



THE INTERNATIONAL
LIVER CONGRESS™ 2011

46th ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER

Berlin, Germany
30 March - 3 April 2011

ACP/BSG Liver Update Meeting, Southampton , November 2011

Stefan Hübscher,

School of Cancer Sciences, University of Birmingham

Dept of Cellular Pathology, Queen Elizabeth Hospital, Birmingham



Postgraduate Course

Cholestatic Diseases of the Liver and Bile Ducts

1. Developmental defects and congenital disorders
2. Diseases of hepatobiliary metabolism and transport
3. Immune mediated bile duct diseases
4. General issues in cholestatic liver diseases
5. Neoplasia and liver transplantation
6. Controversial issues
 - The role of the pathologist and radiologist in diagnosing biliary disease

Main Meeting

1376 Abstracts (vs 2306 at AASLD November 2011)

- 137 oral presentations
- 1239 posters

ABSTRACTS FROM EASL MEETING IN BERLIN, MARCH 2011

ABSTRACT NO.	CATEGORY	COMMENTS
151	Fibrosis (CPA)	86 HCV+ patients with cirrhosis on biopsy. CPA predictive of SVR on multivariate analysis.
161	Fibrosis (CPA)	CPA in cirrhotic patients correlates with decompensation. Also predicts decompensation in compensated cirrhosis.
219	Neoplasms (HCC/CC)	Cancer stem cells (CD133+/EpCAM+) account for up to 1% of cells in HCC and CC by flow cytometry and immunohistochemistry. (Stefan note at poster. No co-localisation. Cells resemble "oval cells").
322	Fibrosis (non-invasive)	Fibrosis classified by "best performing blood tests" better than local pathologist. (statistics difficult to understand).
332	Fibrosis (CPA)	Size of sample required for accurate DIA determined using 1cm ² images of explant livers. Similar size to other staging requirements.
338	Fibrosis (non-invasive)	417 HCV positive patients undergoing liver biopsy and TE. Factors correlating with stiffness include METAVIR fibrosis stage, sinusoidal fibrosis (which stain?) and steatohepatitis.

Notes from 45 Abstracts
13 selected for this meeting

1. Indications for liver biopsy
2. Assessment of liver fibrosis
3. NAFLD
4. Neoplasms
5. Progenitor cells/ductular reaction
6. Autoimmune hepatitis

1. Indications for liver biopsy

Abstract 342

MAJOR TRENDS IN LIVER BIOPSY PRACTICES IN FRANCE: RESULTS
OF A MULTICENTER NATIONWIDE 2009 SURVEY AND COMPARISON
WITH 1997 PRACTICES

J-F. Cadranel, J.B. Nousbaum, B. Hanslik
Multicentre Study, France

	2009	1997
No of centres	107	89
No of biopsies	8581	16,000
Transjugular	22.4%	9%
Main indications		
• HCV	23.6%	54.1%
• HBV	14%	5.8%
• NAFLD	8.9%	N/K
Severe complications	1.07% (1 death)	

2. Assessment of Liver Fibrosis

Abstracts 151 & 161

Collagen Proportionate Area Measurement (Sirius Red Staining + Image Analysis)

Advantages over conventional histological staging:

- More objective and reproducible
- More reliable in predicting outcomes
- May allow sub-staging of cirrhosis

LIVER COLLAGEN PROPORTIONATE AREA CORRELATES WITH
ESOPHAGEAL VARICES AND SVR IN PATIENTS WITH COMPENSATED
HCV CIRRHOSIS

V. Calvaruso, V. Di Marco, D. Cabibbi, M.G. Bavetta, A. Craxì
Palermo Italy

86 HCV-positive patients with histologically confirmed cirrhosis

- CPA correlates with presence of oesophageal varices
- CPA predicts likelihood of sustained virological response (SVR) to antiviral therapy
- On multivariate analysis CPA most strongly predictive of oesophageal varices and SVR

COLLAGEN PROPORTIONATE AREA: BEST INDEX TO PREDICT
DECOMPENSATION IN PATIENTS WITH LIVER CIRRHOSIS OF
DIFFERENT ETIOLOGIES

G. Isgro, L. Andreana, M. Garcovich, T.V. Luong, A. Hall, P. Manousou, N. Goossens,
J. O'Beirne, D. Patch, A.P. Dhillon, A.K. Burroughs
Royal Free Hospital, London

184 consecutive patients with cirrhosis of various causes

1. CPA correlates with decompensation at time of biopsy
 - (15% in compensated vs 27% in decompensated)
2. CPA predicts subsequent decompensation at 2 years (OR = 1.09) and 4 years (OR = 1.105)

3. NAFLD

Abstracts 1259 & 1271

CELL CYCLE ARREST AND ACCELERATED TELOMERE SHORTENING IN NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

A. Aravinthan, C. Scarpini, P. Tachtatzis, S. Penrhyn-Lowe, S. Verma,
S. Davies, R. Brais, N. Coleman, M. Allison, G. Alexander
Cambridge, U.K.

Liver biopsies from 70 patients with NAFLD

Immunohistochemistry for cell cycle phase markers. Compared with :

- Normal liver (resected for metastatic CRC, n=5)
- Regenerating liver (post-transplant biopsies with acute ischaemic-reperfusion injury, n= 12)

Telomere length measured by Q-FISH.

- Compared with 43 age-matched donor liver biopsies obtained post-reperfusion at liver transplantation (time zero biopsies)

Cell Cycle Markers

	NAFLD	IRI	normal
MCM-2 Cell cycle entry	9.3%	25%	<0.01%
Cyclin A S phase	1.7%	20.1%	<0.01%
PH3 Mitosis	1.2%	18.2%	<0.01%
P21 G1/S arrest	40%	17.9%	<0.01%

Telomere Studies

- Hepatocyte telomeres shorter in NAFLD (mean FI 599) than controls (1018)
- Nuclear size increases with age in NAFLD, but not controls.

Other findings

- MCM-2 expression, p21 expression and nuclear size correlate with fibrosis stage

Conclusion:

- Hepatocytes in NAFLD liver have accelerated ageing, may be associated with disease progression

1271

HIGH COFFEE INTAKE IS ASSOCIATED TO LOWER GRADE OF HEPATIC
STEATOSIS. THE ROLE OF PERIPHERAL ANTIOXIDANT ACTIVITY

Y. Gutiérrez-Grobe, V. Sánchez-Valle, N.C. Chávez-Tapia, A.A. Gutiérrez-Jiménez, J.G.
Gavilanes-Espinar, R.A. Kobashi-Margain, M. Uribe, N. Méndez-Sánchez.

Mexico City

- 57 patients with NAFLD
- Steatosis diagnosed by ultrasound
 - 45 mild, 9 moderate, 3 severe
- Significant differences in coffee intake between different groups
- No significant differences in serum levels of antioxidant enzymes or lipid peroxidation –associated substances

4. Liver Neoplasms

Abstracts 958, 970, 977 & 1030

1. Liver adenoma

- Role of biopsy (Bordeaux Group) - Abstract 958

2. Hepatocellular carcinoma

- Progenitor cell markers – Abstracts 970 & 1030

3. Cholangiocarcinoma

- Epithelial –mesenchymal transition - Abstract 977

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DIAGNOSIS OF BENIGN HEPATOCELLULAR TUMORS/VALUE OF A SIMPLE ALGORITHM BASED ON SPECIFIC HISTOCHEMICAL MARKERS PERFORMED ON LIVER BIOPSIES, COMPARED WITH SURGICAL SPECIMEN

P. Bioulac-Sage, G. Cubel, B. Le Bail, G. Couchy, C. Balabaud, J. Zucman-Rossi
Bordeaux, France

Glutamine synthetase in distinguishing FNH and liver cell adenoma

- Perivenular distribution in normal liver
- Map-like pattern in FNH
 - Seen 70% of biopsies, 90% of resections
- Other patterns in LCA (absent, perivascular or diffuse), depending on subtype
 - Seen in 90% of biopsies, 98% of resections

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Algorithm for subclassifying adenomas

STEP 1.

Stain for LFABP. If positive = HNF mutated LCA (steatotic).

- Low risk of malignant transformation

STEP 2.

Stain for SAA and CRP. If positive = Inflammatory LCA (up to 10 % of I-LCA may be b-catenin mutated)

STEP 3.

Stain for GS and B –cat. Diffuse GS staining and nuclear B-cat indicate B-catenin mutated LCA. Equivocal cases may need molecular studies

Diagnostic Histopathology, December 2011

Microscopic techniques for assessing specimen containing HCA Recommended techniques performed on both tumour and non-tumour tissue, biopsy or resection specimens

Step 1. Routine (H&E, trichrome, CK7) and first step of IHC: glutamine synthetase

Glutamine synthetase

Map-like pattern in FNH

Negative or focal zonal positivity in HCA other than b-HCA – go to step 2

Step 2. H&E diffuse steatosis, favours H-HCA
H&E inflammation, sinusoidal dilatation, favours IHCA
H&E does not suggest a specific type of HCA

LFABP

Diffuse positivity in HCC or b-HCA – go to step 3
Tumour –ve, non-tumour +ve confirms diagnosis of H-HCA

SAA and/or CRP

Tumour +ve and non-tumour –ve confirms diagnosis of IHCA

LFABP, SAA and CRP

Type HCA according to immunohistochemistry results

Step 3. Abnormal GS staining, strong/diffuse or heterogeneous
H&E features + abnormal reticulin staining suggest possibility of HCC

β -Catenin

Nuclear staining confirms diagnosis of b-HCA; if negative consider molecular techniques

Glypican 3, CD34, β -catenin

Focal or +/-diffuse positivity confirms HCC

Diffuse positivity Nuclear staining confirms diagnosis of β -catenin mutated HCC

4. Liver Neoplasms

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OCCURRENCE AND CLINICOPATHOLOGICAL RELEVANCE OF PROGNOSTIC MARKERS IN HEPATOCELLULAR CARCINOMA

O. Govaere, A. Katoonizadeh, M. Komuta, C. Janssen, F. de Luca, S. Vander Borgh, C. Verslype, R. Aerts, B. Topal, F. Nevens, V.J. Desmet, M. Pinzani, T. Roskams
Leuven, Belgium

- 411 biopsies with HCC
- Immunostained for K19, EpCAM and AFP (> 5% cells = positive)
 - 12 % K19+, 17% EpCAM+, 7% AFP +

	Association with adverse clinicopathological parameters
K19	Size, poor differentiation, metastasis , microvascular invasion
EpCAM	N/A
AFP	poor differentiation, microvascular invasion

BUT. No multivariate analysis or correlation with overall survival

EPCAM EXPRESSION BY TUMOR CELLS IS AN INDEPENDENT PREDICTIVE FACTOR FOR DISTANT RECURRENCE IN UNINODULAR HEPATOCELLULAR CARCINOMA (≤ 5 CM) TREATED BY RADIOFREQUENCY ABLATION

N. Ganne-Carrié, N. Bäret, O. Seror, M. Aout, V. Leroy, J.-F. Blanc, N. Sturm, P. Bioulac-Sage, G. N'Kontchou, J.-C. Trinchet, E. Vicaut, M. Beaugrand, M. Ziol
Paris, Grenoble, Bordeaux, France

Biopsies from 132 consecutive patients with cirrhosis and HCC, successfully treated with RFA

Immunostaining for :

- EpCAM, CK 19, glutamine synthetase, B-catenin, E cadherin in tumour tissue
- EpCAM and CK7 in non-tumoral tissue

EpCAM positive (> 5% cells)	12%
CK 19 positive (> 5% cells)	7%
Strong GS staining	56%
B-catenin positive	14%
Strong E-cadherin staining	52%

EpCAM positivity independently associated with recurrence

- ?progenitor cell population resistant to RFA

Non-tumoral tissue:

- EpCAM + in 62% of EpCAM+ HCCs
- EpCAM + in 44% of EpCAM- HCCs

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INTRAHEPATIC CHOLANGIOCARCINOMA WITH EPITHELIAL-
MESENCHYMAL TRANSITION PHENOTYPE IS ASSOCIATED WITH
POOR PROGNOSIS

J. Jin, H.Y. Jung, S.H. Kim, K. Lee, H.S. Ryu, J.-J. Jang
Seoul, Korea

- Tissue microarray of 120 cholangiocarcinomas
- Immunostaining for:
 - Snail-1, S100A4, Vimentin
 - CK 19, E-cad, B-catenin
- EMT expression classified as “low” (0-3 markers positive) or “high” (4-6 markers positive)
- High expression independently associated with reduced survival

5. Progenitor cells/ductular reaction

Abstracts 686, 1074, 1092

1. Progenitor cells in peribiliary glands of extrahepatic biliary tree – Abstract 686
2. Hepatic progenitor cell niche – Abstract 1074
3. Progenitor cells/ductular reaction in HCV – Abstract 1092

5. Progenitor cells/ductular reaction

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*IN SITU, IN VITRO AND IN VIVO AND DEMONSTRATION OF
MULTIPOTENT STEM CELLS (MPS) IN HUMAN ADULT EXTRAHEPATIC
BILE DUCTS (HEHBDS)*

V. Cardinale, G. Carpino, Y. Wang, M. Gatto, C.-B. Cui, A. Cantafora, R. Semeraro, A. Torrice, M. Rossi, P.B. Berloco, L. Inverardi, J. Dominguez-Bendala, C. Ricordi, E. Gaudio, L. Reid, D. Alvaro
Rome, Italy, North Carolina & Miami, USA

Tissues obtained from extrahepatic biliary tree

- common hepatic duct, bile duct, cystic duct, gallbladder

Immunohistology and RT-PCR used for stem/progenitor and mature cell markers

Expression of stem cell markers in peribiliary glands

- Mainly seen at branching points
- Reduced expression towards luminal surface

Cultured cells could differentiate towards hepatocytes, cholangiocytes or pancreatic islets under appropriate 2D/3D conditions

Implications for regeneration and carcinogenesis

5. Progenitor cells/ductular reaction

Abstracts 686, 1074, 1092

1. Progenitor cells in peribiliary glands of extrahepatic biliary tree – Abstract 686
2. **Hepatic progenitor cell niche – Abstract 1074**
3. Progenitor cells/ductular reaction in HCV – Abstract 1092

THREE-DIMENSIONAL RECONSTRUCTION OF THE HEPATIC PROGENITOR NICHE IN HEALTH AND DISEASE

L. Boulter, S. Soo Seo, P. Ramachandran, J.P. Iredale, S.J. Forbes
Edinburgh UK

Mouse models of chronic liver disease

- CDE – models hepatocellular regeneration
- DDC – models biliary repair

- Immunostaining for :
 - PanCK (hepatic progenitor cell marker)
 - F4/80 (macrophage marker)
 - Alpha SMA (marker of activated myofibroblasts)

- Digital reconstruction in 3D

THREE-DIMENSIONAL RECONSTRUCTION OF THE HEPATIC PROGENITOR NICHE IN HEALTH AND DISEASE

L. Boulter, S. Soo Seo, P. Ramachandran, J.P. Iredale, S.J. Forbes
Edinburgh UK

- Marked increase in HPCs in both hepatocellular and biliary regeneration
- Associated with migration of macrophages and myofibroblasts

Distinct patterns of macrophage/myofibroblast migration:

Biliary

- Myofibroblasts completely surround HPCs and prevent contact with macrophages (? Protection from macrophage derived factors)

Hepatocellular

- Heterogeneous mingling of macrophages and myofibroblasts
- Geographical variation in regenerative niche depending on context of regeneration

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IMMUNOPHENOTYPE OF DUCTULAR REACTION IN HUMAN LIVERS WITH HCV

E. Prakoso, D. Bowen, J. Kench, A. Clouston, G. McCaughan, N. Shackel
Sydney & Brisbane, Australia

Four-marker immunolabelling and confocal microscopy to assess the immunophenotype of ductular reaction

Dominant population (“mature” DR) - CK7+/EpCAM+/ CK19+/ NCAM+

- Stepwise loss of expression with transition towards hepatocytes
 - CK7+/EpCAM+/ CK19+/ NCAM-
 - CK7+/EpCAM+/ CK19-/ NCAM-
 - CK7 weak /EpCAM - membranous/ CK19-/ NCAM-
(correspond to intermediate hepatocytes)
 - Individual small CK7+ EpCAM-/ CK19-/ NCAM cells (progenitor cell)
- Zonal distribution (intermediate heps periportal, mature heps perivenular)

DR closely related to SMA-positive cells (without co-localisation)

6. Autoimmune hepatitis

IgG4 –associated AIH - Abstract 1284

IgG4-associated Autoimmune Hepatitis

Chung 2007

- 9/26 cases of AIH had >5 IgG4+/cells/HPF (vs 0/33 PBC/PSC/HCV)
- Compared with IgG4-negative cases:
 - More intense portal inflammation
 - Higher IgG levels
 - “Marked response” to prednisolone therapy

Umemura 2011

- 2/ 60 patients with AIH had elevated serum IgG4 levels (> 135 mg/dL) **and** > 5 IgG4+ plasma cells/HPF
 - High inflammatory activity (interface hepatitis and zonal necrosis)
 - Biochemical response and normalisation of IgG4 levels after corticosteroids
 - One patient developed biliary strictures and abundant IgG4 plasma cell infiltration in biopsy of common bile duct (? progression to IgG4-SC)

CIRRHOSIS DEVELOPMENT ASSOCIATED WITH ELEVATED SERUM IGG4 IN TYPE I AUTOIMMUNE HEPATITIS

K. Abe, F. Katsushima, K. Monoe, Y. Kanno, H. Saito, A. Takahashi, J. Yokokawa, M. Seike, O. Yokosuka, M. Sata, H. Ohira
Mulicentre Study, Japan

194 patients with type 1 AIH

1. Cirrhosis present in 45 (23%) – 40 at presentation, 5 during follow-up.
 - Lower survival at 10 years (81% vs 97.5%)
 - Higher relapse rate (80% vs 11%)

2. Serum IgG4 and IgG4 plasma cells in liver biopsies evaluated in 34 patients before treatment
 - 5 (15%) patients had high serum IgG4 levels
 - Higher rate of cirrhosis (80% vs 24%)(no information about histological findings)

Saturday 22 October 2011



1. What is the name of the player?
2. Against whom has he just scored, leading to an historic victory?