



AASLD: Boston 2014

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AASLD

By AASLD

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Description

Vision To Prevent and Cure Liver Disease Mission To advance and disseminate the science and practice of hepatology, and to promote liver health and quality patient care AASLD is the leading organization of scientists and healthcare professionals committed to preventing and curing liver disease. AASLD was founded in 1950 by a small group of leading liver specialists (including Hans Popper, Leon Schiff, Fred Hoffbauer, Cecil Watson, Jesse Bollman, and Sheila Sherlock, to name a few) to bring together those who had contributed to the field of hepatology. AASLD has grown to an international society responsible for all aspects of hepatology, and our annual meeting, The Liver Meeting®, has grown in attendance from 12 to over 9,500 physicians, surgeons, researchers, and allied health professionals from around the world. Hepatology has been recognized as a discipline only in the last few decades, and AASLD played a seminal and unifying role in focusing interest on hepatological problems, as well as the founding of other hepatological societies. Our three monthly journals, HEPATOLOGY, Liver Transplantation, and Clinical Liver Disease provide the latest research findings for hepatology and surgery of the liver. AASLD's membership includes ALL professionals dedicated to hepatobiliary discoveries and patient care. Mentoring, the sharing of knowledge, and dedication to professional growth and development are among the core values of AASLD and its members.

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Autoimmune hepatitis

31

Does “genuine” acute autoimmune hepatitis have a better prognosis?

32

Patients with Autoimmune Hepatitis and Advanced Disease have Less Biochemical Response and Worse Outcomes

“AIH diagnosis was based on international criteria by International Autoimmune Hepatitis Group for chronic AIH patients,
<http://www.aasld.org/practiceguidelines/Documents/AIH2010.pdf>

and criteria described by Stravitz et al was used for patients with findings compatible with acute hepatitis.”

[Hepatology. Feb 2011; 53\(2\): 517–526.](#)

The histological diagnosis of acute liver failure due to autoimmune hepatitis was based upon 4 features suggestive of an autoimmune pathogenesis:

- distinctive patterns of massive hepatic necrosis (42%),
- presence of lymphoid follicles (32%),
- a plasma cell-enriched inflammatory infiltrate (63%), and
- central perivenulitis (65%)

Although most autoimmune hepatitis patients are classified at diagnosis as having chronic hepatitis or cirrhosis, acute clinical presentation is not rare.

However, this type of acute clinical presentation may represent “genuine” acute AIH or acute-on-chronic AIH.

Advanced disease was defined by biopsy (Ludwig stage III or IV) or by clinical, endoscopic or radiographic findings consistent with cirrhosis.

“Genuine” acute AIH was not a frequent finding (7,5% of all acute presentation cases).

“Genuine” acute AIH presented with more preserved liver function tests, suggesting that most cases presenting with loss of function are acute-on chronic AIH.

Lastly, “genuine” acute AIH revealed a better biochemical response to treatment.

1059

Histological Changes That Reliably
Differentiate Autoimmune
Hepatitis from Drug-Induced
Autoimmune Hepatitis:
Important Role of Liver Biopsy

Thirteen cases of AIH-like DILI were identified:
10 female and 3 male, mean age of 50 years

Medication history revealed use of drugs:

- herbal medications (3 cases),
- infliximab(1),
- fenofibrate(1),
- statins(1),
- INH(1) ,
- highly active antiretroviral therapy(1),
- phenobarbital(1),
- moxifloxacin(1),
- azathioprine(1),
- sertraline(1) and
- polypharmacy(1).

Of all the features assessed:

- venulitis, either portal or central or both,
- presence of ceroid macrophages,
- lobular disarray and
- panacinar necrosis and
- ballooning degeneration

were much more common in AIH-like DILI

Presence and number of plasma cells, confluent necrosis, and interface hepatitis, all classic histological features of AIH, were not significantly different between the two groups.

330

Prevalence, Natural History And
Outcome Of Overlap
Syndrome Versus Autoimmune
Hepatitis In The Indian
Continent

The Paris Criteria

Chazouilleres O *et al.* Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy *Hepatology* 1998;28:296-301

Patients must meet 2 of 3 criteria for both entities to qualify as overlap

PBC

1. Florid duct lesions
2. AMA
3. Alkaline phosphatase >2x or GGT >5x

AIH

1. Moderate to severe interface hepatitis
2. IgG >2x or SMA positive
3. ALT >5x

The diagnosis was confirmed using simplified AIH score and Paris criteria for AIH and OS respectively.

Of the 7686 patients analysed:

3.3% patients were found to fulfil the criteria for AIH or OS.

Out of this, 2/3rd were AIH and 1/3rd were OS.

Patients with OS are older and present more often as cirrhosis with decompensation with a poor prognosis.

We propose that high suspicion in diagnosis and lower threshold in performing liver biopsy in seemingly non-classical AIH would yield early diagnosis and could improve survival benefit in this group.

NASH

The prognostic relevance of liver histology features in NAFLD

To determine the long-term prognostic relevance of liver histological features in patients with NAFLD.

A cohort of 619 patients with NAFLD confirmed by liver biopsy were included. Liver biopsies were scored by a single liver pathologist (Dr. David Kleiner).

Fibrosis stage but no other histological features or presence of NASH is independently associated with overall death/liver transplantation and liver related events in patients with NAFLD.

185

Pediatric Nonalcoholic Fatty
Liver Disease:

Histological Feature Changes
Over Time in Paired Biopsies
from the NASH CRN

Histopathology of pediatric nonalcoholic fatty liver disease

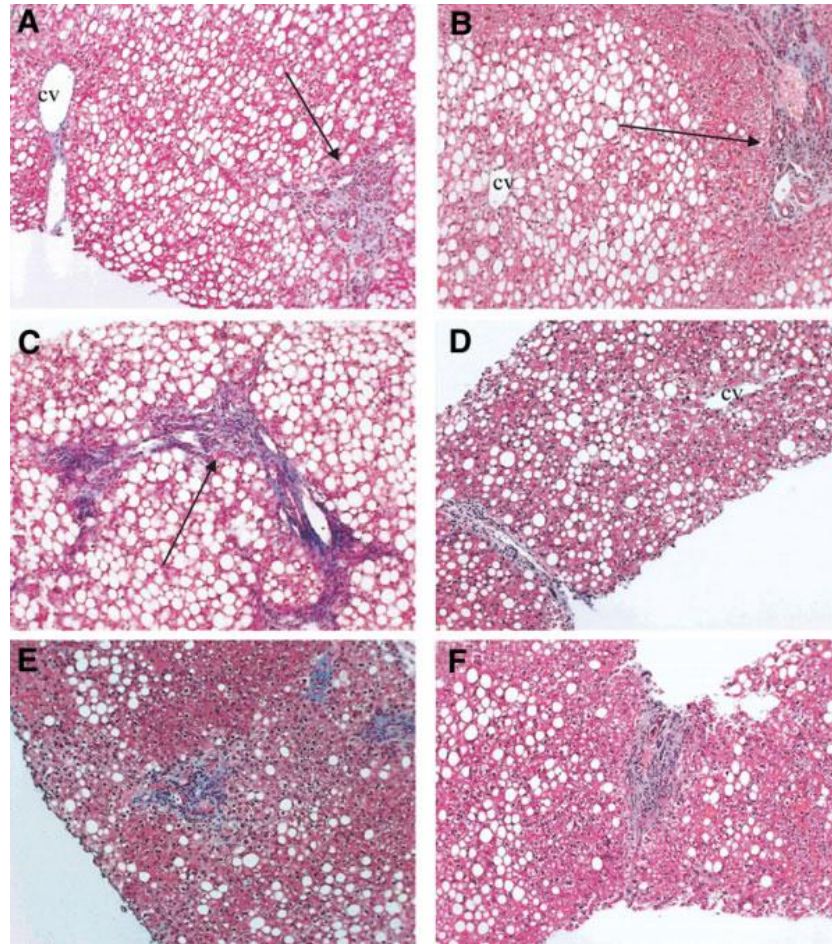
Agglomerative hierarchical cluster analysis demonstrated two different forms of steatohepatitis:

Type 1: steatosis, ballooning degeneration, and perisinusoidal fibrosis

Type 2: steatosis, portal inflammation, and portal fibrosis.

HEPATOLOGY 2005;42:641-649.

Histopathology of pediatric nonalcoholic fatty liver disease



Little is known about changes in liver histology over time in children with NAFLD.

Children (n=102) with two sets of biopsies separated by 1-11 years (median 2.2y) from either the NASH CRN TONIC trial placebo group (Lavine et al, JAMA, 2011) or the NAFLD Database were included.

Biopsies were reviewed centrally in a masked fashion by the NASH CRN Pathology Committee.

Fibrosis patterns changed:

The portal predominant (1c) fibrosis in 30.4% in the first biopsy decreased to 15.7% in the last;

“no fibrosis” increased from 28.4% to 40.2% and

a smaller increase was seen in bridging fibrosis from 12.8% to 17.7%.

Significant decreases in steatosis and increases in ballooning were also noted.

In subgroup analyses, girls showed more overall feature changes than boys, as did children who were older at first biopsy than those who were younger at first biopsy.

The changes in fibrosis and diagnostic categories represent changes in patterns of injury, from those of “pediatric” to those of “adult” NASH.

The Severity of Steatosis
Overestimates Liver Fibrosis
Diagnosis by Liver Stiffness
Measurement in Patients
with Nonalcoholic Fatty Liver Disease

In patients with NAFLD, the presence of severe steatosis lead to an overestimation of liver fibrosis by LSM.

811

Natural history of NAFLD:
A study of 108 patients with
paired liver biopsies

- Contrary to current dogma, this study suggests that NAFL is not entirely benign and has the
- potential to progress to NASH and clinically significant fibrosis, particularly if patients develop diabetes

In general it is thought that fibrosis progression in patients with “NAFL” is uncommon, whereas non-alcoholic steatohepatitis more frequently progresses.

Patients with 2 liver biopsies >1 year apart were identified.
75% patients had NASH and 25 % patients had NAFL.

Overall:

- 42% patients had progression of fibrosis,
- 40% had no change in fibrosis,
- 18% had fibrosis regression.

The mean rate of fibrosis was 0.08 ± 0.25 stages/ year overall, increasing to 0.29 ± 0.24 stages/year in progressors.

Importantly, no significant difference in the proportion exhibiting fibrosis progression was found between those with NAFL or NASH at index biopsy 37% vs. 43%.

44% with NAFL at baseline progressed to NASH at follow-up biopsy
8% with NASH regressed to NAFL

Clinical and Histologic Differences Between HIV-associated NAFLD and Primary NAFLD: A Case- control Study

HIV infected patients are more likely to have higher NAS scores and increased presence of nonalcoholic steatohepatitis than patients with primary NAFLD who have similar age, sex, BMI, and metabolic risk factors.

213

Effects of bariatric surgery on severe liver injury
in morbid obese patients with proven NASH:
a prospective study

Non Alcoholic Steatohepatitis (NASH) is observed in around 10% of severe obese patients.

The main surgical procedures in 109 NASH patients were 70 gastric bypass and 32 gastric band

At 1 year, 82/109 patients had paired liver biopsies

Patients were significantly improved in terms of BMI

NASH disappeared in 85% of cases and all histological features improved

Patients with persistent NASH had higher baseline IR index, NASH grade and fibrosis stage

Alcoholic Liver Disease

1234

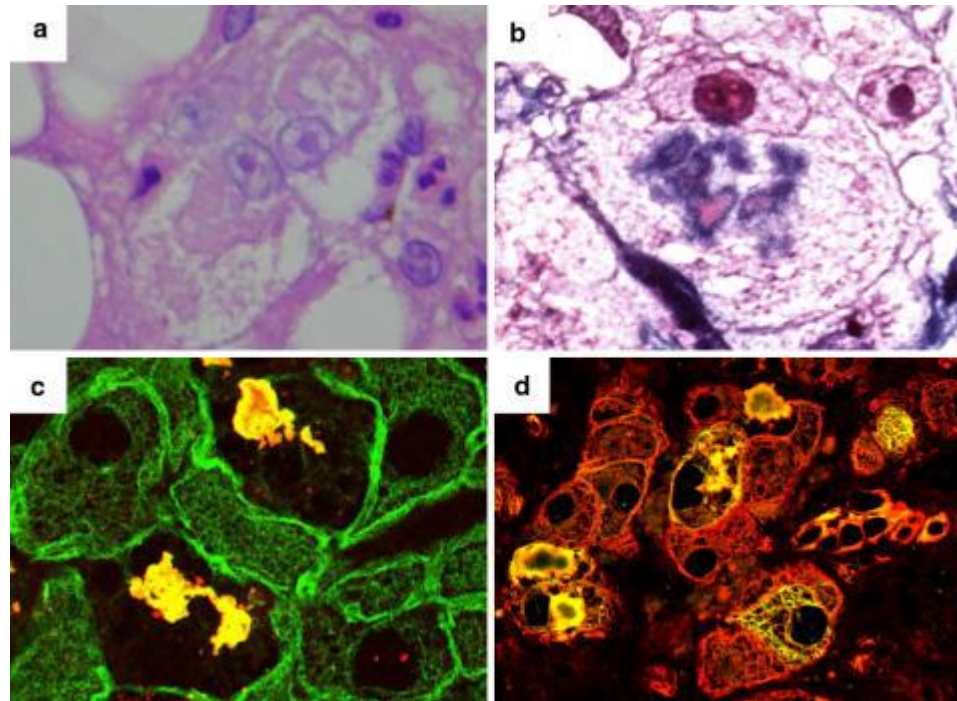
Hepatic cell proliferation and outcome in
alcoholic hepatitis: histology, gene expression
and effect of stem cell therapy

Higher liver macrophage expansion,
increased proliferative hepatocyte,
increased liver progenitor cell number as well as
up-regulation of cell proliferation related genes
area associated with a favourable outcome

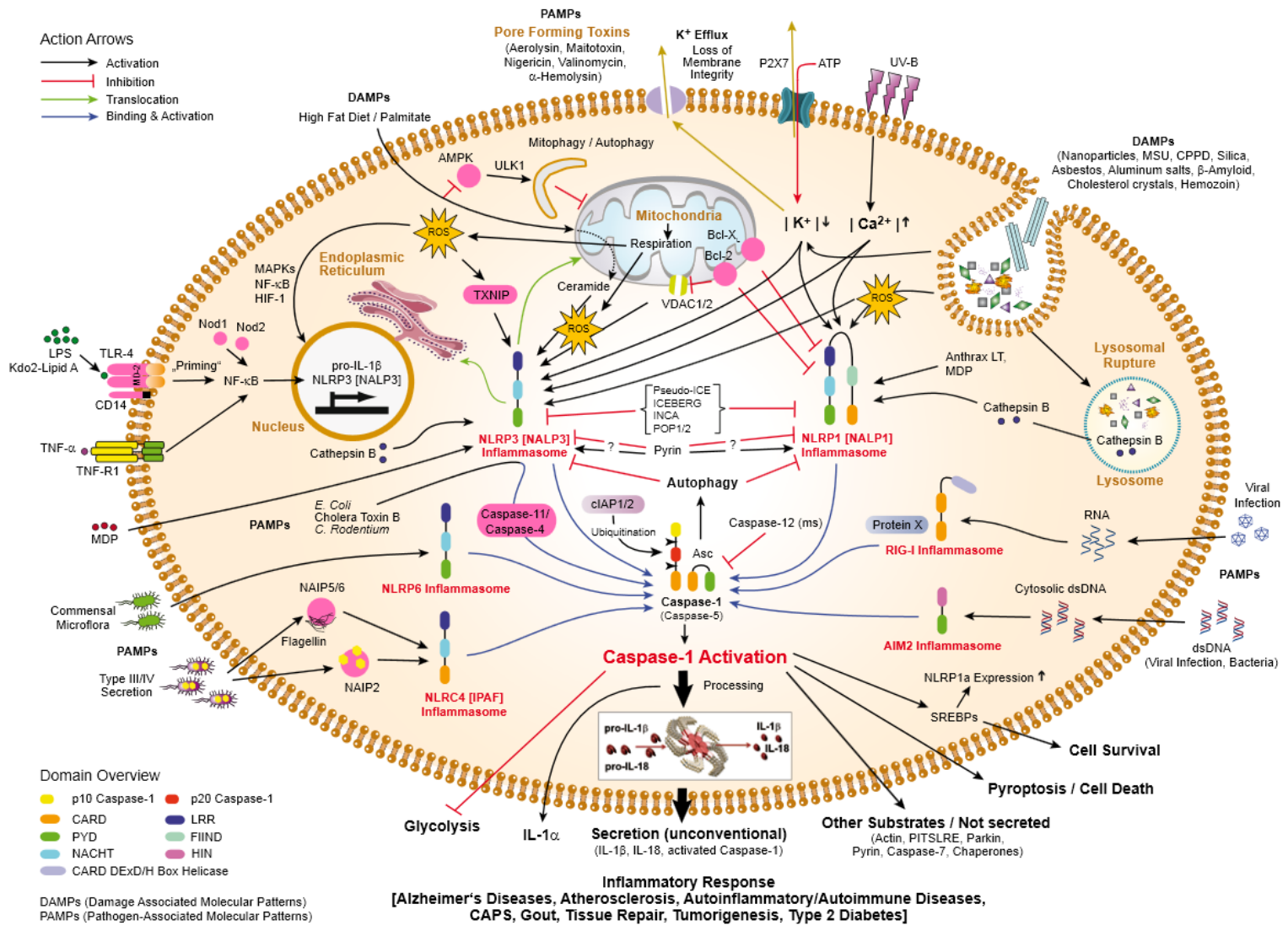
1223

The inflammasome in alcoholic
hepatitis: its relationship
with Mallory-Denk body formation

Mallory-Denk Bodies



- (a) Hematoxylin and eosin stained
- (b) Chromotrope aniline blue staining
- (c) Immunofluorescence using antibodies against K8/K18
- (d) Immunofluorescence using antibodies against p62

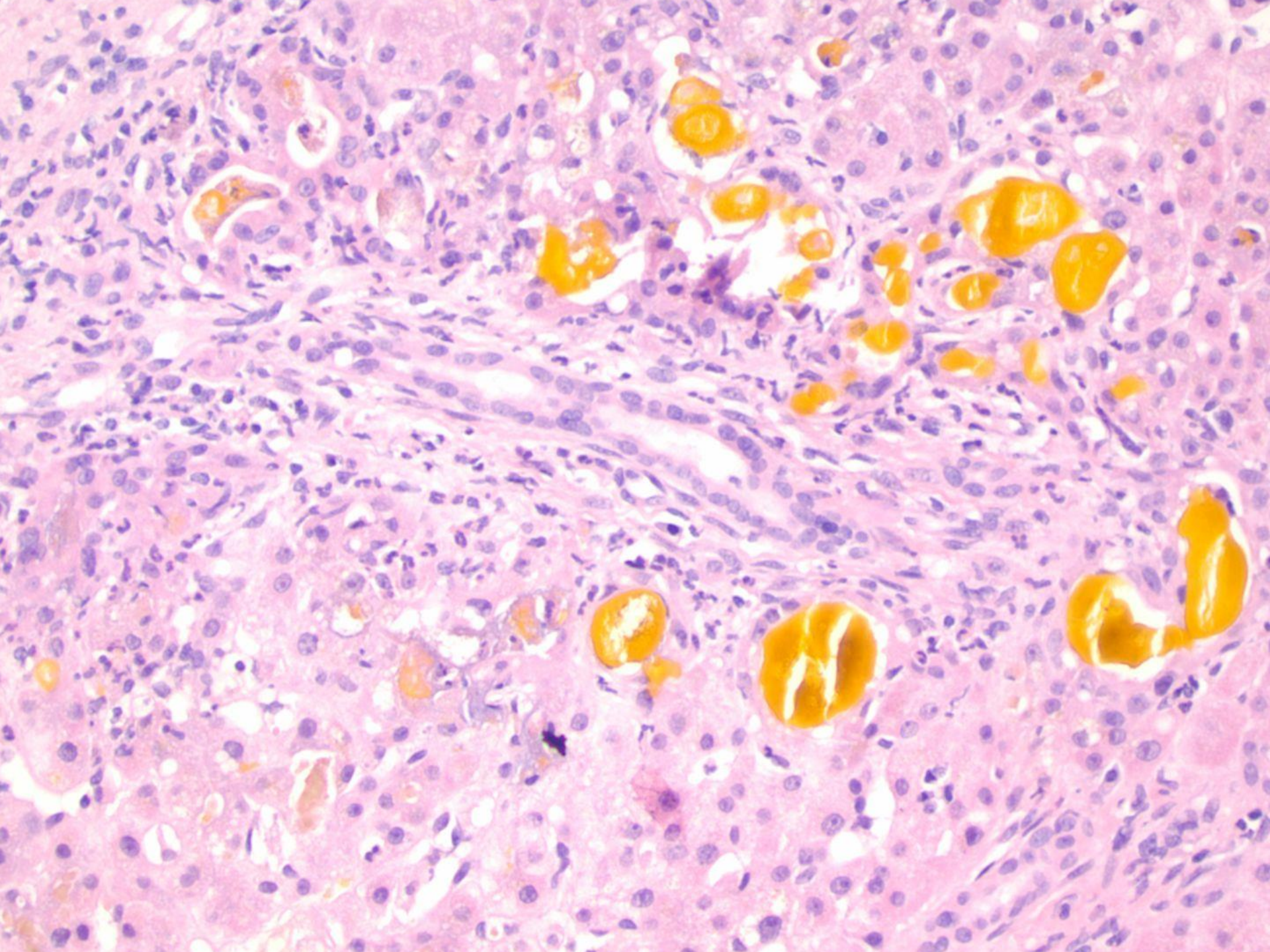


There was a trend that NOD1, ASC, NLRP3, NAIP, MAVS, and IL-18 overexpression correlated with the number of MDB found focally.

Our results demonstrate the activation of inflammasome in alcoholic hepatitis and suggest that MDB could be an indicator of the extent of inflammasome activation.

1196

Ductular bilirubinostasis predicts
the evolution to acute on-
chronic liver failure in patients
suspected with severe
alcoholic steatohepatitis



Current guidelines consider a liver biopsy optional to diagnose severe alcoholic steatohepatitis and based on clinical criteria patients are initiated on corticosteroids.

However, in patients with acute decompensation of alcoholic cirrhosis, this diagnosis may be challenging since it clinically resembles acute on- chronic liver failure.

We recently identified ductular bilirubinostasis a histological marker of endotoxemia, as an early risk factor for acute on-chronic liver failure

One third of patients suspected with severe alcoholic steatohepatitis were misdiagnosed without histology.

Ductular bilirubinostasis on early liver biopsy predicts evolution to ACLF and is associated with poor outcome.

Patients with both severe alcoholic hepatitis and ductular bilirubinostasis benefited most from corticosteroid treatment.

Biliary Tract Disease

279

The Fraction of Bile Ducts Lost in
Portal Areas Correlates
with Degree of Fibrosis and
Alkaline Phosphatase Levels
in Patients with Primary Biliary
Cirrhosis

Inflammation and fibrosis were evaluated using the Ishak scoring system.

Semi-quantitative scoring (0-3) was used to evaluate ductular reaction and aberrant hepatocyte staining with keratin 7 (K7).

The bile duct loss fraction (BDLF) was calculated by $[1 - (\text{number of portal areas with ducts} / \text{total number of portal areas identified})]$.

“BDLF reflects the percentage of bile duct loss in portal tracts in PBC. ‘

It correlates with alkaline phosphatase and degree of fibrosis.

This finding may allow for development of a more rigorous and clinically predictive histological scoring system for PBC.

296

Noninvasive testing are poor surrogate markers for fibrosis staging and liver-related outcomes in patients with primary biliary cirrhosis who do not respond to ursodeoxycholic acid

Survival in patients with PBC, even in cirrhotic patients who do not respond to UDCA, is in excess of 10-15 years, which emphasizes the challenge in using clinical endpoints as outcome measures in clinical trials.

Non-invasive testing does not accurately predict the presence of fibrosis in patients with PBC.

297

Applicability and Prognostic Value
of Histologic Scoring
Systems in Primary Sclerosing
Cholangitis

The aim of this study was to assess if three scoring systems designed primarily to assess disease severity in

- chronic hepatitis (Ishak 1995) or
- PBC (Ludwig 1978, Nakanuma 2010) could also be used for grading and/or staging PSC.

Nakanuma

Scoring for the staging of PBC:

A. Fibrosis

B. Bile duct loss

C. Deposition of orcein-positive granules

Grading of the necro-inflammatory activity of PBCL

A. CA (cholangitis activity)

B. HA (hepatitis activity)

Human Pathol. 2013 Jun;44(6):1107-17.

Grading was scored using the Nakanuma system (cholangitis activity, hepatitis activity) and the Ishak system.

Staging was scored using the Nakanuma system (fibrosis, bile duct loss, copper binding protein deposition) the Ishak system and the Ludwig system.

The Nakanuma, Ishak and Ludwig scoring systems are applicable to PSC liver biopsies.

A significant association was shown between Ishak grade and time to liver transplantation.

Staging of PSC using all three systems is highly associated with transplant-free survival.

Our observations suggest that these staging systems may be useful in the evaluation of disease severity and as response parameters to therapeutic interventions in PSC patients.

320

Secondary Sclerosing Cholangitis
Following Major Burn
Injury

Ductopaenia

- **PBC or PSC**
- Sarcoidosis
- Drugs (vanishing bile duct syndrome; bile duct sclerosis due to 5-FU infusions)
- Hodgkin's disease
- Allograft chronic rejection
- Graft vs Host disease
- Genetic abnormalities (Turner, trisomies)
- Ischemic cholangiopathy
- Idiopathic

- Secondary sclerosing cholangitis in critically ill patients (SSC-CIP) is a relatively new previously unrecognized entity which may lead to severe biliary disease with rapid progression to cirrhosis.
- It is possibly mediated by ischemic damage of the biliary tree, followed by bacterial colonization and progressive destruction of biliary ducts.

- SSC-CIP was diagnosed in 6 consecutive patients hospitalized due to major burn injuries.
- The diagnosis of SSC-CIP was confirmed by ERCP in one patient, MRCP in 4 patients and in 2 patients by a liver biopsy.
- Two patients developed multiple hepatic abscesses that were drained and grew hospital acquired multiple resistant bacteria.
- Two patients underwent orthotopic liver transplantation.

Viral Hepatitis

450

Fibrosis regression in hepatitis C
patients with cirrhosis:
Ishak fibrosis score and CPA pre
treatment predict
regression post sustained
virological response

57.7% of patients demonstrated fibrosis regression,
12.5% presumed fibrosis resolution and
42.3% no fibrosis regression.

Patients with presumed fibrosis regression had a significantly lower mean CPA (9.6 vs 18.0) and mean % alpha-smooth muscle actin expression (10.86%) on pre-treatment biopsies than patients with no presumed regression.

Ishak fibrosis score 5 was significantly more likely to result in presumed fibrosis regression (93.3% vs 39.3%) compared to Ishak score 6.

In HCV cirrhotics with a SVR, pre-treatment Ishak fibrosis stage, CPA and % alpha-smooth muscle actin expression predict fibrosis regression.

These parameters may be used to stratify patients at risk of remaining cirrhotic post SVR, in order to prioritise patients for therapy with the new interferon free regimens.

Computer-assisted image analysis of fibrosis on liver biopsy

Liver fibrosis participates to the development of portal hypertension (PHT).

Hepatic venous pressure gradient (HVPG) evaluates PHT in clinical practice.

We aimed to generate a simple cut-off value of liver fibrosis density that would be associated with several clinical, biological and histological endpoints.

In patients with advanced chronic liver disease, % of fibrosis correlates with PHT, elastometry, and features of liver injury.

We determined a threshold of 4.8% useful to identify patients with particular clinical, biological and histological parameters that are commonly measured in clinical practice.

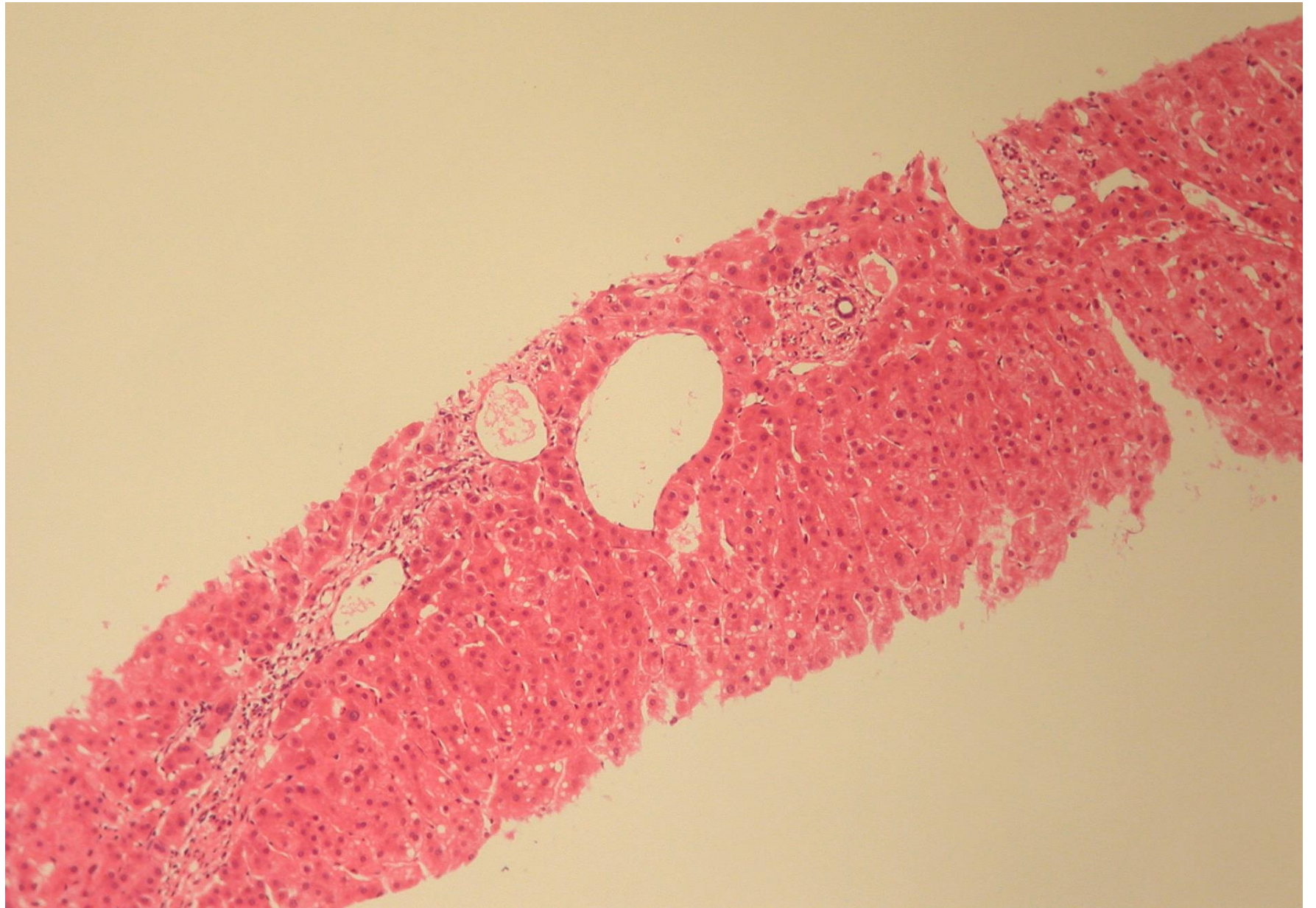
Can expression of interferon-stimulated genes in pre-treatment liver biopsy of chronic hepatitis B patients predict therapy response and long-term HBV infection outcome?

High viperin and low CXCL10 mRNA expression in pre-treatment liver biopsy predicted

- therapy response and
- 10 years follow-up outcomes

post-IFN based therapy in immunotolerant CHB patients

Vascular Disease



375

High Prevalence of Nodular
Regenerative Hyperplasia in
Patients with End-Stage Heart
Failure and Outcomes after Cardiac
Transplantation

Nodular regenerative hyperplasia (NRH) has an estimated prevalence of 2.56% seen in autopsies.

At a large transplant center we have noted a high prevalence of NRH in patients with end-stage heart failure NRH was found in 23 of 65 (35%) patients with end-stage heart failure on pre-transplant liver biopsy.

NRH is not associated with worse 1-year or long term post-transplant survival. NRH in the absence of significant fibrosis or cirrhosis should not be considered a contraindication to OHT.

2008

Obliterative Portal Venopathy in
subjects without portal
hypertension:
an unknown planet

Obliterative portal venopathy represents a spectrum of histological lesions traditionally associated to non-cirrhotic portal hypertension (NCPH).

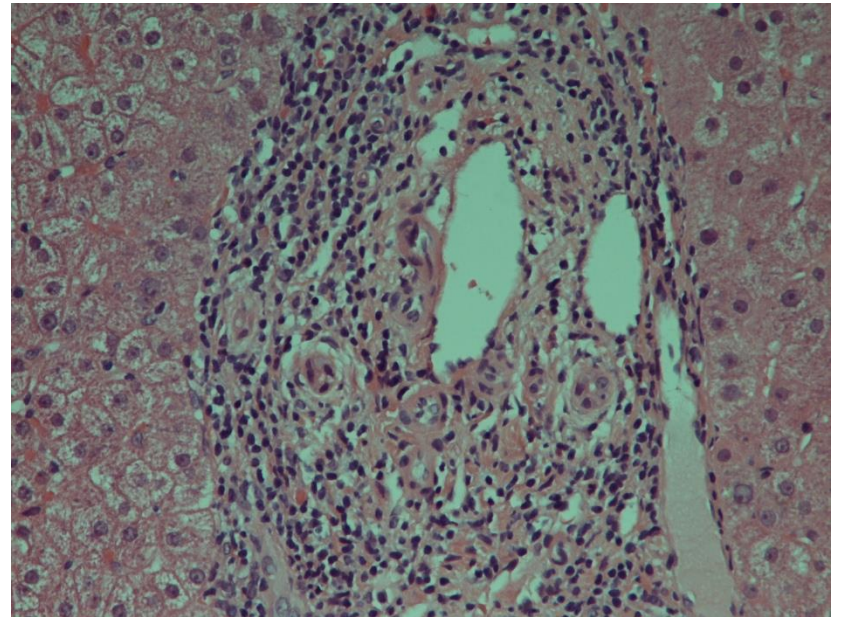
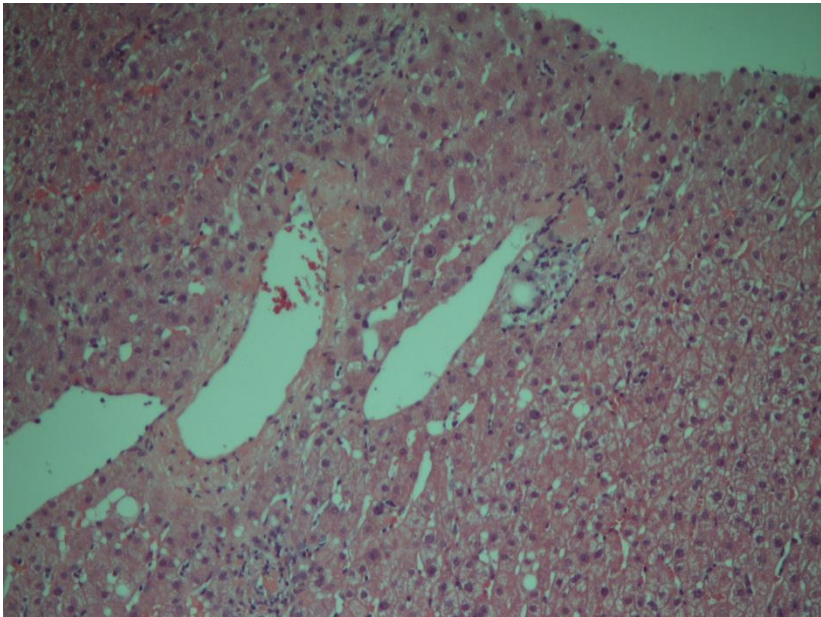
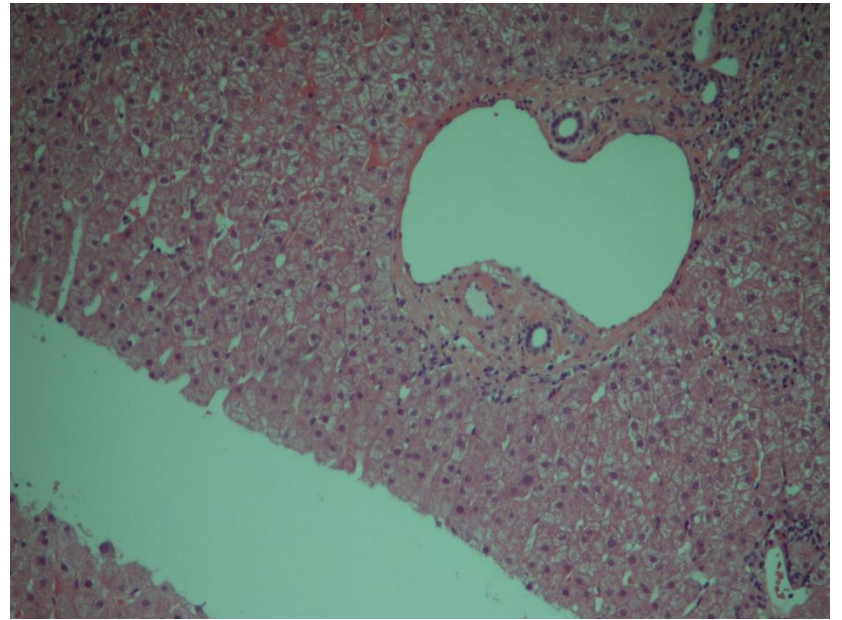
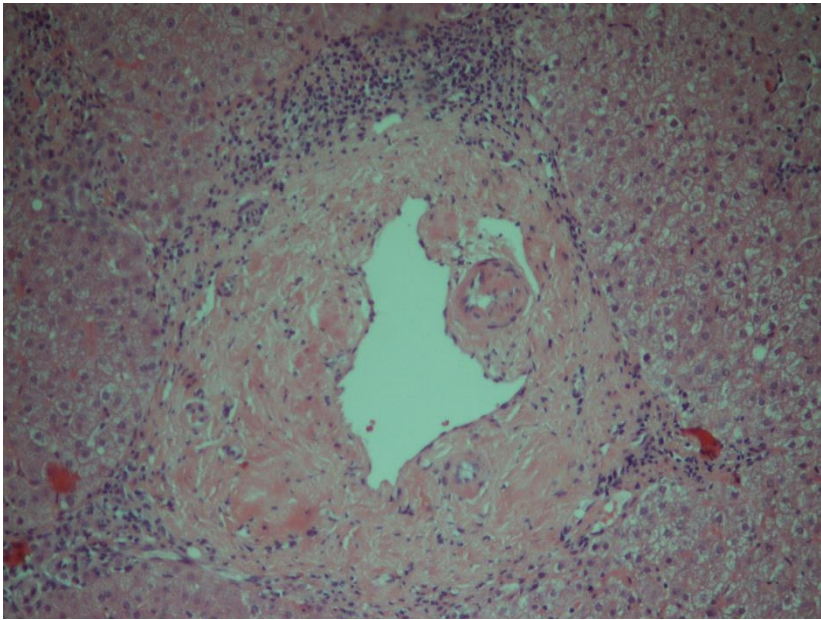
This retrospective study aimed to assess the prevalence of obliterative portal venopathy in patients without clinical signs of portal hypertension who underwent liver biopsy for long-lasting abnormal liver function tests of unknown etiology.

482 consecutive biopsies were reviewed to evaluate the presence of portal vessel abnormalities belonging to the spectrum of obliterative portal venopathy (i.e. phlebosclerosis, aberrant portal vessels, portal vessel fragmentation, intrahepatic portal vein thrombosis).

In positive biopsies, other lesions usually reported in NCPH were also assessed, (i.e. portal fibrosis/inflammation, incomplete fibrous septa, sinusoidal dilatation/fibrosis, abnormal central veins, lobular necrosis/inflammation, and nodular regenerative hyperplasia).

[Am J Surg Pathol.](#) 2005 Oct;29(10):1382-8.

Hepatology. 1994;20:302–308



Screening for serum autoantibodies turned positive in 49% while 5.9% pro-thrombotic condition (factor V Leiden mutation, MGUS , protein C alteration.

No cases were associated with HIV-infection or exposure to vascular injury-inducing toxins.

In 13.5% of cases, obliterative portal venopathy was associated with systemic and/or organ-specific immune disorders

Aberrant portal veins and portal vein fragmentation were the most prevalent vascular changes (96.9% and 74%), while phlebosclerosis and portal vein thrombosis were only rarely reported (9.4% and 1.1%).

Nodular regenerative hyperplasia was detected in 9.4% of cases.

Among the other evaluated lesions, sinusoidal dilatation and portal fibrosis were most frequently documented (65.6% and 60.4%, respectively).

Obliterative portal venopathy changes are fairly common among patients with unexplained LFT abnormalities, even in the absence of PH.

It was frequently associated with histological and/or clinical findings known to occur in NCPH, suggesting that the patients may be in a early pre-clinical phase of NCPH.

This condition is probably largely underestimated in the clinical practice.

Others

1056

Characteristics of Efavirenz drug induced liver injury

50 patients

3 histological patterns of injury were identified:

- submassive necrosis 32%,
- nonspecific hepatitis 32% and
- mixed cholestasis-hepatitis 36%

submassive necrosis was significantly associated with a CD4>200 and younger age

mixed cholestasis-hepatitis was associated with a lower CD4 count

Hepatic sarcoidosis: To treat or not to treat?

Of 55 patients who had a liver biopsy:

- 55% had no fibrosis,
- 25% had stage 1-2, and
- 16% had stage 3-4.

13 patients (11 treated) had paired liver biopsies over a 59-38 months interval:

- 6 (46%, 1 untreated) showed no change,
- 6(46%, 1 untreated) showed improved fibrosis, while
- 2(15%) showed worse fibrosis at follow-up.

Liver chemistry tests may improve in hepatic sarcoidosis with or without therapy, although untreated patients had lower AP at baseline in this study.

Transplant-free survival is similar in treated and untreated patients.



AASLD: San Francisco 2015
November 13th -17th