in ALD cases.
- HCCs in ALD were observed mostly in male, with more severe fibrosis and iron deposition in the liver tissues.
- Positive staining of HNE, 8-OHdG, and Nanog, may be useful markers of HCC risks.

Progenitor cell markers in
hepatocellular carcinoma:
clinico-pathological correlations and
prognostic value.

Liver Stem Cell Markers

Hepatic Stem Cells (hHpSCs) in Canals of Hering	Biliary Tree Stem/Progenitor Cells (BTSC) in Peribiliary Glands
/	Nanog, OCT4
/	CXCR4
/	FoxA 1/2
/	PDX1, NGN3
AFP	AFP
Sox 9/17	Sox 9/17
Hes1	Hes1
Prox1	Prox1
HNF 4/6	HNF6
CK7/8/18/19	CK7/8/18/19
Prominin-1 (CD133)	Prominin-1 (CD133)
EpCAM	EpCAM
NCAM	NCAM
Thy-1	Not assessed

- Keratin 19 (K19) immunopositivity has been proposed to represent hepatic progenitor cell (HPC) origin of HCC and has been correlated with poorly differentiated histology and aggressive tumor behaviour.
- Epithelial Cell Adhesion Molecule (EpCAM) immunophenotype has been used to classify HCC into different subtypes with prognostic implication and may represent a possible biomarker for HPC origin.

- K19 immunopositivity correlated with micro-vascular invasion but there was no correlation with other clinico-pathological parameters.
- EpCAM immunopositivity was significantly correlated with advanced TNM stage.

- In multivariate analysis, K19 positivity was the only independent predictor of relapse free survival
- Another presentation concluded:
“The expression of CK19 and/or SOX9 in HCC could be a useful predictor for postoperative recurrence. “

RCPATH Guidelines

“Poorly differentiated HCCs that are CK19 positive but do not have morphological features of cholangiocarcinoma appear to have a poorer prognosis (Evidence level D), but at present are best regarded as hepatocellular carcinoma for staging and treatment purposes.”

http://www.rcpath.org/Resources/RCPATH/Migrated%20Resources/Documents/G/G050_LiverDataset_Jun12.pdf

Fatty Liver Disease

Extended treatment with
pioglitazone improves liver histology
in patients with prediabetes or type
2 diabetes mellitus and NASH:
Results from the TONIC trial

NASH CRN scoring system

Steatosis grade	Lobular inflammation	Hepatocellular ballooning
0: <5%	0: None	0: None
1: 5-33%	1: <2 foci/20x field	1: Mild, few
2: 34-66%	2: 2-4 foci/20x field	2: Moderate – marked,
3: >66%	3: >4 foci/20x field	many
NAFLD activity score (NAS): 0-8		
Steatosis (0-3) +	Lobular Inflammation (0-3)	+ Ballooning (0-2)

- More patients on PIO (55%) vs. placebo (19%) had improvement in steatohepatitis (primary outcome)

- This was defined as:

an improvement by ≥ 1 points in the hepatocellular ballooning score and no increase in the fibrosis score

and

either a decrease in the nonalcoholic fatty liver disease activity score (NAS) to ≤ 3

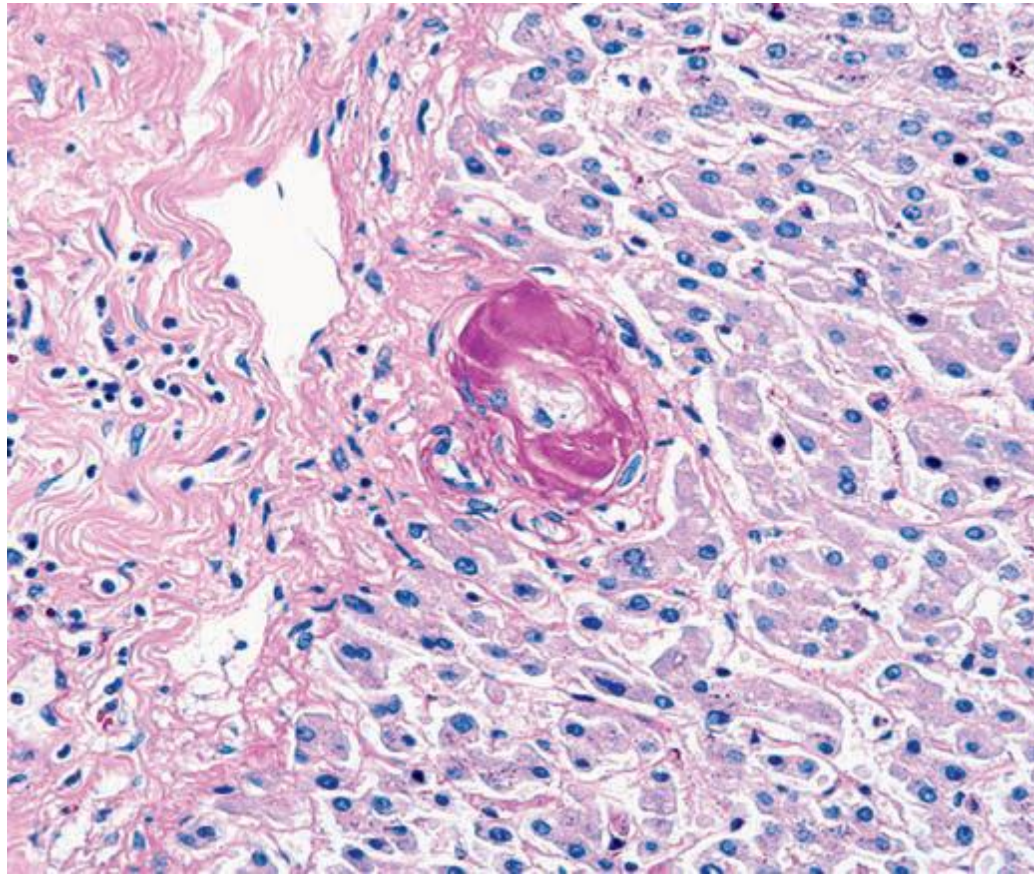
or a decrease in the activity score of at least 2 points (with 1-point decrease in either the lobular inflammation or steatosis score).

Progression to bridging fibrosis in
non-alcoholic fatty liver disease over
4 years in the NASH CRN

- The first biopsy had a fibrosis stage less than 3 were included
- 270 patients had at least 2 biopsies, with a mean time between first and last biopsies of 4.4 years
- Initial biopsies of progressors had more ballooning, portal inflammation, Mallory Denk bodies, higher NAFLD Activity Scores, and more often showed steatohepatitis

Hyaline Arteriosclerosis: A Diabetic Complication of the Liver

- Hyaline arteriosclerosis (microangiopathy) is a well-known complication of diabetes. Diabetic nephropathy and retinopathy are two well-established manifestations of small vessel hyaline arteriosclerosis in diabetes.
- Based on our observation of isolated cases of patients with diabetes and liver enzyme abnormalities in whom the only finding on liver biopsy was hyaline arteriosclerosis, we decided to undertake a cross-sectional blinded study assessing this and other histological findings in diabetics.



Am J Clin Pathol 2009;132:494-499

- Sex, BMI, insulin use, hypertension, and dyslipidemia were not associated with hyaline arteriosclerosis among diabetics
(What about age ?)
- Hyaline arteriosclerosis of hepatic arterioles is a small vessel hepatic complication of diabetes described for the first time.

Liver diseases which have been associated with diabetes

- NAFLD (including NASH)
- Glycogenic hepatopathy
- Liver cell adenoma / adenomatosis
- Nodular regenerative hyperplasia
- Liver cell cancer
- Xanthomatous neuropathy 2005;25(2):236.

Cancer. 1982 Feb 1;49(3):543-6.

Reticulo-endothelial Cell System Iron
Staining is a Predictor of Progression
to Borderline or Definite
Steatohepatitis in Patients without
Fibrosis

- The presence of reticulo-endothelial cell system (RES) iron staining has been associated, in cross-sectional studies in subjects with NAFLD with several histological features of disease including:
 1. advanced fibrosis,
 2. increased apoptosis,
 3. increased ballooning and a
 4. definitive diagnosis of NASH

- Only RES iron grade, independent of any other histologic feature, as well as age, sex and duration between biopsies, predicted both:
 1. the initial development of any fibrosis in all patients and
 2. progression to NASH/borderline NASH in patients without fibrosis and having a diagnosis of “not NASH” or “not NAFL”

Liver Biopsy

Preoperative tumour biopsy does not affect the oncologic course of patients with transplantable HCC

- No
- Preoperative tumour biopsy doesn't influence the oncologic course of HCC patients eligible for LT, and there is no argument to restrict biopsy in doubtful situations.

Quantification of elastin as a predictor of clinical outcomes in cirrhosis caused by chronic hepatitis C infection.

- As hepatic fibrosis progresses, elastin content and matrix crosslinking increase. This may limit reversibility of cirrhosis

- Patients with a biopsy showing Ishak stage 5 or 6 fibrosis were selected.
- An elastin-specific antibody (Abcam ab21610) was used for quantitative immunohistochemistry.
- A digital image analysis algorithm was developed with ImageJ software (NIH)

- Elastin % area was significantly associated with the time to a clinical outcome in univariate analysis.
- We used median elastin % area as a threshold (3%) to stratify the cohort and found that those with higher elastin progressed to outcomes more quickly.

Semi-automated digital scan
technology allows fibrosis
measurement in small liver biopsy
samples that accurately correlates
with clinical outcomes

- Severity of liver fibrosis correlates with adverse clinical outcomes.
- Histopathological scoring systems mainly assess architectural abnormalities and need a minimum biopsy size ($\geq 10\text{mm}$).
- Quantification of liver collagen has the potential to use small size biopsies and improve the prediction of clinical outcomes.

- Simple digital technologies allowed measurement of CPA in previously inadequate sized liver biopsy samples.
- CPA stage was superior to Metavir stage in its ability to stratify risk of LRD, HCC and liver decompensation for CHC patients

Drug-Induced Liver Disease

The Rising Burden of Herbal and Dietary Supplement Induced Hepatotoxicity in the U. S. A.

- The Drug Induced Liver Injury Network (DILIN) prospectively assesses patients with drug induced liver injury (DILI), as well as herbal and dietary supplement (HDS) induced liver injury (HILI).

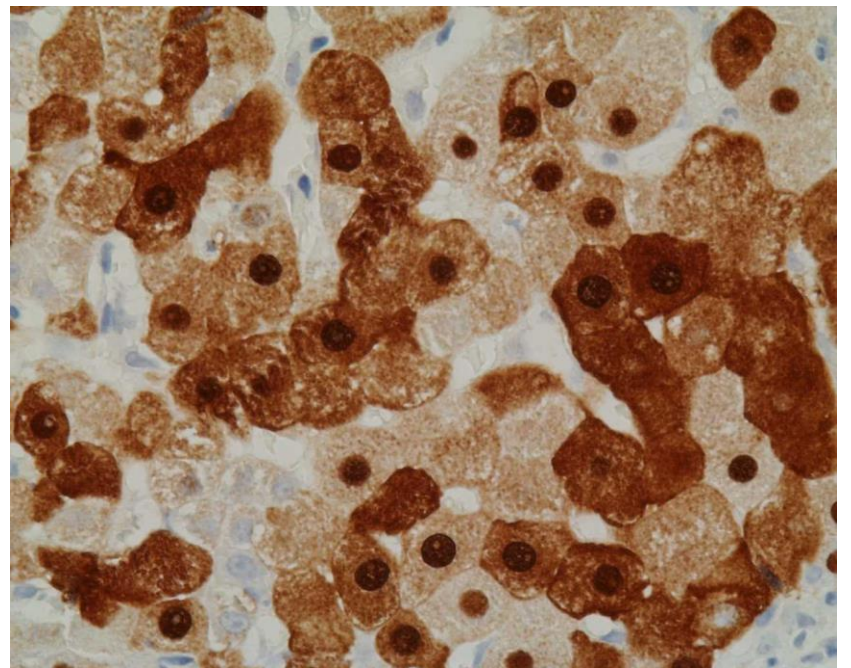
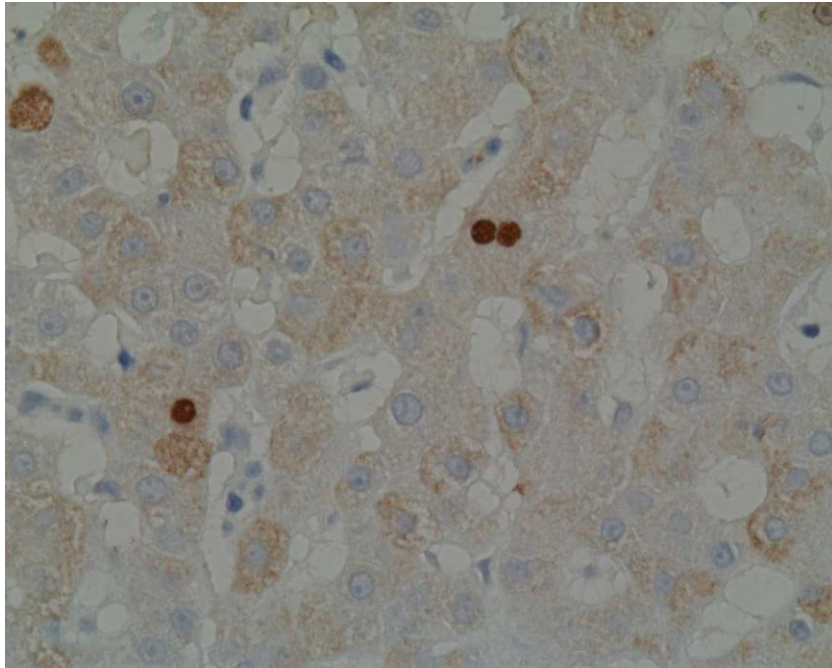
- HDS products have accounted for an increasing percent of cases of hepatotoxicity in the USA during the last 10 years.
- Body building products are the most common cause for HILI, producing a cholestatic syndrome that is rarely, if ever, fatal.
- Overall, death or transplantation occurred twice as commonly with HILI as with DILI agents, underscoring the hepatotoxic potential of some HDS products.

Viral Hepatitis

Differential Hepatitis B virus core nuclear/cytoplasmic staining is a marker of longevity of chronic infection but not disease phase.

- The cytoplasmic processing and presentation of viral antigen is a key driver of the T-cell response in Chronic Hepatitis B (CHB).
- Hepatitis B virus (HBV) core protein localises in the cell nucleus and/or cytoplasm depending on the viral life cycle and timing of infection, and thus may vary with patient age.
- We evaluated the distribution of the core protein in liver tissue in a cohort of young adults and compared it to older patients

Expression of HBcAg



HBV – Four Different Diseases

- Phase 1 – Immunotolerant
(HBeAg+ve/ normal LFTs)
- Phase 2 – Immunoactive
(HBeAg –ve/ abnormal LFTs)
- Phase 3 – Immunosurveillance
(HBeAg –ve/normal LFTs)
- Phase 4 – Immunoescape
(HBeAg –ve/abnormal LFTs)

- We demonstrate that younger patients, who have lower NI scores and higher levels of HBV DNA, typical of an immune tolerant profile, show increased nuclear HBV core protein staining.
- Conversely, older patients with longer duration of CHB infection had demonstrably higher cytoplasmic core staining.
- However, no correlation between serum ALT and HBV core staining was noted to confer immune activity.

- Immunohistochemical HBV core staining may provide additional information about longevity of CHB infection, but does not distinguish disease phase.

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Hepatitis C, a Silent Killer, Meets Its Match



Edward Linsmier for The New York Times

Arthur Rubens, 63, of Naples, Fla., was cured of hepatitis C after taking part in a clinical trial for a new drug.

By ANDREW POLLACK

Published: November 4, 2013 | 28 Comments

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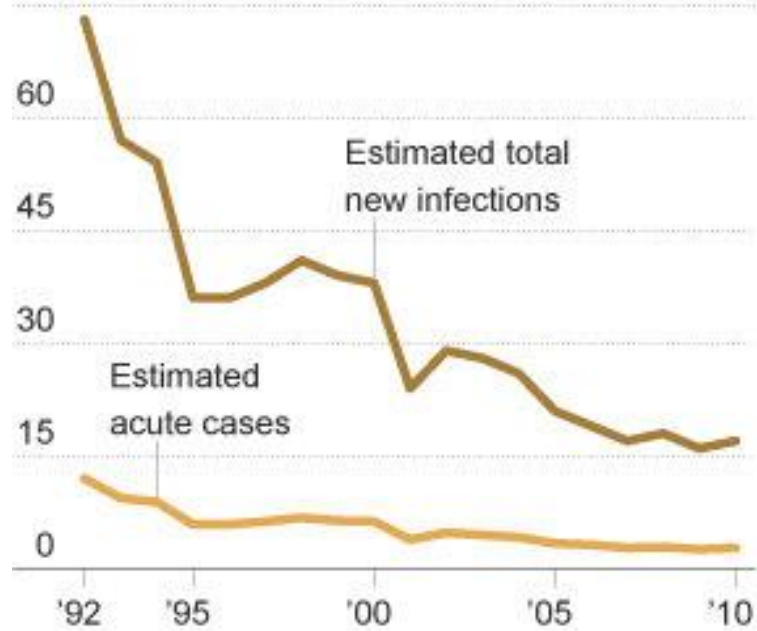
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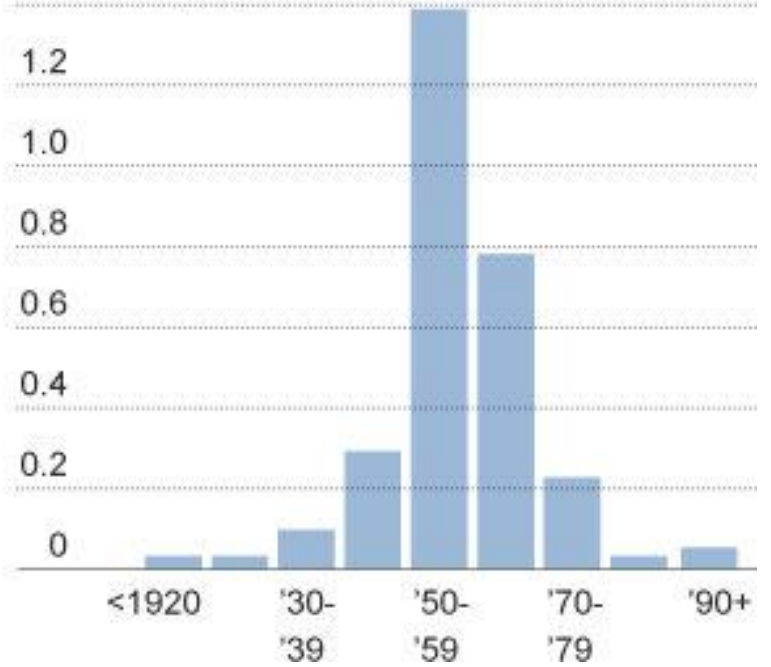
HEPATITIS C CASES

75,000 cases



CHRONIC CASES, BY BIRTH DECADE

1.4 million people*



Liver diseases in pregnancy

The effect of Pregnancy on Liver Disease

Hepatitis A : No effect

Hepatitis B: No effect

Hepatitis C: No effect. Increased obstetric cholestasis

Hepatitis E: Increased susceptibility to severe disease

AI hepatitis: May improve during pregnancy but get worse after delivery.

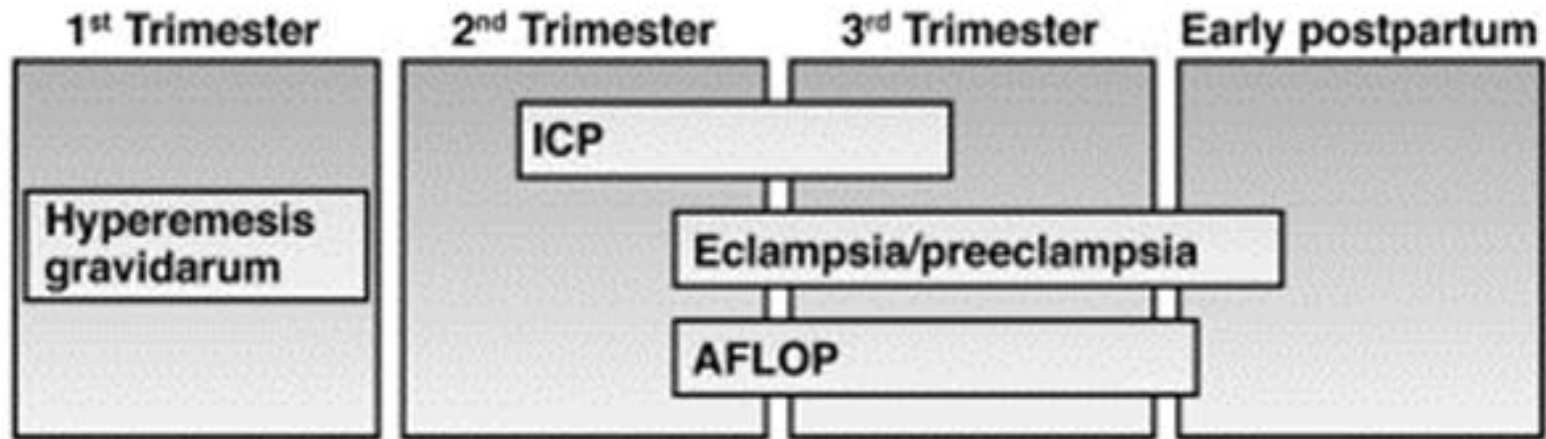
PBC: Cholestasis may worsen

Budd-Chiari: More common during pregnancy

Liver transplantation: No effect

Hepatic adenoma: Increased risk of bleeding, especially if bigger than 5 cms.

Pregnancy Associated Liver Disease

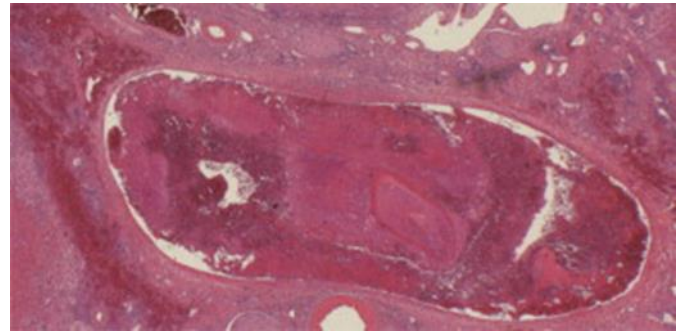
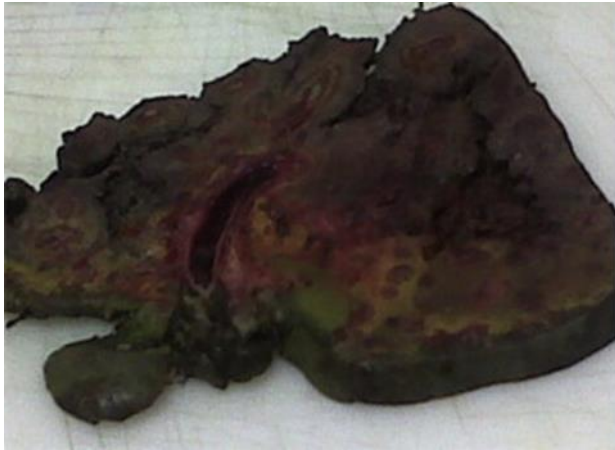


Best Pract Res Clin Gastroenterol. 2013 Aug;27(4):565-75

HELLP

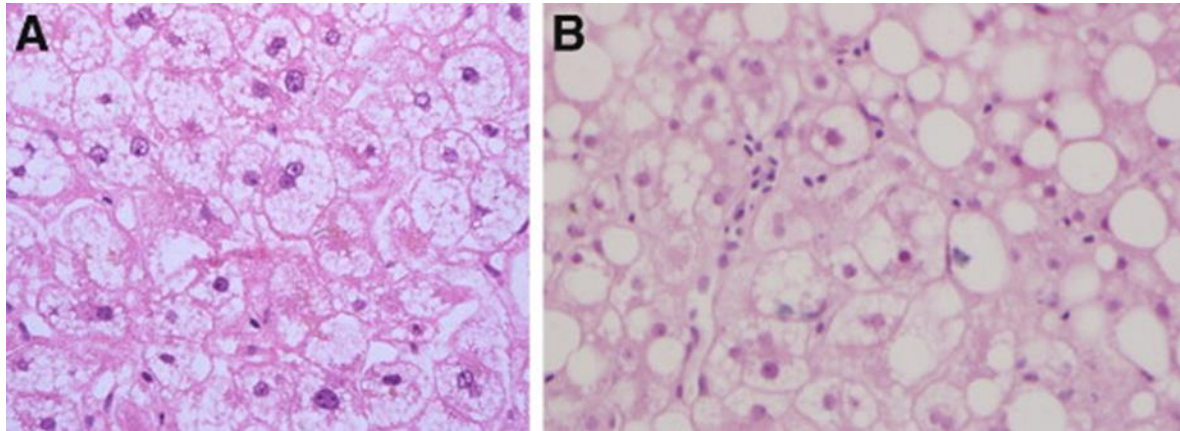
- Hemolysis, Elevated Liver enzymes, and Low Platelets.
- characterized by periportal or focal parenchymal necrosis with hyaline deposition of fibrin material in the sinusoids

HELLP



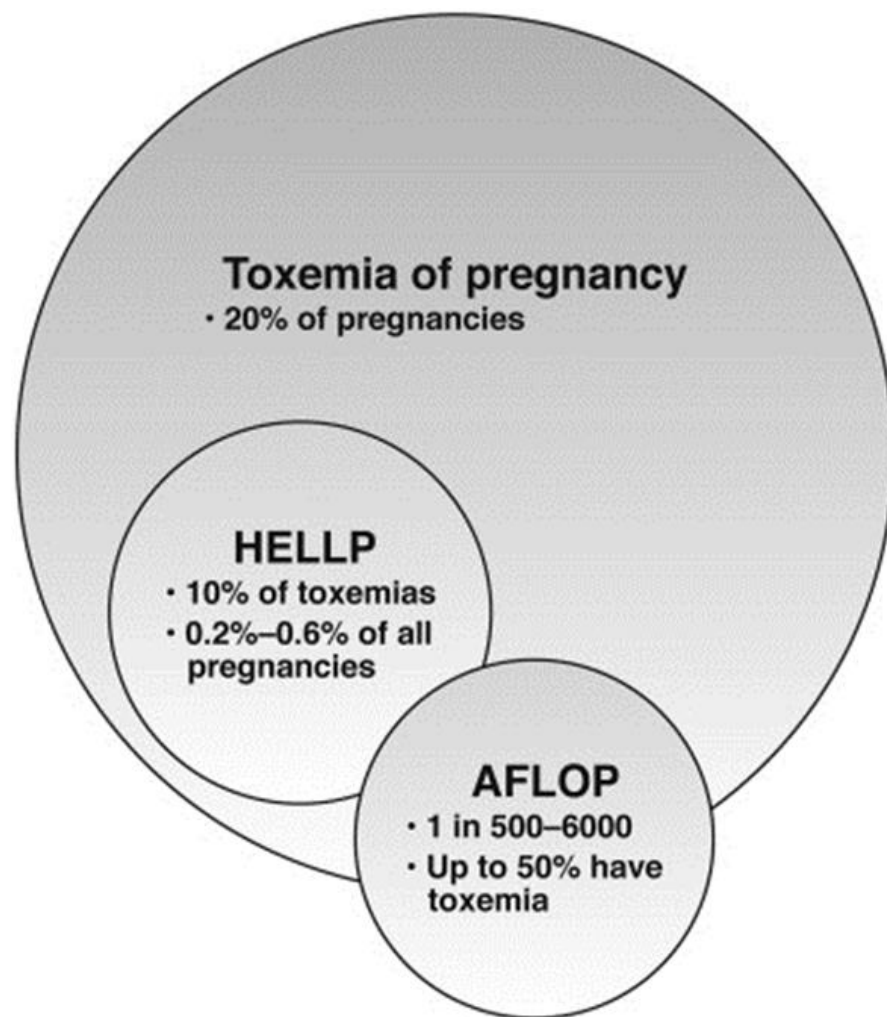
Best Pract Res Clin Gastroenterol. 2013
Aug;27(4):565-75

Acute Fatty Liver of Pregnancy



Acute Fatty Liver of Pregnancy

- The diagnosis of AFLOP is based on clinical criteria, imaging suggestive of steatosis and liver biopsy showing microvesicular fatty change.
- Although liver biopsy is the gold standard, it carries risk and should be pursued only when the diagnosis is in question and/or urgent delivery is not optimal.



Iron Overload

Traditional indications for liver biopsy

- Liver biopsy was for many years the cornerstone of the diagnosis of haemochromatosis, allowing assessment of:
 1. the degree of iron overload and
 2. fibrosis

Liver biopsy is rarely requested because:

1. Genetic testing for human haemochromatosis (HFE) mutations has proved to be very reliable in the diagnosis of haemochromatosis in Caucasian populations, and
2. The majority of patients with are now diagnosed at an early stage well before advanced fibrosis develops

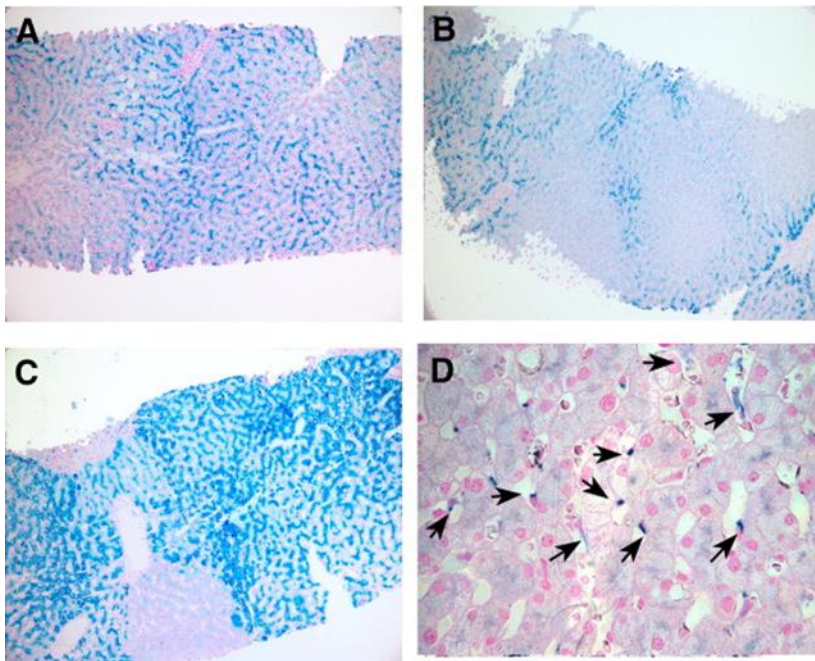
Current indications for liver biopsy

- Liver biopsy is essential for the accurate assessment of patients with non-HFE haemochromatosis and in patients who have dual pathology.
- It is also useful where there appears to be a discrepancy between HFE genotypes and iron studies (particularly in HFE heterozygotes).
- It is (still) currently the 'gold standard' for the diagnosis of fibrosis and cirrhosis.

Types of hereditary hemochromatosis

Type of HH	Genetics	Protein	Onset and phenotype
Type 1	AR	HFE	Adult, moderate
Type 2 A	AR	Hemojuvelin	Child, severe
Type 2 B	AR	Hepcidin	Child, severe
Type 3	AR	Transferrin rec.	Young adult moderate
Type 4	AD	Ferroportin	Adult, moderate

AR: autosomal recessive; AD: autosomal dominant



- (A) HFE-related hemochromatosis is characterized by purely parenchymal iron overload that is heaviest in the periportal areas and less intense in the centrolobular areas.
- (B) TfR2-related hemochromatosis. The histopathologic picture is identical to HFE-related hemochromatosis with iron accumulation in periportal parenchymal cells.
- (C) HJV-related juvenile-onset hemochromatosis: massive pan-lobular parenchymal iron overload.
- (D) Classic ferroportin disease. Unlike the previous 3 cases, this liver displays iron overload that predominantly affects the Kupffer cells (arrows).

The (AASLD) Liver Meeting 2013 Washington

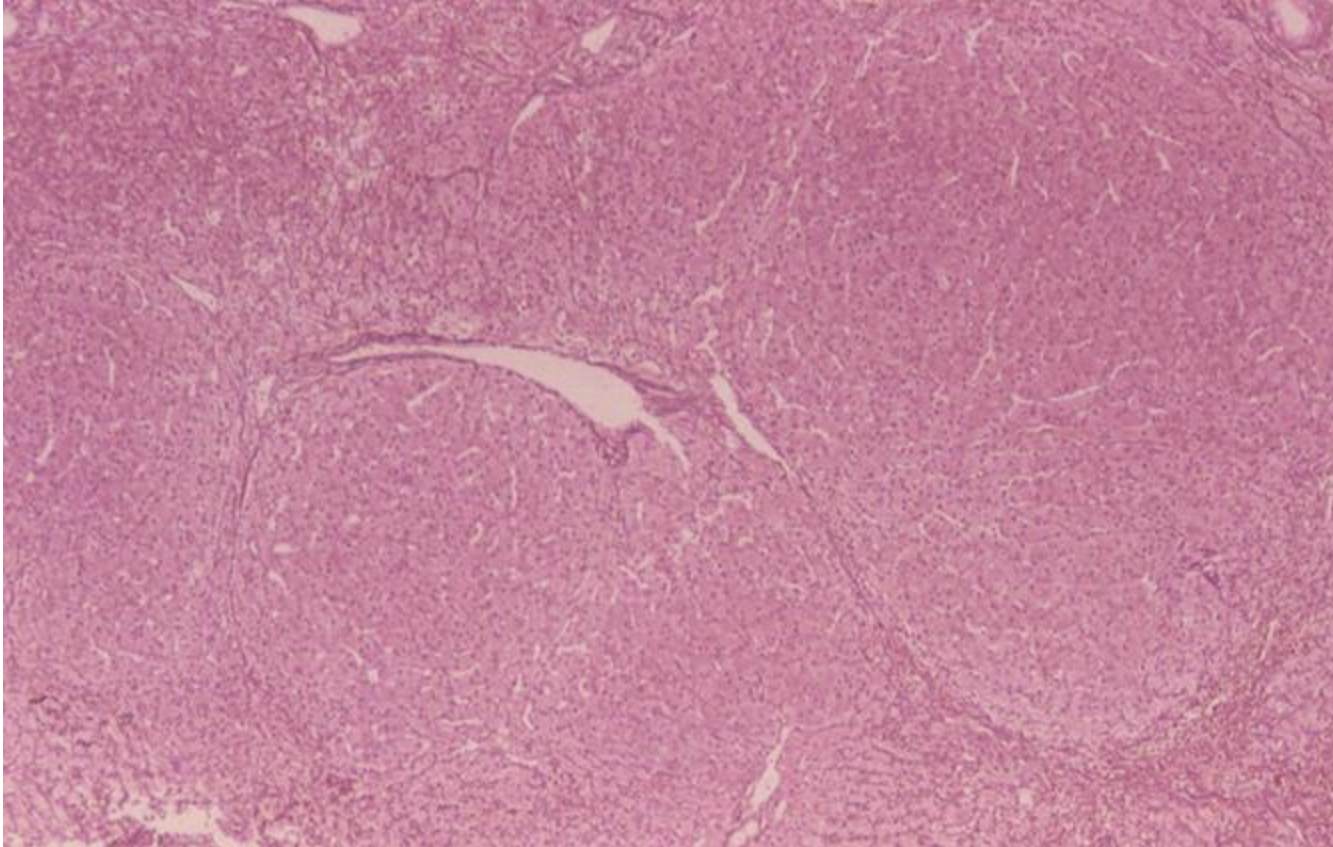
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Vascular Disease

Nodular regenerative hyperplasia: a new subclassification based on the distribution of hepatic microvascular obstruction and arterialization

Nodular regenerative hyperplasia



- Nodular regenerative hyperplasia (NRH) is defined histologically by small regenerative nodules of hepatocytes separated by regions of atrophy with minimal fibrosis.
- The prevailing hypothesis is that NRH is caused by microvascular obstruction, especially obstruction of portal veins (OPV), with secondary heterogeneity of blood supply (Wanless 1980, Verheij 2013)

- Recently, NRH in the absence of OPV has been described in patients with oxaliplatin-induced sinusoidal injury (SOS-VOD)(Rubbia-Brant 2010) and in animal models with knockout of genes involved in VEGF expression (Dill 2012).

- Samples were examined for distribution of hyperplasia and atrophy/congestion in relation to portal tracts and hepatic veins. Obliteration of portal and hepatic veins (HV) and sinusoidal endothelial cell CD34 were graded.
- Occluded portal veins and sinusoidal CD34 expression correlate, defining the state we refer to as “arterialization”, where arterial supply replaces portal vein supply at the acinar level.

We identified 4 patterns of NRH:

1. NRH-1 has zone 1 atrophy without arterialization.
2. NRH-2 has zone 1 and 2 arterialization, OPV, and atrophy in zone 3.
3. NRH-3 has obliteration of small portal and hepatic veins, approximation of portal tracts and hepatic veins, and arterialization of entire acini that are compressed between non-arterialized nodules.
4. NRH-4 is congested without arterialization.

Clinical Correlates

- NRH-1 is associated with PV thrombosis and early biliary disease that cause arterial hyperemia without arterIALIZATION.
- NRH-2, associated with primary portal tract inflammation, develops as OPV and arterIALIZATION is established.
- NRH-3 develops in a setting of chronic hepatitis with regressed cirrhosis, when obstructed PVs and hepatic veins remain after resorption of fibrosis.
- NRH-4 is caused by primary outflow obstruction (congestive heart failure or HV thrombosis).

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