Liver

779 Hepatotoxic Effects of Long-Term Inhibition of MiR-122 in Mice

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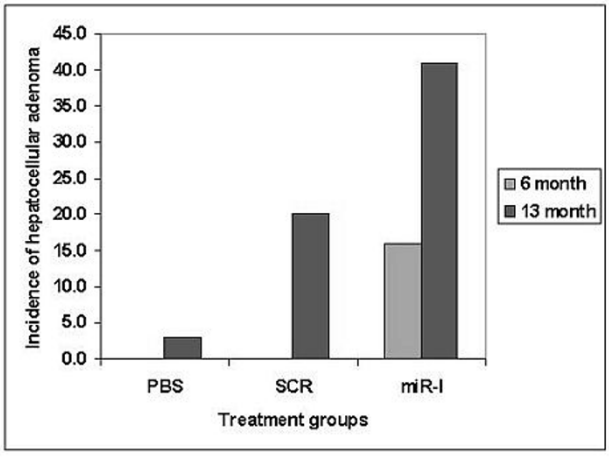
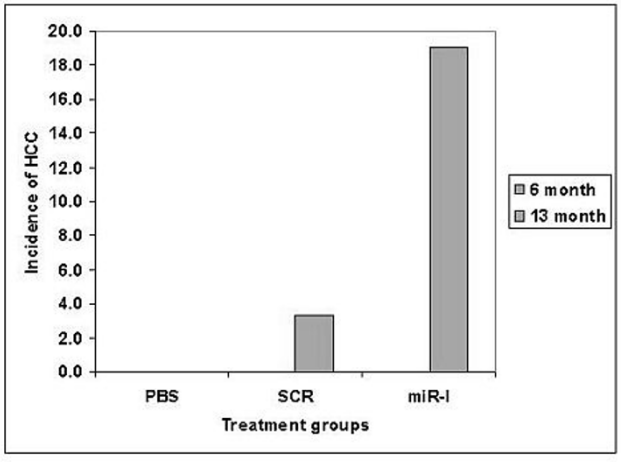
Background: MicroRNAs (miRs) play important pathophysiological roles. MiR-122 is a predominant and conserved liver-specific miRNA. Knockdown of miR-122 in mice lowered serum cholesterol and reduced hepatitis C viral load. Studies also linked low miR-122 level to the development of hepatocellular carcinoma (HCC). MiR-122 antisense oligonucleotides are in phase II clinical trial for HCV treatment, but the paradoxical effects from long-term miR-122 inhibition need to be addressed.

Design: A total of 212 C57/b6 mice were randomly divided into 3 groups and injected with $6x10^{11}$ copies of recombinant Adeno-associated virus vectors expressing miR-122 inhibitor (miR-I), scramble (SCR), or phosphate buffered saline (PBS). After 1, 6 and 13 months of injection, liver was harvested. Microscopic examination was performed on H&E stained sections after formalin fixation. Reticulin stain was performed for all hepatic nodule(s).

Results: The incidence of hepatocellular adenoma (figure 1) and HCC (figure 2) was significantly increased in miR-I group, compared to both controls. The size of nodules measures up to 0.8 cm in greatest dimension. Other pathologic changes including macrovesicular steatosis, mitotic activity, apoptosis, mononuclear infiltrates, and swelling were also higher in miR-I group, especially after 13-month of treatment. No significant fibrosis or cholestasis was identified. Inflammation was minimal to moderate and predominately perivascular. Steatosis is mainly within the nodule and in the background in some cases. Mitosis (up to 16/10 HPF) and apoptosis were identified exclusively in the nodules especially HCCs.





Conclusions: Long term inhibition of miR-122 causes significant hepatocellular injuries including increased occurrence of adenoma, HCC, steatosis, inflammation, and swelling. These date suggest that miR-122 plays an essential role in tumor suppression, fat metabolism, and anti-inflammation.

1656 Immuno-Labeled Treg, T-Cells and Their Ratios Predict the Immunosuppression Therapy Effectiveness in Liver Allograft Recipients

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Background: Complete immunosuppression withdrawal (i.e., operational tolerance) has been possible in only ~[/underline] 20% of liver transplant recipients (LT). Identification of specific T cell populations responsible for immunoregulation may give clues toward achieving tolerance in LT. Previous reports have demonstrated differences in the effects of calcineurin and mTOR inhibitors (sirolimus) on Tregs and T cell populations. We present a prospective study and extensive analysis of morphology of Treg (FOXP3+), CD3, CD4, and CD8 T cell populations in liver biopsies from 20 LT recipients before and after conversion from calcineurin inhibitors to sirolimus monotherapy. This would support larger scale studies utilizing sirolimus conversion as an intermediate step toward more clinically successful immunosuppression withdrawal in LT.

Design: In 20 liver allograft recipients, a 2-cm core liver biopsy was obtained, once before and once 6 months after the conversion to the sirolimus monotherapy. Hematoxylin and eosin, tri-chrome, and immunohistochemistry (IHC) was performed using antibodies to FOXP3 (Treg), CD3, CD4, and CD8. The number of CD3, FOXP3, CD4 and CD8 positive lymphocytes per high power field were counted. Ratios of FOXP3:CD3 and CD4:CD8 were calculated, and an average of three portal-tract ratios was recorded. 5 documented rejection cases were used for comparison.

Results: The Tregs presented mostly as single cells scattered throughout the portal area with occasional clustering in the biopsies before conversion to sirolimus monotherapy. Semi-quantitative analysis revealed that the Tregs were significantly increased after six months of conversion to sirolimus monotherapy in comparison to the rest of the T cells with the ratio of FOXP3:CD3 positive cells being (0.19 ± 0.1), compared to beginning of the therapy (0.11 ± 0.1; $P = 0.01$) or rejection cases (0.09 ± 0.01; $P = 0.005$). In addition, the ratio of CD4:CD8-positive cells also increased significantly (1.2 ± 0.5), compared to beginning of the therapy (0.86 ± 0.2; $P = 0.02$) or those with rejection (0.9 ± 0.1; $P = 0.01$), consistent with the increased number of the Tregs. The vast majority of T cells in the rejection cases are composed of CD8+ T cells with very rare FOXP3 + and CD4+ cells.

Conclusions: T cells immunophenotyping by IHC in liver core biopsies of liver allograft recipients is a practical and reliable method of prediction the effectiveness of immunosuppression therapy, particularly conversion to sirolimus monotherapy. Also the T cells immunophenotype characterization will help in detecting early rejection cases.

1657 Hepatobiliary Aggressive B Cell Lymphomas: Histologic, Immunohistochemical and Genetic Evaluation of a Large Series

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Background: Diffuse large B cell lymphoma and related entities are the commonest type of non-Hodgkin lymphomas. Within this diagnosis are several distinct clinicopathologic entities. Lymphomas of the hepatobiliary tract are exceedingly rare and poorly studied. We evaluated a series of 449 aggressive B cell lymphomas and identified 12 cases involving the hepatobiliary tract.

Design: 449 cases were evaluated using an extensive panel of immunohistochemical stains (CD20, CD3, CD5, CD10, cyclin D1, bcl6, bcl2, EBER, Ki67, CD30) and a panel of FISH studies (including MYC, IGH/bcl2 and bcl6). Twelve cases (2.7%) were identified in the pancreas, liver and gallbladder.

Results: The majority of cases were diffuse large B cell lymphoma (DLBCL)(10/12; 83%) with two cases of Burkitt lymphoma identified (17%). The majority of cases (~67%) were of germinal center origin by both Hans and tally classifiers. CMYC translocations were seen only in the BL, and no MYC-positive DLBCL or "double hit" lymphomas were identified. Compared to a large group of lymphomas from both the upper and lower gastrointestinal tract, hepatobiliary lymphomas were less often positive for BCL6 translocations (9% vs. 22%) and more often positive for IGH/BCL2 translocations (36% vs. 18%).

Conclusions: Our series shows that aggressive lymphomas are quite rare in the hepatobiliary tract. They show heterogeneity of immunophenotype and genetics. Hepatobiliary aggressive lymphomas have pathologic and genetic differences from those of the upper and lower GI tract as well as from nodal aggressive B cell lymphomas.

1658 Pathological Features and Prognosis of Combined Hepatocellular and Cholangiocarcinoma by World Health Organization Classification

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Background: According to the World Health Organization (WHO) classification, combined hepatocellular and cholangiocarcinoma (CHC) include classical type and subtypes with stem cell features, however, these subtypes of CHC are not distinctive clinicopathologic entities and the prognosis for CHC with stem cell features is unknown.

Design: We selected CHC cases using morpholgoical and immunohistochemical approach using hepatocellular markers (Heppar1, AFP, Glypican3) and biliary markers (CK19, CA19-9, NCAM, mucin production). Based on the WHO classification, we classified 100 cases of CHC into classical type (n=69), subtypes with stem cell features (n=25), such as cholangiolocellular subtype (n=8) and intermediate-cell subtype (n=17), and unclassified type (n=6). Classical type tumors were further divided into hepatocellular carcinoma predominant type (Cl-HCC, n=47) and cholangiocarcinoma predominant type (Cl-CC, n=22). Then we compared CHC subtype and clinicopathologic features.

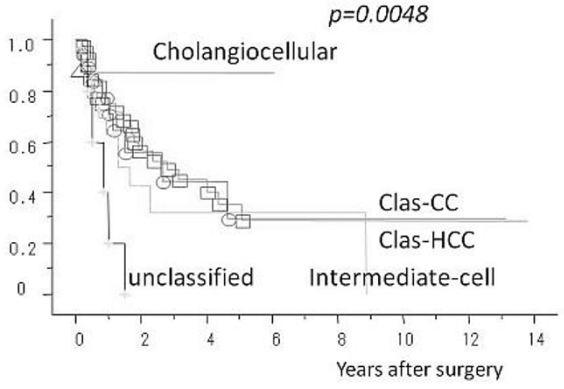
Results: Tumor size of intermediate-cell type is larger than other types. Cholangiolocellular subtype shows only one case with vascular invasion and no cases with intrahepatic metastasis. Cl-CC type, intermediate-cell type and unclassified type show frequent vascular invasion and intrahepatic metastasis.

Pathological features and subtypes of CHC

Variable	Classical type		Subtypes with stem cell features		Unclassified type	p-value
	Clas-HCC	Clas-CC	Cholangiolo-cellular	Intermediate-cell		
	n=47	n=22	n=8	n=17	n=6	
Tumor size, average	3.8cm	4.4cm	3.7cm	6.6cm	4.4cm	*
Vascular invasion (+)	40.4%	77.3%	12.5%	70.6%	66.7%	0.003
Intrahepatic metastasis (+)	29.8%	50%	0%	58.8%	66.7%	0.0131
Viral infection (+)	82.2%	72.7%	71.4%	52.9%	66.7%	N.S.

*Clas-CC vs. intermediate-cell, p=0.0374; CLas-HCC vs. intermediate-cell, p=0.001

Cholangiolocellular subtype showed favorable prognosis, in contrast, intermediate-cell subtype and classical type showed poor prognosis. Unclassified type showed more aggressive course.



Conclusions: Cholangiolocellular type is minority of CHC, but it should be recognized as definite entity. Intermediate-cell type was similar tumor behavior to that of classical types.

1659 Steatohepatitic Hepatocellular Carcinoma Did Not Increase in the Last Decade: Metabolic Syndrome May Not Be the Only Contributing Factor

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Background: Steatohepatitic hepatocellular carcinoma (SH-HCC) is a recently described HCC variant in which the tumor cells have histological changes that resemble steatohepatitis. Several studies have found an association between the SH-HCC morphology and the metabolic syndrome. Since the prevalence of the metabolic syndrome has steadily increased in recent years, we hypothesized that the prevalence of SH-HCC may have also increased in the past decade.

Design: We studied all surgically resected or explanted HCC cases from 3 tertiary centers in two separate 2-year intervals a decade apart (2000-2001 and 2010-2011,respectively). Pathology slides and clinical data were reviewed. Slides of liver distant from tumor were also reviewed and steatosis was scored according to NASH-CRN. We studied the frequency and clinicopathological correlates of HCC with the described SH-HCC features (steatosis, ballooning of HCC cells, inflammation, Mallory-Denk bodies, and pericellular fibrosis).

Results: SH-HCC was present in 80 of 298 (27%) cases. In the first time interval (2000-2001), 100 HCC cases were identified, of which 23 (23%) had the SH-HCC morphology. 10 years later, the second two year time interval (2010-2011) had a total of 198 HCC cases, of which 57 (28%) had a SH-HCC morphology. There was no significant difference in the prevalence of SH-HCC in these two periods (p=0.28). Background steatosis was significantly more common in 2010-2011, when each grade was analysed separately (p=0.0008), and when grades 1-3 were grouped together and compared with grade 0 (p=0.0002). Overall, those with SH-HCC morphology had a higher BMI when compared to those without (29.7 vs. 27.3; p=0.005), but the prevalence of metabolic syndrome was similar among the two groups. There was a significant association between SH-HCC and background steatosis when grades 1-3 were grouped together and compared with grade 0 (p=0.03), and there was a trend when each grade was analysed separately (p=0.09).

Conclusions: Our findings confirm the association between SH-HCC and some aspects of the metabolic syndrome. However, our data also suggests the metabolic syndrome/fatty liver may not entirely explain the carcinogenesis of SH-HCC in all cases and other pathways and genetic alterations should be further investigated. These results also indicate that the frequency of this morphology has been stable over a 10 year time interval. Longer time intervals may be needed to identify changing patterns in HCC morphology.

1660 Fatty Liver Contributes to Hepatocarcinogenesis in Cirrhotic Livers

J Alexander, M Torbenson, T-T Wu, MM Yeh. University of Washington, Seattle, WA; Johns Hopkins University, Baltimore, MD; Mayo Clinic, Rochester, MN.

Background: Some specific etiologies of hepatocellular carcinoma (HCC) are well known, such as viral hepatitis and cirrhosis. Diabetes and obesity, two conditions strongly associated with nonalcoholic fatty liver disease, have been established as independent risk factors for the development of HCC. Recent studies have suggested an association between non-cirrhotic fatty liver and risk of HCC. However, morphological data directly linking fatty liver to HCC in the setting of cirrhosis are lacking.

Design: All cirrhotic livers explanted in 3 tertiary centers in 2010-2011 were retrieved, including 131 cases with HCC and 162 cases without HCC. 85 HCC cases arising in non-cirrhotic liver resected during the same period were also compared. Slides of tumor and liver distant from tumor were reviewed and steatosis was scored according to NASH-CRN. Clinical data including metabolic profile were collated.

Results: The prevalence of significant steatosis (≥grade 1) in non-tumor (NT) liver in 54/131 (41%) cirrhotic cases with HCC was significantly higher than that in 29/162 (18%) cirrhotic cases without HCC (p<0.0001), but similar to 42/85 HCC cases (49%) arising in non-cirrhotic liver (p=0.2). NT liver steatosis was associated with obesity (p=0.04), dyslipidemia (p=0.02), but not diabetes (p=0.2) or hypertension (p=0.07). 33/96 (34%) cirrhotic cases with viable tumor slides available to review showed the steatohepatitic(SH)-HCC morphology, in which 18/33 (54%) cases had significant steatosis in NT liver, while 22/63 cases (35%) without SH-HCC morphology had significant steatosis in NT liver (p=0.06). 23/63 (36%) non-cirrhotic cases with viable tumor slides available to review showed the SH-HCC morphology, in which 14/23 (60%) had significant steatosis in NT liver, while 18/40 (45%) cases without SH-HCC morphology had significant steatosis in NT liver (p=0.2). There was no difference in the frequency of SH-HCC between cirrhotic and non-cirrhotic livers (34% vs 36%, respectively, p=0.78). Irrespective of background cirrhosis, cases with SH-HCC had a statistically significant association with higher BMI (29.9 vs. 27.5; p=0.01), but not with diabetes, hypertension, and dyslipidemia.

Conclusions: Steatosis in cirrhotic liver is strongly associated with the occurrence of HCC and metabolic risks. This multi-center and large cohort study highlights the role of hepatic steatosis and metabolic syndrome in hepatocarcinogenesis in cirrhotic liver. Further, the occurrence of SH-HCC does not differ between cirrhotic and non-cirrhotic livers.

1661 Evaluation of Cholangiocarcinomas (CCA) by Next Generation Sequencing (NGS) Reveals Frequent Actionable Genomic Abnormalities and New Routes to Targeted Therapies

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Background: Metastatic CCA has a poor prognosis and systemic therapies are commonly extrapolated from those used in other GI malignancies. We hypothesized that comprehensive genomic profiling of clinical CCA samples by NGS could identify genomic-derived drug targets of therapy for patients with this lethal cancer in a single diagnostic test.

Design: NGS was performed on hybridization-captured, adaptor ligation based libraries using DNA extracted from 4 formalin-fixed paraffin embedded sections cut at 10 microns from 13 CCA. The exons of 182 cancer-related genes were fully sequenced using the Illumina HiSeq 2000 to at an average sequencing depth of 936X and evaluated for genomic alterations (GA) including point mutations (mut), insertions, deletions, copy number alterations (amp), and select gene fusions/rearrangements. Actionable GA were defined as those identifying anti-cancer drugs on the market or in registered clinical trials (CT).

Results: There were 8 (61.5%) female and 5 (38.5%) male CCA patients with a median age 55.2 years (range 46-69years). There were 7 (54%) grade II and 6 (46%) grade III tumors. Nine (69%) CCA were Stage I and 4(31%) were Stage III at time of NGS. Thirteen (100%) of CCA has NGS performed on a needle biopsy of the primary tumor in the liver. All 13(100%) had GA on NGS with a total of 31 GA and an average of 2.4 GA per tumor. The most common GA were *ARID1A* (39%), *IDH1/2* (39%), *TP53* mut (39%) and *MCL1* amp (30%) which are currently not actionable. Seven/thirteen (54%) CCA had at least 1 actionable GA with an average of 0.85 actionable GA per patient including: *MET* amplification (15%), *CDK6* amplification 15%), *CDKN2A splice* (15%), *FGFR2* amp (8%), *PTEN splice* (8%), *NF1 truncation* (8%), *KRAS mut* (8%), *NRAS* mut (8%), and *ERBB3* mut (8%).

Conclusions: When CCA is evaluated by deep NGS, over half the patients in this study harbored GA which have the potential to influence and personalize therapy selection and guide patients to CT using novel agents. Given the limited treatment options and poor prognosis of patients with metastatic disease, comprehensive NGS genomic profiling has the potential to identify new treatment paradigms and meet an unmet clinical need for this disease.

1662 Detailed Evaluation of the Lymph Nodes in N0 Cases with Additional Levels Ought To Be Considered for the Accurate Staging of Proximal Biliary Tract Cancers

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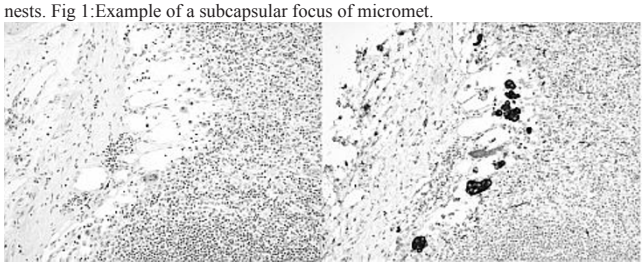
Background: Biliary tract cancers (BC) are notorious for very frequent local spread to lymph nodes (LNs). Oncologic operations of this region typically have a low LN yield; some advocate 6 LNs for proper staging. We hypothesized that standard pathologic LN analysis may understage patients.

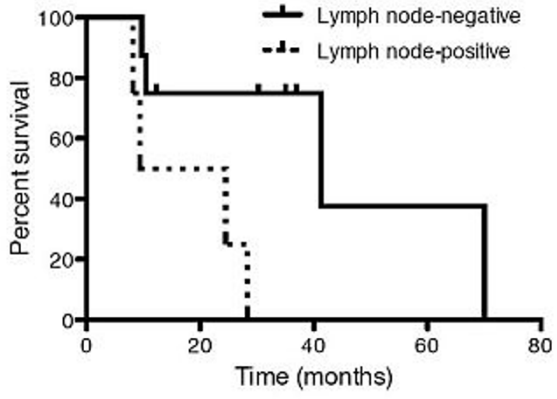
Design: We identified 38 patients who underwent resection for proximal BC and had been reported as N0. Each LN (n=187) was re-reviewed in detail for metastases using 4 levels on 2 slides and immunohistochemical staining for pancytokeratin (2 levels on 1 slide).

Results: 5 of 38 patients with negative LNs on standard analysis had mets on detailed examination (13%). One patient had 2 positive LNs. LN diameters were 1.1-2.1cm,

mean 1.54 cm. All positive LNs were portal with subcapsular micromets. Micromets were seen as 1 focus in 2; 2 in 1, and 4 in 2 LNs, composed of 7-cell cluster to 1.5mm nests. Fig 1:Example of a subcapsular focus of micromet.



Only 1case was revealed by IHC while the others discovered by H&E. None were missed in the original slides. Mean survival of patients with mets was 19mos vs. 30mos without mets. There was no association between LN mets detected on detailed analysis and T-stage, grade, margin-status, satellite-lesions, and perineural or lymphovascular invasion. The median number of LNs harvested was 3. One of 26 patients with <6 LNs retrieved had mets (4%), as compared with 4 of 12 patients with ≥6 LNs removed (33%;p=0.04). In this latter-cohort of well-staged patients, LN mets were associated with reduced median-survival of 9mos vs. 41mos (p=0.01). Fig 2:Overall survival comparison for LN positive and negative cases.



Conclusions: Considering the commonness of LN mets and well-known morphologic subtleness of BC, along with the frequent microscopic nature of mets and the clinical impact of LN-positivity on prognosis and management of the cases, it is important that the LNs of BC resections be evaluated carefully with additional levels.

1663 Cellular Phenotypes in Gallbladder Dysplasia: Diagnostic Significance and Clinical Associations in an Analysis of 318 Cases

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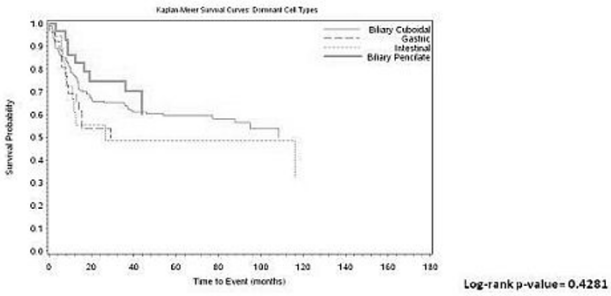
Background: The literature on the cellular patterns of high-grade dysplasia (HGD) of the gallbladder (GB) is highly limited.

Design: 318 cases with conventional (non mass-forming) HGD, 189 with accompanying invasion, were analyzed.

Results: Four distinct cell types were recognized, often occurred in a mixture: **I) Biliary-cuboidal,** identified in 90%, predominant in 69%, characterized by monotonous cells, round centrally/suprabasally located nuclei, cherry-red macronucleoli, and abundant cytoplasm showing either clear-cell (13%), chromophobe-like (8%) and oncocytoid (3%) features. **II) Biliary-pencillate,** identified in 48%, predominant in 14%, crowded thin elongated nuclei with no nucleolar prominence, minimal amount of cytoplasm, creating an overall basophilia recapitulating the pencillate cells of GB epithelium. **III) Gastric,** identified in 48% and predominant in 10%, abundant apical pale cytoplasm, basally located mildly enlarged nuclei. **IV) Intestinal,** identified in 13%, predominant in 6%, resembling adenomatous epithelium of GI tract (not defined by goblet cells, which can occur in any type). **Associations:** Pencillate type appeared to be the least aggressive (lowest rate of invasion, 54%, and longest 5-yr, 60%), going along with its relatively bland cytology and organized appearance. Biliary-cuboidal type had the highest degree of atypia but had intermediate aggressiveness. In contrast, the metaplastic phenotypes, intestinal and gastric, were more aggressive (associated with invasion in 70 and 67 % and with 5-yr of 49, and 50% respectively) despite their often subtle and difficult to recognize appearance, especially for the gastric type.



Conclusions: In addition to the ordinary biliary cuboidal cell HGD characterized by macronucleoli and abundant cytoplasm with clear-cell, chromophobe or oncocytoid features, a previously unrecognized pattern, biliary-pencillate type is elucidated in this study. More importantly, metaplastic phenotypes, gastric (foveolar) and intestinal akin to those recently recognized in other segments of GI tract (such as the stomach, by Lauwers et al.) also occur in the GB, and appear to be more aggressive despite their lesser degree of cytologic atypia.

1664 Focal Nodular Hyperplasia or Mass Effect?

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Background: Focal nodular hyperplasias (FNH) are liver masses that often do not warrant surgical resection. However, it is possible that directed biopsies may miss true target lesions and biopsy adjacent liver with findings similar to FNH. Recently, glutamine synthetase (GS) has been demonstrated to express a distinctive map-like immunoreactivity in FNH. We tested GS in multiple types of non-FNH liver lesions, hypothesizing that the hepatic parenchyma around these lesions may demonstrate FNH-like staining patterns, with the potential pitfalls of a misleading diagnosis of FNH on biopsy and the risk of missing resectable target lesions.

Design: 19 metastatic neuroendocrine tumors (NE), 21 metastatic colon carcinomas (CC), 5 FNH, and 7 chemoembolized hepatocellular carcinomas (HCC) from 28 men and 24 women (age range 34-81, mean age 55.8) were evaluated based on H&E characteristics and GS immunostaining. Each lesion was assessed for size, degree of fibrosis present within the main mass (scored 1-3), the presence or absence of FNH-like features in the liver surrounding the mass, and pattern of GS staining in the liver surrounding the mass.

Results: The mean lesion size was 2.6 cm for NE, 3.0 cm for CC, 3.4 cm for FNH, and 6 cm for HCC. The mean fibrosis score was 1.6 for NE, 2.45 for CC, and 1 for HCC. 7/19 NE and 17/21 CC had some features of FNH surrounding the main lesion by H&E, including fibrous septa with bile ductules, aberrant vessels, and cholestatic features. However, only 1 NE and 1 CC case had both FNH features surrounding the metastatic lesion as well as map-like GS staining. All other NE as well as HCC and CC cases demonstrated hepatic perivenular staining similar to that observed in normal liver, regardless of FNH-like features on H&E. All 5 FNH exhibited map-like GS staining.

Conclusions: GS may assist in distinguishing true FNH from FNH-like mass effect. FNH is a malformation thought to develop secondary to abnormal blood flow; our study shows that although metastasizing lesions are often fibrogenic, may distort vasculature, and cause FNH-like features in the surrounding parenchyma, these do not represent true FNH in most cases. The infrequent case of a lesion surrounded by liver with both FNH features and GS map-like staining is likely a true FNH with a simultaneous occurrence of a second lesion.

1665 Detailed Histological Assessment of Primary Sclerosing Cholangitis: Confirmation Utilizing Significance Analysis of Microarray (SAM) and Hierarchical Clustering Analysis (HCA)

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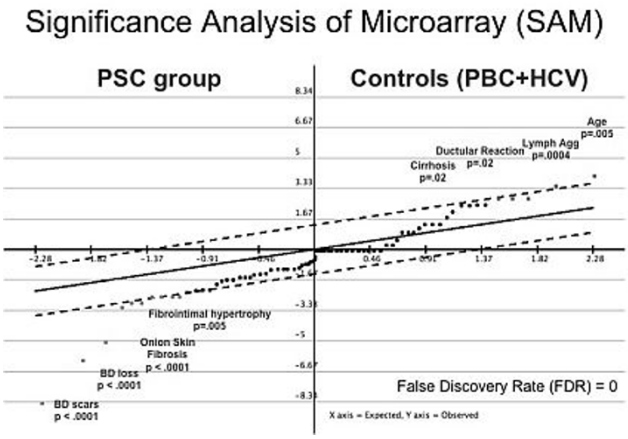
Background: The histological diagnosis of primary sclerosing cholangitis (PSC) is often difficult to make on needle biopsy. Definitive diagnosis of PSC can only be made by cholangiography and there may be histologic overlap with other liver conditions. Employing a detailed histological analysis and utilizing a powerful statistical system, we sought to identify specific features of PSC.

Design: Explants from 20 PSC and 10 primary biliary cirrhosis (PBC) & 10 HCV control cases were examined. Clinical parameters such as age at transplant, gross and microscopic features subdivided into abnormalities of vascular structures, various-sized bile ducts (BD), such as %BD loss, BD scars, atrophy and scalloping of the epithelium, periductal onion-skin fibrosis, cholestatic features and inflammatory changes were scored. Fibrosis was assessed using both the modified Knodell and PSC staging schemes. Twenty-five fields/case were analyzed for each of the 39 variables. Data were analyzed by contingence 2x2 tables, Fisher exact 2-tail test and T-test (significant if $p<.05$) where applicable and integrated by SAM (significant if q-value=0) and HCA.

Results: A total of 1800 scores were recorded. Specific features seen in PSC were BD scars, onion-skin fibrosis of both small and medium-sized BDs, >50% BD loss of both small and medium-sized BDs, bile infarcts, and fibrointimal hyperplasia of hepatic arteries; hepatolithiasis, cholangitis and cholestasis were all significant ($p<.05$). SAM integration and comparison between PSC and PBC/HCV show that PSC is typified by BD scars, medium-size BD loss and periductal onion-skin fibrosis even in the smallest BD radicles (q-value=0).



Unsupervised HCA correctly grouped PSC, PBC & HCV cases.

Conclusions: PSC patients were younger at time of transplant. A histologic diagnosis of PSC can be reliably made by the presence of BD scars, medium-sized BD loss and terminal BD onion-skin fibrosis and, by extrapolating from these findings, these features can be employed when evaluating liver needle biopsies. SAM allows the integration of quantitative clinical and qualitative histological variables for this assessment.

1666 Immunohistochemical Examination of Arginase-1 Expression in Hepatoblastomas

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Background: Hepatoblastomas are the most common pediatric malignant tumors of the liver, typically presenting by the age of 3 years. Histologically, these tumors may be composed of a combination of fetal, embryonal and mesenchymal components; the prognosis is variable, depending on the constituent histologic subtypes. Recently, arginase-1 (Arg-1) has been shown to be a sensitive and specific immunohistochemical marker in hepatocellular carcinomas; however, little is known about its expression in hepatoblastomas. In this study, we investigated the expression of Arg-1 in a large series of hepatoblastomas to assess its utility as a diagnostic marker.

Design: 26 cases of hepatoblastomas were retrieved from the surgical pathology files of a large pediatric hospital. Immunohistochemistry was performed on whole-section slides following antigen retrieval using a polyclonal rabbit antibody to Arg-1 and monoclonal mouse antibody to HepPar-1, and the staining pattern was semi-quantitatively assessed. The extent of immunoreactivity was graded according to the percentage of positive tumor cell, and the intensity of staining was graded as weak, moderate, or strong.

Results: All 26 (100%) cases of hepatoblastomas showed immunoreactivity for Arg-1 with 25/26 (96%) cases showing strong, diffuse positivity. Almost all cases with fetal patterns (24/25, 96%) and all cases with embryonal patterns (17/17, 100%) showed strong, diffuse positivity for Arg-1, whereas mesenchymal patterns seen in 6 cases were completely negative for Arg-1 (0/6, 0%). By comparison, 25/26 (96%) hepatoblastomas were immunoreactive for HepPar-1. Almost all cases with fetal patterns(25/26, 96%) showed strong, diffuse positivity. One case consisting exclusively of fetal pattern was completely negative for HepPar-1. Embryonal patterns tended to show weaker, patchy positivity; the staining for HepPar-1 was only present focally in 3/17 tumors containing embryonal patterns. Similarly, mesenchymal patterns seen in 6 cases were completely negative for HepPar-1 (0/6, 0%).

Conclusions: Our data demonstrated that Arg-1 is a useful marker for hepatoblastomas and shows superior sensitivity compared to HepPar-1. The addition of Arg-1 may aid in the diagnosis of pediatric small round blue cell tumors which have inconclusive immunohistochemical profile, especially on small biopsies and metastases.

1667 Different Collagen Types Show Variable Increases from Early to Late Stages of Hepatitis-C Related Liver Fibrosis

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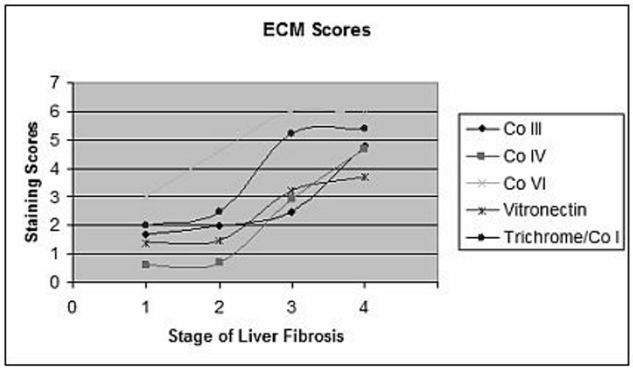
Background: During progression from normal liver to cirrhosis, significant changes occur in extracellular matrix (ECM). Total collagen (Co) increases 3 to 10 fold with an abnormal increase in fibril-forming Co and other ECM molecules. Little is known regarding changes each Co type undergoes during fibrogenesis. We evaluated 4 common types of Co and vitronectin at different stages of hepatitis-C related liver fibrosis to assess differential staining.

Design: 73 liver core biopsies from Hepatitic C patients (2007-2012) were identified. Transplanted livers and cases with other known liver diseases, except steatosis, were excluded. Cores were immunostained for Co III, IV, VI, Vitronectin, and Trichrome (Co I). Staining intensity was graded as negative (0), weak (1), and strong (2); and distribution as patchy if <50% of the portal areas stained (1), or diffuse (2). The final score was calculated as the product of intensity and distribution. Statistical analysis was performed using an unpaired student's T-test.

Results: Patient age ranged from 48 to 55, with male predominance in all stages. Co III, IV, VI, vitronectin and trichrome all showed increases from early to late stages of fibrosis ($P < 0.0001$), but with temporal and quantitative differences. Co IV and Trichrome show greatest differences from early to late fibrosis, while Co VI shows strong reactivity even in stage 1.

ECM Scores

Stage	# of Cases	Co III	Co IV	Co VI	Vitronectin	Trichrome (Co I)
1	21	1.7 ± 0.6	0.6 ± 0.7	3.0 ± 1.2	1.4 ± 0.6	2.0 ± 0.6
2	20	2.0 ± 1.0	0.7 ± 0.8	4.6 ± 1.3	1.5 ± 1.0	2.5 ± 0.9
3	17	2.5 ± 1.5	2.9 ± 1.3	5.9 ± 0.5	3.2 ± 1.5	5.2 ± 1.1
4	15	4.8 ± 1.5	4.7 ± 1.4	6.0 ± 0.0	3.7 ± 2.0	5.4 ± 1.0
Average (1 + 2)	41	1.8 ± 1.1	0.6 ± 0.7	3.8 ± 1.5	1.4 ± 0.8	2.2 ± 0.8
Average (3 + 4)	32	3.6 ± 1.9	3.7 ± 1.6	5.9 ± 0.4	3.4 ± 1.7	5.3 ± 1.0



Conclusions: Co IV and Trichrome appear to be the most useful discriminators between early and late stages of fibrosis. Co VI shows strong expression in early fibrosis while Co IV is weaker than all others until stage 3 fibrosis. Further studies will be helpful to evaluate usefulness in staging and reversibility of fibrosis.

1668 Expression of Liver Fatty Acid Binding Protein (LFABP) in Hepatocellular Carcinomas

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Background: Recently, loss of expression of liver fatty acid binding protein (LFABP) by immunohistochemistry has been shown to be characteristic of a subset of hepatocellular adenomas (HCAs) in which the HNF-1α gene is inactivated. Transformation to hepatocellular carcinoma (HCC) is thought to be a very rare phenomenon in the HNF-1α inactivated variant of HCA. However, we recently observed two cases at our institution, one definite HCC and one possible HCC, in which loss of LFABP staining was seen, raising the possibility that LFABP downregulation may be associated with hepatocellular carcinogenesis. Our aim is to evaluate HCCs arising in various backgrounds and with varying degrees of differentiation for LFABP loss.

Design: 17 total cases of HCC were examined. 13/17 HCCs arose in a background of cirrhosis due to hepatitis C (HCV; 8) or steatohepatitis (SH; 5). 4/17 HCCs arose in a noncirrhotic background, with one arising within an inflammatory HCA. Differentiation of HCC ranged from well-differentiated (WD; 6) to well to moderately differentiated (WD-MD; 2) to moderately differentiated (MD; 5) to moderately to poorly differentiated (MD-PD; 1) to poorly differentiated (PD; 3). Immunohistochemical staining for LFABP was performed in all cases.

Results: Expression of LFABP varied from intact/positive (++; 7) to diffusely but weakly positive (+; 2) to focal loss (+/-; 2) to complete loss/negative (-; 6) (summarized in table).

Summary of LFABP expression in HCCs.

Case	Cirrhosis	Degree of HCC differentiation	LFABP expression
1	Yes (HCV)	WD	++
2	Yes (SH)	WD	++
3	Yes (SH)	WD	++
4	Yes (HCV)	WD	+
5	Yes (HCV)	WD	+
6	No (inflammatory HCA)	WD	++
7	No (mild steatosis)	WD-MD	++
8	No	WD-MD	-
9	No	MD	++
10	Yes (HCV)	MD	++
11	Yes (SH)	MD	+
12	Yes (SH)	MD	+/-
13	Yes (HCV)	MD	-
14	Yes (HCV)	MD-PD	-
15	Yes (SH)	PD	+/-
16	Yes (HCV)	PD	-
17	Yes (HCV)	PD	-

Conclusions: LFABP loss is common in HCC and may rarely be seen in more well-differentiated HCC. Therefore, LFABP loss should not be interpreted as evidence for HCC over HCA when other features support a diagnosis of HCC. The findings raise the possibility of HNF-1α inactivation in HCC, particularly in less differentiated tumors.

1669 Histopathologic Features of Primary Hepatocellular Carcinomas Are Poor Predictors of Extrahepatic Metastasis

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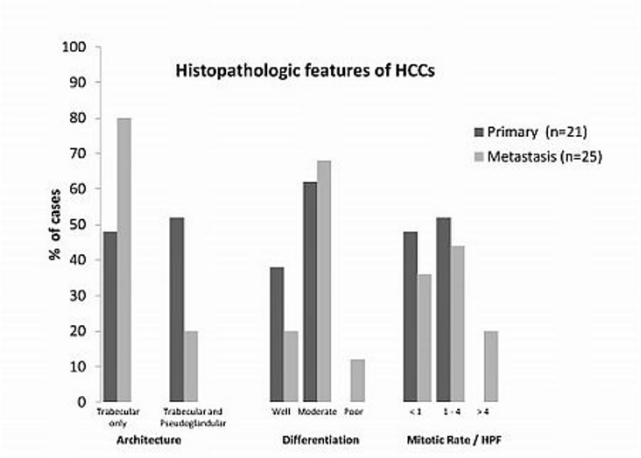
Background: Extrahepatic metastases of hepatocellular carcinoma (HCC) are uncommon, and studies characterizing this subset of HCCs are lacking. This study aims to 1) compare the histopathologic features of primary and metastatic HCCs and 2) determine whether any histologic features of primary HCC are predictive of extrahepatic metastasis.

Design: In this retrospective study, patients with tissue diagnoses of both primary and metastatic HCC between 1996 –2012 were identified from our institution's pathology archives. A blinded re-review was performed on the original diagnostic slides. Tumor architecture, histologic grade, and mitotic rate were evaluated. Primary tumors were additionally assessed for lymphovascular invasion.

Results: Twenty-five metastatic HCCs and their corresponding primary tumors were identified from 21 patients (81% male, 19% female, mean age at primary diagnosis 57.6 years, range 44-74 years). Primary tumors were from 17 explanted livers and 4 partial hepatectomies. Time between resection of primary and metastatic tumors ranged from 3 to 69 months (average = 21.6 months). Lymphovascular invasion was identified in 17 of 21 (81%) primary HCCs. Metastatic sites and histologic features are shown below.

Metastatic site	n (%)
Lung	9 (36)
- Left	4 (16)
- Right	4 (16)
- Unspecified (endobronchial)	1 (4)
Abdominal wall	3 (12)
Rib	3 (12)
Adrenal	2 (8)
Ostomy site	2 (8)
Pleura	1 (4)
Vertebrae	1 (4)
Vertebral meninges	1 (4)
Diaphragm	1 (4)
Small bowel	1 (4)
Unspecified soft tissue	1 (4)



Conclusions: Lymphovascular invasion is observed in the majority of primary HCCs with extrahepatic metastases, with lung being the most frequent metastatic site. Extrahepatic metastases show similar histologic features with their primary counterparts, and histologic features do not significantly vary among metastatic sites. Neither architectural pattern, histologic grade, nor mitotic index are predictive of extrahepatic metastases, nor do these features significantly correlate with time to metastasis. Therefore, these findings indicate that histopathologic features of primary HCCs are unreliable indicators of disease progression.

1670 Hepatic Portal Fibrosis but Not Central Fibrosis Is Associated with Elevated Right Atrial Pressure in Patients with Right Heart Failure

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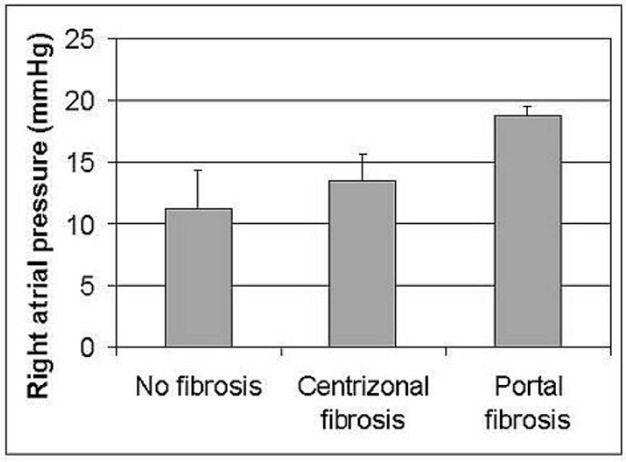
Background: Chronic right heart failure predisposes to hepatic passive congestion and centrizonal necrosis, which may lead to hepatic fibrosis (cardiac sclerosis). While there have been several studies in the histologic features of hepatic passive congestion and fibrosis in individuals with right heart failure, the correlation of right heart physiology and the pattern of hepatic fibrosis remain unclear.

Design: Liver biopsies were examined in patients with right heart failure (n=36) of various etiologies including congenital heart disease, idiopathic cardiomyopathy, ischemic heart disease and valvular heart disease. The exclusion criteria were underlying chronic liver diseases, alcoholic liver disease, significant steatosis (> 10%), and malignant neoplasm. Right heart structure and function were examined by echocardiography and / or right heart catheterization. The pattern of fibrosis was correlated with echocardiographic parameters.

Results: The presence of portal fibrosis is associated with significantly higher right atrial pressure measured by echocardiography (see figure below), when compared with subjects with no fibrosis (p=0.029) or subjects with centrizonal fibrosis only (p=0.03).



The presence of portal fibrosis is also significantly associated with increasing severity of right atrial dilatation (p=0.02) and right ventricular dilatation (p=0.04), indicating long standing volume and / or pressure overload. Centrizonal fibrosis without portal fibrosis is significantly associated with right atrial dilatation (p=0.01), but not with right ventricular dilatation. Other histopathologic features include moderate to marked sinusoidal dilatation and centrizonal hepatocyte atrophy.

Conclusions: Although sinusoidal dilatation and centrizonal fibrosis are the hallmarks of hepatic passive congestion, the presence of portal fibrosis is suggestive of more advanced disease, as it correlates with more severe impairment of right heart function, regardless of the etiologies of right heart failure.

1671 Clinical Significance of Subacute Nonsuppurative Cholangitis: A Study of 25 Cases

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Background: Subacute nonsuppurative cholangitis (SNC) is a unique type of cholangitis, characterized by ductular reaction with inspissated bile plugs in dilated ductules. The few studies on a limited number of cases have suggested an association between SNC and sepsis and/or intraabdominal infection. However, we believe this is an under-recognized finding in liver biopsies. Our goal in this study was to histologically evaluate a larger number SNC cases and to correlate the diagnosis with various clinical parameters.

Design: Pathology database was searched retrospectively to identify liver biopsies that carried the potential diagnosis of SNC using various histologic descriptions and diagnostic terms. Seventy cases were identified spanning a period of 12 years. Twenty-five cases fulfilled the histologic criteria for SNC. Clinical information was obtained from electronic medical records.

Results: Twenty-two patients were liver transplant recipients; 21 were transplanted within 1-12 months, and one transplanted 14 years ago. Twenty-two (88%) patients, including all 3 non-transplant patients, had clinical presentations of sepsis at the time of the liver biopsy or shortly thereafter. Four patients (16%) had intraabdominal infection with abscess formation. Twenty patients (80%) had positive bacterial cultures from bile, blood and/or sputum reported from days prior to days following the liver biopsy. None of the cases had evidence of large bile duct obstruction or vascular abnormality by imaging studies. Follow-up liver biopsies were available in 5 patients. Four had follow-up biopsies within 2-4 weeks, which all showed minimal histologic improvement. One patient had a repeat biopsy 97 days later, which showed areas of infarction and pronounced canalicular cholestasis in addition to continued features of SNC. Thirteen patients (52%) died shortly after the initial biopsy with no follow-up biopsies.

Conclusions: Our study examined the largest number of SNC cases and our findings support the notion that SNC in a liver biopsy is associated with the presence of sepsis and/or intraabdominal infection. In addition, our data show that the histologic features of SNC can stay for a prolonged period of time and that patients with SNC bear a poor prognosis. Familiarity with this entity and recognition of the association with sepsis/intraabdominal infection may help avoid unnecessary clinical work-up and/or incorrect management, especially in the transplant setting where there is generally a broad list of differential diagnosis for abnormal liver tests.

1672 The Prevalence of True Non-Alcoholic Steatohepatitis (NASH) in Patients Presenting with Autoimmune Hepatitis (AIH) and Pericellular Trichrome Staining, a Potential Mimicker of NASH in Active AIH

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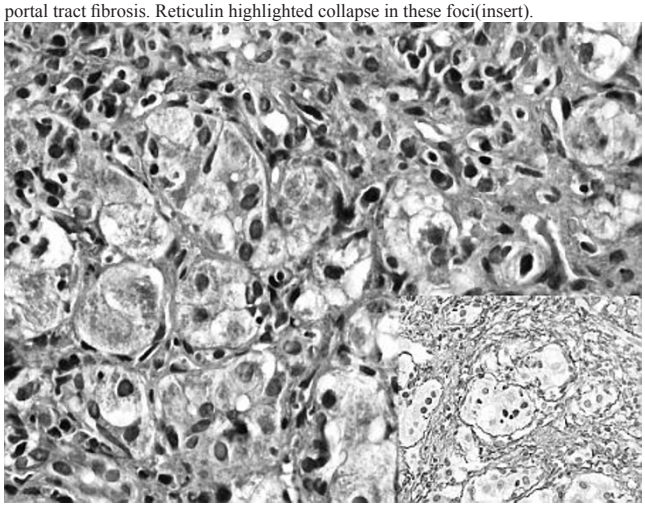
Background: Given the increasing burden of NASH in the general population, a similar rise might be expected in AIH patients. This is a clinical concern as AIH treatment can exacerbate NASH. We sought to determine the prevalence of NASH in pts presenting with AIH and to document their clinical and histologic findings.

Design: We identified all AIH cases at our institution in the last 35 yrs. with documenation of age, gender, comorbidities(DM, hyperlipidemia, obesity, HTN), alcohol abuse, lab data(auto-Abs,Igs,HBV/HCV serologies) and history of steroid response. Only cases meeting 2008 simplified Autoimmune Hepatitis Group(AHG) criteria were accepted as AIH. These biopsies were further evaluated for Grade/Stage(Batts-Ludwig), steatosis,

and NASH(Brunt). Statistical analysis used point estimates supplemented with exact 95% confidence intervals. Associations between NASH and other conditions were assessed using contingency table methods.

Results: Of the database pts(n=127) 73 (Age 11-78;mean 50:62% female) met AHG criteria for AIH. Overall prevalence of NASH at AIH diagnostic biopsy was 16.4%(12 of 73;CI 8.8-27%). An additional 15% had steatosis. The only comorbidities significantly association with NASH were type 2 diabetes(p=0.059) and older age(p=0.043). 19 of the 73 biopsies had "NASH-like" features without meeting criteria for NASH:5 had pericellular trichrome staining(PCTS) and 14 had PCTS directly associated with ballooned hepatocytes(Fig 1). The PCTS was focal/non-zonal and paler compared to portal tract fibrosis. Reticulin highlighted collapse in these foci(insert).



Conclusions: The prevalence of NASH in pts presenting with AIH was 16.4%. In addition, 26% of our AIH diagnostic biopsies displayed a "NASH-like" feature of PCTS often associated with ballooning. Although most consistent with necrosis/parenchymal collapse secondary to active AIH, this finding has the potential to be misinterpreted as NASH, particularly in the presence of steatosis. Attention to strict NASH criteria and examination of reticulin stain was essential in making this distinction.

1673 Is 1 cm a Valid Cut-Off as the Cholecystectomy Indication for Gallbladder Polyps?: Clinicopathologic Analysis of 432 Cases

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Background: Polyps of the GB are common incidental lesions. 1 cm is the arbitrary criteria widely employed as the indication for cholecystectomy. The value of this cut-off has not been systematically verified from histopathology perspective.

Design: Clinicopathologic characteristics of 432 polypoid lesions >3mm were analyzed.

Results: See Tables 1&2. *(NNP: non-neoplastic polyp; ICPN: intracholecystic papillary neoplasm; i.e., WHO's "adenomas" and "intracystic papillary neoplasms";FMG: Fibromyoglandular/fibroepithelial polyp;CP: Cholesterol polyp)*

Table 1

Tumor Characteristics†	Polypoid Invasion (n = 29)	ICPN (n = 120)	Incipient ICPN (n = 41)	Cholesterol-like polyp (n = 148)	Dysplasia in otherwise NNP (n = 18)	FMG (n = 76)	p-value‡
Age (±SD)	70.7 (8.6)	61.0 (14.3)	59.9 (11.7)	49.7 (11.8)	58.6 (10.5)	55.6 (15.3)	<0.001
Gender							
Female	24 (85.7%)	79 (67.5%)	29 (85.3%)	93 (65.0%)	11 (64.7%)	60 (81.1%)	0.019
Male	4 (14.3%)	38 (32.5%)	5 (14.7%)	50 (35.0%)	6 (35.3%)	14 (18.9%)	
Average Size, cm (range)	2.8 (0.9 - 6.0)	2.6 (1.0 - 7.7)	0.45 (0.3 - 0.9)	0.52 (0.3 - 2)	1.1 (0.3 - 5.0)	0.47 (0.3 - 1.3)	<0.0001
<1cm	4 (13.8%)	0	41 (100%)	139 (93.9%)	9 (50.0%)	72 (94.7%)	<0.0001
≥1cm	25 (86.2%)	120 (100%)	0	9 (6.1%)	9 (50.0%)	4 (5.3%)	
Inflammation degree							
Score 0	0	2 (1.8%)	0	3 (2.1%)	0	0	<0.0001
Score 1	4 (28.6%)	39 (33.9%)	18 (56.3%)	109 (75.7%)	10 (62.5%)	30 (43.5%)	
Score 2	4 (28.6%)	48 (41.7%)	11 (34.4%)	25 (17.3%)	5 (31.3%)	25 (36.2%)	
Score 3	6 (42.8%)	26 (22.6%)	3 (9.3%)	7 (4.9%)	1 (6.2%)	14 (20.3%)	

Table 2

Polyp Size	Neoplastic GB Polyps† (n = 208)	Non-neoplastic GB Polyps‡ (n = 224)	p-value*
<1cm (n (%))	54 (26.0%)	211 (94.2%)	<0.0001
≥1cm (n(%))	154 (74.0%)	13 (5.8%)	

†Neoplastic GB Polyps = Polypoid invasion + ICPNs of all types+ Dysplasia in otherwise NNP. ‡Non-neoplastic GB Polyps = Cholesterol-like polyp + FMG + Others. ∗Based on Fisher's chi square test.

Conclusions: GB polyps >2cm are virtually all neoplastic. 1 cm is a reasonable but less reliable cut-off for cholecystectomy indication: While only 6% of the more common non-neoplastic polyps are >1 cm, at the same time, about a quarter of the neoplastic polyps are <1 cm. Other paramaters elucidated in this study that may help in the management algorithm in favor of holding off a cholecystectomy include absence of severe background inflammation (which may be helpful in the radiologic differential diagnosis), younger age, and male gender, which are in favor of a cholesterol-polyp.

1674 Does Size Matter? – Assessing the Adequacy of Core Biopsies for Medical Liver Diseases

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Background: Core biopsy is a key tool in diagnosis and staging of many medical liver diseases. There are concerns that the small size of the specimen obtained and the patchy nature of many of these diseases may result in misdiagnosis or inaccurate staging. In the United Kingdom, the Royal College of Pathologists has issued guidelines for minimum (at least 10 mm in length and 6 portal tracts) and optimum (at least 20 mm in length and 11 portal tracts) sizes. We performed a retrospective review of our cases over the last 15 years to assess our compliance with this guideline and the outcome of technically inadequate specimens.

Design: All core biopsies performed for medical liver diseases reported between January 1997 and December 2011 were identified using our pathology report archive and the search term "liver". Cases were included if the post-processing core length and number of portal tracts and central veins were present in the report. Referral cases and biopsies of mass lesions were excluded. Reports were reviewed and the following data extracted; number of cores, length of longest core, overall core length, number of portal tracts, number of central veins, Ishak stage. Any comments regarding adequacy were also recorded. For inadequate biopsies, the report archive was searched to determine if a repeat had been performed, and at what time after the original biopsy.

Results: 2796 core biopsies were reported in the study period, of which 1342 (48%) met the inclusion criteria. Applying the Royal College of Pathologists' guideline 266 (19.8%) would be considered adequate, 757 (56.4%) suboptimal and 319 (23.8%) inadequate, but in only 40 (15%) of the biopsies called inadequate by this standard was a comment to that effect included in the report. Only 2 (0.6%) of the inadequate biopsies were repeated within three months.

Conclusions: Diagnosis of medical liver diseases on core biopsy is usually supported by biochemical, microbiological and serological testing. Staging of diseases by core biopsy is subject to intraobserver variability, and there are increasing advances in non-invasive tests to detect fibrosis. Our review shows greater than 80% of our core biopsies would be considered inadequate or suboptimal for diagnosis and staging of medical liver diseases based on the Royal College of Pathologists' guidelines, but only a minority of these patients required a repeat biopsy. Therefore, with good clinicopathological correlation, auxiliary tests and improvements in technology perhaps, ultimately, core biopsy size does not matter at all.

1675 Routine Liver Biopsy of the Background Liver Is Potentially Useful in Patients with Hepatocellular Carcinoma

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Background: In patients with hepatocellular carcinoma (HCC), treatment options depend not only on tumor characteristics, but also on the background liver. In many instances, confirmation of cirrhosis may limit potential for resection or necessitate liver transplantation listing. Though these are important considerations, routine biopsy of the non-tumoral parenchyma in the evaluation of liver masses has not been previously evaluated. The goal of this study was to evaluate the role of biopsying the background liver in patients with HCC.

Design: The pathology database was searched for liver biopsies with a diagnosis of HCC from 2000 to 2011. All available cases were divided into two groups. The first group (unpaired) comprised HCC patients with only liver mass biopsy while the second (paired) group comprised patients with biopsies available from the liver mass and the non-neoplastic liver. Demographic and treatment data was abstracted for both groups. The paired group was also evaluated for background chronic liver disease and/or cirrhosis, treatment proposed prior to biopsy, impact of biopsy results and treatment pursued after the biopsy.

Results: 28 unpaired and 20 paired liver biopsies were available for review. In the paired group, biopsies were performed simultaneously in 17 patients, 3 within 6 months of each other. All 14 cases of clinically suspected cirrhosis were confirmed on biopsy. Among the remaining 6 cases without a clinical suspicion of cirrhosis, cirrhosis was uncovered on biopsy in 1. In 3 patients (15%), treatment was altered by the background liver findings, which precipitated surgical management. In 2 patients, the overall management of liver disease was altered based on the background parenchymal biopsy results. Patients in the unpaired group tended to have more advanced disease (7/28 vs 1/20, p= 0.06, Fisher's exact test), when systemic therapy as initial treatment was used as a surrogate for advanced disease. Patients in the unpaired group were more often referred from outside our institution (19/28 vs 2/20; p<0.01, Fisher's exact test).

Conclusions: Though the status of background liver impacts the management of a minority of patients with HCC, this impact is significant in patients with early disease and may potentially trigger definitive treatment with curative intent. In a select population of HCC patients, biopsy of the background liver should be considered.

1676 Hepatocellular Adenomas in a Large Community Population 2000-2010: Reclassification Per Current WHO Classification and Long-Term Follow-Up

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Background: Data for WHO classification of hepatocellular adenoma (HA) is largely based on cases from tertiary care centers. This study examines distribution of HA subtypes in a community setting and determines the impact of immunohistochemistry (IHC) on reclassification, diagnosis, and management.

Design: All cases diagnosed as HA in a large community hospital from 2000-2010 were reviewed (n= 49) to confirm the diagnosis. Where tissue was available (n=35), IHC

was performed for evaluation of HA: liver fatty acid binding protein (L-FABP), serum amyloid A (SAA), C-reactive protein(CRP), beta-catenin (bC), glutamine synthetase (GS), heat shock protein 70 (HSP70) and glypican-3 (GPC).
Results: There were 35 cases available for IHC evaluation. The reclassification of HAs was based on histopathologic and immunophenotypic features.

Table 1: Reclassification of HAs over a 10-year period (n=35)

HNF1alpha inactivated	9/35 (26%)
Inflammatory	7/35(20%)
B-catenin activated/atypical	6/35 (17%)
Unclassified	9/35 (26%)
Very Well-differentiated HCC	1/35 (3%)
Focal Nodular Hyperplasia	3/35 (9%)

There was histopathologic and immunophenotypic agreement in 26 cases (26/35). However, in 9 cases the diagnosis or HA classification was changed upon review of IHC stains. The immunophenotype by HA subtype is shown.

Table 2: Immunophenotype of cases of hepatocellular adenoma (n=31)

	LFABP	SAA	CRP	bC	GS	HSP70	GPC
HNF inactivated	Negative	Negative	Negative	Membrane	Variable	Negative	Negative
Beta-catenin/ atypical	Positive	Negative	Negative	+/- Membrane; Nuclear	Diffuse	Negative	Variable
Inflammatory	Positive	Positive	Positive	Membrane	Variable	Negative	Negative
Unclassified	Positive	Negative	Negative	Membrane	Variable	Negative	Variable

Clinical follow-up was available for 33 cases (33/35), including the HCC case; no case developed metastasis. The majority of HAs (18/30) were treated with resection without recurrence; in 6 cases (6/33) that were untreated and followed, the HAs remained stable.
Conclusions: IHC led to HA reclassification in 26% of cases. Distribution of HA cases (n=31) at a community hospital differs from prior studies (Bioulac-Sage), with fewer HNF-1 inactivated (29% vs 35-40%) and inflammatory subtypes (23% vs. >50%); and greater beta-catenin activated/atypical (19% vs 10-15%) and unclassified subtypes (29% vs. 5-10%). The smaller proportion of inflammatory subtypes may reflect earlier classification of these lesions as telangiectatic FNH.

1677 Hepatic Outflow Obstruction: Underappreciated Histologic Features on Biopsy

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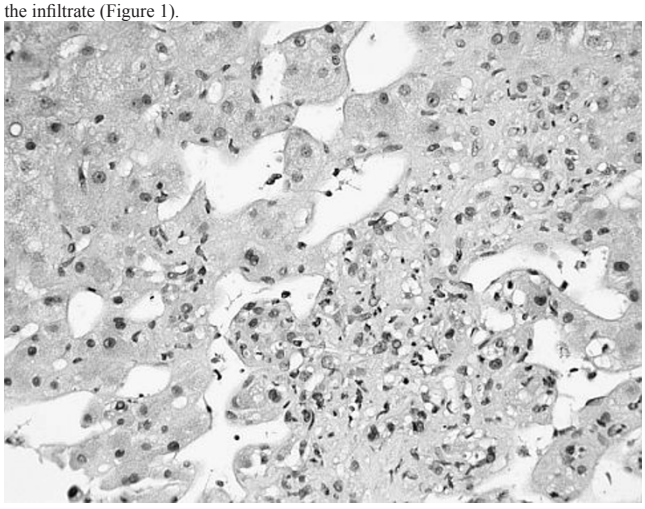
Background: Cardiac hepatopathy (CH) and Budd-Chiari Syndrome (BCS) are two disease entities with significantly different pathophysiology but overlapping histologic findings. We hypothesized that a constellation of biopsy findings can help distinguish between the two, and suggest the diagnosis of CH in previously undiagnosed patients.
Design: 42 patients, 17 with a diagnosis of CH and 25 with a diagnosis of BCS were identified by searching the surgical pathology database from 1983-2012. Hematoxylin & Eosin and trichrome stained slides were evaluated for histologic features listed in Table 1.

Histologic Findings of Cardiac Hepatopathy vs. Budd Chiari Syndrome

	Cardiac Hepatopathy	Budd Chiari Syndrome
Sinusoidal Dilatation	94.1%	88%
Bile Ductular Reaction	70.6%	72%
Centrilobular Inflammation	52.9%	8%
Portal Inflammation	41.2%	52%
Centrilobular Dropout/Necrosis	41.2%	76%
Portal-based Fibrosis	71.4%	68%
Centrilobular Fibrosis	92.6%	60%
Sinusoidal Fibrosis	85.7%	48%
Cholestasis	5.9%	16%
Steatosis	23.5%	8%

Results: Features common to both forms of hepatic outflow obstruction were sinusoidal dilatation, and portal tract changes of fibrosis, chronic inflammation, and bile ductular reaction (Table 1). Histologic findings significantly more common in CH included centrilobular fibrosis (p=0.02), sinusoidal fibrosis (p=0.014), and patchy centrilobular mixed inflammation (p<0.01). Only centrilobular hepatocyte dropout/necrosis was significantly more common in BCS (p=0.01). The focal zone 3 inflammation seen in CH, albeit mild, was unusual in that admixed neutrophils were frequently present in the infiltrate (Figure 1).



Conclusions: The finding of centrilobular and sinusoidal fibrosis in CH compared to BCS is not unexpected, given the chronic nature of most CH. Portal tract changes are common in both forms of hepatic outflow obstruction and should not deter one from making the diagnosis of hepatic outflow obstruction. An unusual pattern of patchy mixed zone 3 inflammation with neutrophils was noted in CH. Centrilobular and sinusoidal fibrosis and dilatation, with or without focal zone 3 inflammation may be suggestive of CH in biopsies from patients without a prior diagnosis.

1678 GLUT1 Expression in Adult Hepatic Vascular Neoplasms

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Background: GLUT-1 is a glucose transport protein expressed in several vascular lesions, notably in cutaneous juvenile hemangioma (CJH) and hepatic infantile hemangioma (HIH), leading some to suggest that HIH is the visceral counterpart to CJH. GLUT-1 expression has recently been demonstrated in malignant vascular neoplasms involving soft tissue, suggesting that expression may not be restricted to benign vascular tumors. This study aims to further characterize a spectrum of adult hepatic vascular neoplasms for GLUT-1 expression.
Design: We used immunohistochemistry in formalin fixed paraffin embedded tissue to evaluate benign vascular liver tumors (cavernous hemangiomas (CH), n=10) as well as malignant vascular liver tumors (epithelioid hemangioendotheliomas (EHE), n=8, and angiosarcomas (AS), n=4)) and the recently described small vessel hepatic hemangioma (SVH) (n=5), which is of uncertain malignant potential.
Results: GLUT1 was variably expressed in 38% of hepatic EHE (3/8) and 50% of hepatic angiosarcoma cases (2/4), but in none of the cavernous hemangioma (0/10) or SVH cases (0/5).
Conclusions: GLUT1 expression is common in malignant vascular tumors of the liver and should be interpreted with caution as a diagnostic marker of HIH. SVH often has an infiltrative border and may histologically mimic well-differentiated angiosarcoma and therefore, while absence of GLUT-1 staining does not exclude angiosarcoma, positive GLUT-1 staining should raise further suspicion for angiosarcoma in such cases.

1679 Isolated Extrahepatic IgG4-Related Sclerosing Cholangitis Mimicking Cholangiocarcinoma

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Background: Extrahepatic bile ducts are the most commonly involved extrapancreatic site in patients with autoimmune pancreatitis (AIP). IgG4-related sclerosing cholangitis (IgG4-SC) without evidence of pancreatic or other organ involvement is less common and less well recognized. This entity is very difficult to preoperatively distinguish from cholangiocarcinoma. Here we describe 9 cases of isolated IgG4-SC.
Design: We retrospectively identified patients with biliary strictures seen between January 2001 to January 2011 who were clinically suspected to have cholangiocarcinoma, but in whom pathologic assessment showed IgG4-SC. All cases with a previous history of IG4-related disease in another organ (including AIP) were excluded. We examined the clinical, cytologic (including fluorescent in situ hybridization [FISH] results) and radiologic features of these cases. The histologic slides (n=9) were reviewed and appropriate blocks selected for IgG4 immunohistochemistry.
Results: All nine patients were males with a median age of 59 years (range 45 to 76 years). All 9 presented with obstructive jaundice and a cholestatic liver profile and were clinically and radiologically suspected to have cholangiocarcinoma. The strictures involved the common hepatic duct (n=3), common bile duct (n=3) or left and right hepatic ducts (n=3).Serum IgG4 was measured in 8 patients at presentation and was mildly elevated (<2 x of upper limit of normal or 240 mg/dL) in only 3 (38%). Cytology was interpreted as negative in 6 cases, atypical in 1 and suspicious for adenocarcinoma in 1. FISH was positive for aneuploidy of chromosomes 3, 7 and 17 in one case and was equivocal (trisomy 7) in 2. Eight of 9 (89%) patients underwent radical resection for suspected cholangiocarcinoma. Histologic sections revealed a prominent lymphoplasmacytic infiltrate with storiform fibrosis and increased IgG4 positive plasma cells (>30/high power field) in all cases. Obliterative phlebitis was seen in 7 of 8. One patient was diagnosed on biopsy which showed typical morphology of IgG4-SC. On median follow-up of 2.8 years, none of the 9 patients has developed a relapse in any organ.
Conclusions: Extrahepatic IgG4-SC may present as an isolated lesion without evidence of AIP or other organ involvement. The normal serum IgG4 and the absence of other organ involvement, coupled with imaging findings suggestive of cancer and equivocal findings for cancer on cytology and FISH, make surgical resection unavoidable in such patients. Better diagnostic clues for IgG4-SC are needed to avoid major surgery in such patients.

1680 A Novel Fibrosis Staging System for Cardiogenic Liver Disease and Relationship with Clinical, Biochemical, and Heart Physiologic Parameters: Development of a Common Language for Liver Transplant Decisions

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Background: Standard fibrosis staging schemes, which drive clinical decisions, are well established for many chronic liver diseases, however, no such system exists for fibrosis secondary to mechanical vascular etiologies seen in heart disease. For patients undergoing heart transplantation, we are often faced with assessing the need for a joint liver transplantation; unlike other liver diseases, no standard parameters exist for this liver transplant decision. We propose a novel liver fibrosis scoring system specific for outflow obstruction etiologies and determined its relationship with clinical, biochemical, and physiologic parameters and concordance between biopsy and liver explants.

Design: Patients with a diagnosis of changes consistent with venous outflow obstruction were selected for study and those with other patterns of liver injury not due to cardiac causes were excluded. The extent of fibrosis (Masson's Trichrome) was scored: 1. centrovenular (CV) on a scale of 0 (none) to 5 (central to portal bridging), 2. percent (%) space of Disse fibrosis (SOD) and 3. percent surface area of fibrosis (SAF). Cardiac ejection fraction, corrected and free hepatic sinusoidal pressures, liver function tests, serum albumin and total protein were correlated with fibrosis scores.
Results: We evaluated 46 patients (median age 32 years [range 22-78]; 29 men, 17 women; 8 with congenital heart disease), 14 of whom underwent joint heart-liver transplantation. 43 patients had liver biopsies, including 8 who had subsequent explants. The median $\pm$ standard deviation of fibrosis scores are as follows: 1. CV 3$\pm$1.6; 2. SOD 90%$\pm$33%; 3. SAF 20%$\pm$15.6%. There was a strong linear relationship with percent SAF and CV score [SAF=8.3xCV+1.4, R=0.81] but no correlation with any of the biochemical or physiologic parameters (R<0.15). Biopsies and liver explants had concordance of scores.
Conclusions: We propose the percent surface area of fibrosis be used as a single metric for evaluation of liver disease secondary to heart disease. This metric is amenable to future computer image analysis and can serve as a common language to develop decision models for joint heart and liver transplantation. That the fibrosis scores are independent of any clinical, biochemical and physiologic parameters attests to the need for liver biopsy in developing models for clinical decision making in the setting of heart disease.

1681 The Pre-Senescence Features of Chronic Liver Allograft Rejection Can Be Recognized Prior to Full Development of Banff-Defined Criteria

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Background: Chronic rejection (CR) is one of the most serious complications of allograft liver transplant and even though it occurs at a rate of 3% over 5 years, it has great impact on allograft outcome and survival. Banff criteria are used to diagnose CR when specific parameters are documented in biopsy. We however describe series of changes we believe precede earliest Banff criteria of bile duct senescence in majority of sampled ducts, which could help in earlier diagnosis and timely intervention of CR.
Design: Histologically documented CR biopsies between 2003 and 2011, who had at least one biopsy prior (pre-CR) to the one that ultimately diagnosed CR were identified. Clinical information was retrieved from transplant electronic record and corresponding biopsies reviewed. Control biopsies include 10 cases of allograft liver due to recurrent HCV (rHCV) and 10 of proven obstruction.
Results: Twenty-two biopsies in 22 patients with CR were included of which 15 (68.2%) had what we have called pre-senescence changes. These include 7 female and 8 male [ages: 20-69 years (mean 47); time from transplant to CR diagnosis: 13d-84 months (mean: 28months); time between pre-CR and diagnostic CR biopsies: 4 d-16 months (mean 5.8 months.
Features attributable to poor bile drainage seen in periportal areas in 15 of 22 pre-CR biopsies are:
-Peri-portal small cell change with high N: C ratio
-No significant ductular proliferation (confirmed by CK7 immunostain)
-Early but sparse intermediate cells /biliary metaplasia of periportal hepatocytes
-Occasional but less than 50% senescence features in terminal bile ducts
-No significant (i.e. less than 30%) duct loss.
Alkaline Phosphatase was increased in all 15 patients at the time of pre-CR biopsies. 7 of 22 patients showed 0-1 of the above features probably attributed to longer interval between pre-CR and CR biopsies (11.1 months compared to 5.8 months). None of the rHCV showed the above features, but some were seen in obstruction biopsies, although these in addition had ductular reaction and intermediate cells by CK7 was more pronounced in obstruction than pre-CR biopsies.
Conclusions: Our observation suggests that these histologic findings might represent early CR features resulting from relative bile stasis and preceding morphologic evidence of significant duct atrophy/senescence and/or loss. Recognizing and validating these features will help in earlier diagnosis and intervention of patients in whom CR process is already evolving, but could not meet current diagnostic criteria for CR.

1682 Pathological Differences between IgG4-Related Sclerosing Cholangitis with and without Autoimmune Pancreatitis

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Background: IgG4-related sclerosing cholangitis (IgG4-SC) usually accompanies autoimmune pancreatitis (AIP), and IgG4-SC without AIP clinicopathologically mimics primary sclerosing cholangitis (PSC) and cholangiocarcinoma. In this study, we examined pathological differences between IgG4-SC with and without AIP.
Design: Partial hepatectomy and bile duct resection specimens were obtained from 7 patients with IgG4-SC accompanied by AIP (male/female = 6/1, average age 66 yrs) and 5 IgG4-SC without AIP (all male, average age 71 yrs). Using paraffin sections, in addition to HE and EVG staining, immunohistochemistry for IgG4 was performed.
Results: Location of the affected bile ducts: In IgG4-SC with AIP, affected bile ducts were in the middle and lower parts of common bile ducts, but intrahepatic bile ducts and hilar bile ducts were not involved in any cases. In constrast, all cases of IgG4-SC without AIP accompanied hilar hepatic lesions and were also found to various degrees in the upper part of common bile ducts and branches of hepatic ducts. Moreover, inflammatory pseudotumors were found in the hepatic hilus in 2 cases of IgG4-SC without AIP. Histology: Pathological findings of common bile ducts were common features of IgG4-related diseases such as marked lympho-plasmacytic infiltration, follicle formation, fibrosis, obliterative phlebitis, and numerous IgG4-positive cells in the intraductal wall and periductal area, irrespective of being with or without AIP. Biliary epithelium was well-preserved and inflammation was noted in peribiliary glands and the peri-nerve bundle compared with superficial mucosa. In IgG4-SC without AIP, dilatation and stricture of hilar bile ducts, similar to PSC, and proliferation and dilatation of the peribiliary gland were found in some cases. In the hepatic hilus, IgG4-positive cells broadly infiltrated and were noted in fibrous areas and the perineural bund, compared with the periductal area. Biliary intraepithelial neoplasia (BilIN): BilIN lesions were found in 2 of 7 cases of IgG4-S C with A IP and 3 of 5 cases of IgG4-SC without AIP. Erosion: Significant findings of neutrophil infiltration were not seen in IgG4-SC with AIP, but erosive change with neutrophils was found in hilar bile ducts of 3 of 5 cases with IgG4-SC without AIP.
Conclusions: Histology of common bile ducts in IgG4-SC without AIP was basically the same as that in IgG4-SC with AIP; however, IgG4-SC without AIP involved hepatic hilar lesions such as by dilatation and stricture of hilar bile ducts, BilIN, and erosion, suggesting that these findings complicate the differentiation of IgG4-SC without AIP from PSC and cholangiocarcinoma.

1683 IgG4 Reaction in Biliary Intraepithelial Neoplasia and Cholangiocarcinoma Arising from Sclerosing Cholangitis

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Background: The IgG4 reaction, consisting of marked IgG4-positive cell infiltration, was found in cholangiocarcinoma as well as IgG4-related sclerosing cholangitis (IgG4-SC). We have reported that IgG4 reaction in cholangiocarcinoma is a localized cancer-associated immune reaction to evade immune surveillance in an IL-10-related regulatory cytokine milieu. In this study, we examined IgG4 reaction in biliary intraepithelial neoplasia (BilIN) and cholangiocarcinoma arising from sclerosing cholangitis to clarify the significance of IgG4 reaction in the carcinogenesis of cholangiocarcinoma.
Design: Partial hepatectomy and explanted liver specimens were obtained from 6 patients with primary sclerosing cholangitis (PSC) (2 patients associated with overt cholangiocarcinoma) and 7 IgG4-SC. Using paraffin sections, immunohistochemistry for IgG4 and S100P (a phenotypic marker of BilIN and cholangiocarcinoma) was performed.
Results: IgG4-positive cells were scattered 5-23/hpf in S100P-positive BilIN as well as cholangiocarcinoma in 2 cases of PSC with cholangiocarcinoma, but there were none or few in those without cholangiocarcinoma irrespective of accompanying S100P-positive BilIN or not. In IgG4-SC, numerous IgG4-positive cells were found in all cases. Moreover, S100P-positive BilIN was found regionally in 2 of 6 cases, but there was no difference in IgG4 reaction between BilIN and non-BilIN regions.
Conclusions: In PSC cases with cholangiocarcinoma, IgG4 reaction was seen in BilIN as well as cholangiocarcinoma, but not in PSC without cholangiocarcinoma, irrespective of the presence of BilIN or not. These findings suggest that IgG4-related tumor immune reaction is associated with the development from BilIN to cholangiocarcinoma in PSC, rather than the histogenesis of BilIN. In addition to PSC, IgG4-SC, in which the IL-10-related regulatory cytokine milieu is associated with the pathogenesis, possessed S100P-positive BilIN lesions, suggesting that IgG4-SC is also a possible preceding disease of cholangiocarcinoma.

1684 Energy Metabolic Change Induced by ERRa-PGC-1a Axis in Chronic Non-Suppurative Destructive Cholangitis of Primary Biliary Cirrhosis

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Background: Primary biliary cirrhosis (PBC) is characterized by anti-mitochondrial antibody (AMA) against pyruvate dehydrogenase complex (PDC) and chronic non-suppurative destructive cholangitis (CNSDC). PDC catalyzes the conversion of pyruvate to acetyl-CoA and is an important control point in glucose and pyruvate metabolism. Estrogen-related receptor α (ERRα) is associated with the fatty acid degradation system, such as fatty acid oxidation, electron transport, and oxidative phosphorylation, and is functionally activated by a inducible coactivator, peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α). Moreover, the PGC-1α/ERRα axis interrupts glycolytic metabolism via the upregulation of pyruvate dehydrogenase kinase, isozyme 4 (PDK4), which functionally inhibits PDC-E1α by phosphorylation. In this study, we investigated the PGC-1α/ERRα axis to clarify the alteration of the energy metabolism in CNSDC of PBC.
Design: Using liver sections obtained from patients with PBC and control diseases, the expression of PGC-1α, ERRα, PDK4, and PDC-E1α was examined by immunohistochemistry. Using cultured human biliary epithelial cells (BECs), the mRNA expression of PGC-1α, ERRα, PDK4, and PDC-E1α and their alterations by starvation (treatment inducing PGC-1α expression) were examined by RT-PCR and real-time PCR, respectively.
Results: Immunohistochemistry revealed that the nuclear expression of ERRα and PGC-1α was exclusively found in CNSDC of PBC, but not normal bile ducts of PBC or any bile ducts in controls. Moreover, the expression of PDK4 was enhanced in CNSDC of PBC. The expression of PDC-E1α was constantly found in all bile ducts, irrespective of having a diseased or normal liver. Cultured human BECs expressed mRNAs of PGC-1α, ERRα, PDK4, and PDC-E1α and the mRNA of PDK4 increased according the upregulation of PGC-1α by starvation.
Conclusions: In CNSDC of PBC, the expression and activation of the ERRα-PGC-1α axis were found exclusively, suggesting an increase in the fatty acid degradation system and also the supply of acetyl-CoA from this system. Moreover, the upregulation of PDK4 accompanying PGC-1α expression in CNSDC of PBC suggests the interference of PDC-E1α function. The alteration of the energy system from glycolytic to fatty acid degradation was possibly associated with the pathogenesis of CNSDC and AMA in PBC.

1685 IgM Positive Plasma Cells Can Distinguish Primary Biliary Cirrhosis from Autoimmune Hepatitis in Cirrhotic Livers

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Background: Primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH) have similar histologic features, both characterized by dense lymphoplasmacytic portal inflammation. These two diseases may be difficult to distinguish on histology, particularly in end-stage liver. Recent studies have shown that IgG and IgM immunostaining can differentiate AIH from PBC in needle core biopsies; however, it remains unclear if this distinction also applies in cirrhotic liver.

Design: Explanted livers of 20 PBC and 18 AIH cases, each histologically and clinically proven, were included. Immunohistochemistry for IgM and IgG was performed on representative blocks using a polymer-based detection system. The numbers of IgM and IgG positive plasma cells in three representative high power (40X) fields per slide were counted.

Results: The average number of IgG positive plasma cells was 1.87 and 2.69 in PBC and AIH cases, respectively. The average number of IgM positive plasma cells was 6.13 and 1.87 in PBC and AIH cases, respectively. The difference in IgM positive cells was statistically significant (p=0.001). IgM positive plasma cells outnumbered IgG positive plasma cells in 17/20 (85%) PBC cases and in 7/18 (39%) AIH cases (p= 0.006).

Conclusions: Our study extends the known utility of IgM immunohistochemistry in the separation of PBC and AIH in needle core biopsies by demonstrating that the absolute number of IgM plasma cells is also greater in explants of cirrhotic PBC when compared to end stage AIH liver explants. These findings may be of particular clinical utility in the evaluation of end-stage cryptogenic cirrhosis.

1686 Endometrial Cysts within the Liver: A Rare Entity and Its Differential Diagnosis with Mucinous Cystic Neoplasms of the Liver

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Background: Endometrial cysts within the liver are rare occurrences, but can present as diagnostic challenges on small biopsies or frozen sections. One diagnostic pitfall is their clinical, histologic, and immunohistochemical features overlapping with mucinous cystic neoplasm (MCN) of the liver, which also has stroma underlying epithelium. We compare these two entities with respect to the clinical and immunohistochemical profiles.

Design: 4 cases of endometrial cysts within the liver were collected. Clinical and image records were reviewed. Immunostains including CK19, CK7, calretinin, SMA, vimentin, inhibin, ER, PR, and CD10 were analyzed. Immunostains (ER, PR, and inhibin) of 6 cases of MCNs of the liver were also analyzed.

Results: The mean ages of the patients with MCNs and endometrial cysts were 46 yrs (range 31-64) and 50 yrs (range 20-73), respectively. 3 of the 4 cases of endometiral cysts were located in the right lobe of liver (mean size: 8 cm). 2 patients presented with abdominal pain and 3 patients had a prior pelvic operation. 3 of the 4 patients had coexisting endometriosis. All 4 cases of endometrial cysts had positive ER, PR, and vimentin staining within both the epithelium and underlying stroma. 3 cases had additional immunostains performed (not available in the 4th case due to tissue exhaustion), which all showed CK19 and CK7 positivity (only in epithelium), CD10 positivity (only in stroma), and inhibin and calretinin negativity (in epithelium and stroma). 1 case had SMA positive stroma. All 6 MCN cases were located in the left lobe of liver (mean size: 11 cm) with positive ER, PR, and inhibin staining only present in the stroma, but not in the overlying epithelium.

Conclusions: Endometrial cysts of the liver can mimic MCNs both clinically and morphologically. Interestingly, most endometrial cysts occur in the right lobe, while all MCN occurred in the left, suggesting their distinct pathogenesis. The key immunohistochemical distinctions are ER and PR positivity in both the epithelium and stromal cells in endometrial cysts, as compared to ER and PR positivity only present within the stromal cells of MCNs. Also the stromal cells are CD10 positive and inhibin negative in cases of endometrial cysts, with the opposite staining pattern in MCNs. Awareness of this distinct staining pattern and the possibility of hepatic endometrial cysts can lead to accurate diagnoses and appropriate treatment modalities.

1687 Tubulocystic Carcinoma of Bile Ducts: A Hitherto Unrecognized and Diagnostically Challenging Entity Often Mistaken as a Benign Lesion; Clinicopathologic Analysis of 6 Cases

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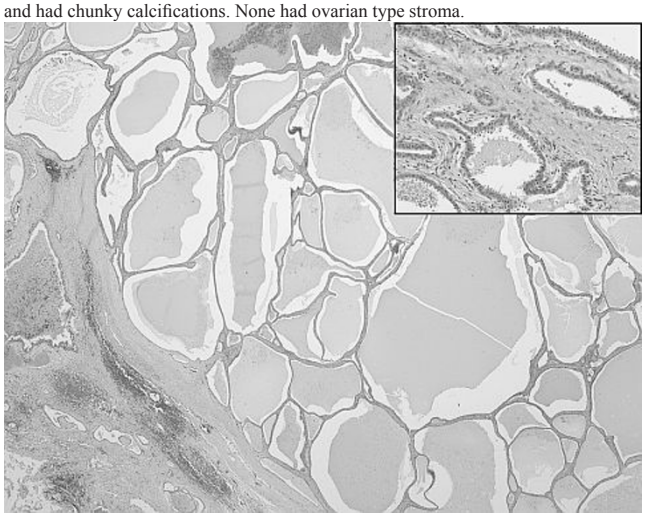
Background: A previously unrecognized type of biliary adenoca characterized morphologically by a distinctive tubulocystic (TC) pattern highly similar to TC carcinoma of kidney is described.

Design: 6 examples of this entity were analyzed.

Results: M/F: 3/3; Mean age, 66 (44-78). Mean size, 4.4 cm (3-7). 3 intrahepatic, 3 perihilar. Microscopically, the tumors were virtually identical to the TC ca of the kidney, composed of a conglomerate of variably-sized cysts forming microcystic pattern (most within millimeters, some up to a centimeter) forming a relatively circumscribed mass with smooth bulging contours and "bubble wrap" appearance. The cysts contained homogenous secretory material, and were mostly lined by a single layer of relatively monotonous but atypical cuboidal to flat/attenuated cells without any overt mucin. The apical cytoplasm often contained projections resembling cilia or snouts, with focal hobnail pattern. Nucleoli were prominent in non-attenuated areas. In some tubules/cysts, daughter nodules composed of small round microtubules or abortive papillary units were noted, and in 2, there was transition into a florid papillary nodules. Nodular clusters of small tubules with cribriforming were also seen. Intervening stroma showed a distinctive nodular hyalinization with vascularity reminiscent of sclerosed hemangioma, and had chunky calcifications. None had ovarian type stroma.



One patient had perineural invasion by cystic units showing identical, bland cytology. In follow up, 1 was dead of disease at 9 mos; others, alive with no evidence of disease at 3,19, 19, 28, 58 mos.

Conclusions: A hitherto unrecognized biliary tumor type characterized by a distinctive TC pattern strikingly similar to the same named entity in the kidney is described. While the compact growth and relatively bland features may raise the impression of an unusual form of "in situ" carcinoma, other characteristics including perineural invasion confirm that, as in its renal kindred, this tumor type represents a peculiar, indolent form of invasive ca that defies the more conventional definition of "invasiveness" employed in the biliary/GI tract.

1688 Histological Features of Primary Biliary Cirrhosis Predict Biological Response to Therapy and Outcome

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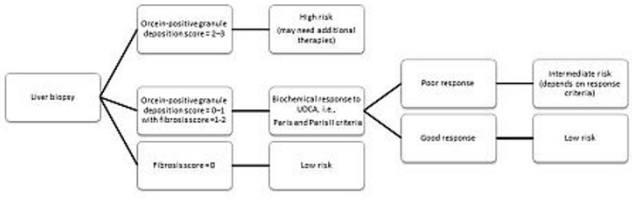
Background: Ursodeoxycholic acid (UDCA) is the standard treatment for primary biliary cirrhosis. UDCA nonresponders have a poorer prognosis and need additional therapies. We retrospectively compared the histological features of nonresponders and responders.

Design: Sixty-nine pretreatment liver biopsy specimens and clinical data were analyzed. Cases were divided into 3 groups: advanced [n = 10, with cirrhosis-related conditions; histologically proven cirrhosis or cirrhosis-related complications and/or symptoms, i.e., ascites, ruptured and/or endoscopically treated gastroesophageal varices, hepatic encephalopathy, hyperbilirubinemia (≥2.0 mg/dL), or hepatocellular carcinoma]; nonresponders (n = 16, with subsequent cirrhosis-related conditions and/or histological stage progression); and responders [n = 43, without these conditions or stage progression during at least 5 (11 ± 5) years of follow-up]. Histological evaluations were performed as per a new system proposed recently, i.e., staging was evaluated as per 3 histological components (fibrosis, bile duct loss, and orcein-positive granule deposition).

Results: Stage distribution of the 3 groups was as follows: stage 1/2/3/4 = 0/2/2/6 in advanced cases, 0/9/5/2 in nonresponders, and 9/31/3/0 in responders. All cases with a fibrosis score of 0 were responders. Almost all cases with an orcein-positive granule deposition score of 2–3 were advanced and nonresponders (except 1 receiving immunosuppressants for rheumatoid arthritis). Orcein-positive granule deposition scores of ≥2, ≥4, and ≥5, sum of orcein-positive granule deposition + fibrosis scores, and sum of bile duct loss + orcein-positive granule deposition + fibrosis scores showed 58% sensitivity and 98% specificity for distinguishing advanced and nonresponders from responders.

Conclusions: Our results showed the association between liver biopsy features and response to therapies and patient outcome. Disease progression risk may be evaluated within 1 year as follows:



1689 Differential Expression of Laminin ß1 and ß2 in Sinusoids and Arteries in Hepatocellular Carcinoma and Cirrhotic Liver

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Background: Laminins are a family of vascular and epithelial basement membrane glycoproteins with various adhesive, migratory and signaling functions. Studies of

gliomas have shown differential expression of β-chain isoforms as a potential therapeutic target. Capillarized sinusoids in hepatocellular carcinoma (HCC) acquire basal lamina material in the space of Disse. We studied the laminin β1 (LB1) and β2 (LB2) chain expression in sinusoidal basal lamina and arteries of HCC versus background cirrhotic liver to evaluate the staining patterns.

Design: 20 cases of HCC (with adjacent cirrhotic liver in 17) were immunohistochemically stained for LB1 and LB2. Staining intensity for sinusoids and arteries in HCC, sinusoids and hepatic artery branches and bile ducts in cirrhotic liver was recorded in a semiquantitative fashion as follows: 0=no staining, 1=weak, 2=moderate, 3=strong. Scores of 0-1 were considered overall negative, and 2-3 were considered positive. Statistical significance was analyzed with Fisher's exact test.

Results: Sinusoids in cirrhotic liver were negative for both LB1 and LB2 (0/17, 0% for both) while sinusoids in HCC showed significantly increased LB1 (14/20, 70%; p=0.0001) and LB2 (7/20, 35%; p=0.0094). LB1 and LB2 were both strong in 5 of 20 HCCs (25%). Difference between extratumoral hepatic artery branches in cirrhotic liver versus arteries in HCC was not significant for LB1 (15/17, 88% vs 18/20, 90%; p=1.000) but significant for LB2 (17/17, 100% vs 15/20, 75%; p=0.0498). Sinusoids and arteries in HCC stained more strongly for LB1 (70% and 90%) than LB2 (35% and 75%), however the difference was not significant (sinusoids, p=0.0562; arteries, p=0.4075). In contrast, extratumoral hepatic artery branches stained more strongly for LB2 (100%) than LB1 (88%) (p=0.4848). Bile ducts had low LB1 (3/17, 18%) and strong LB2 (17/17, 100%) expression.

Table 1. Positive (score 2-3) Staining for Laminin β Chain

LB1 in sinusoids		**LB2 in sinusoids**	
Cirrhosis	HCC	Cirrhosis	HCC
0/17 (0%)	14/20 (70%)	0/17 (0%)	7/20 (35%)

Conclusions: Laminins are differentially expressed in HCC versus cirrhosis. Capillarized tumoral sinusoids show statistically significant LB1 staining as compared to those of cirrhotic liver. The arteries in HCC appear to show a shift towards LB1 approaching statistical significance. Laminin immunohistochemistry offers an opportunity to further study distribution of different laminin components in neoplastic and non-neoplastic liver, and dysregulated cell-laminin interactions which may impact tumor progression and potential anti-angiogenic therapy.

1690 Standardized Histological Evaluation of Primary Sclerosing Cholangitis (PSC): Relationship of Histological Features to Laboratory Findings and Outcome

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Background: Primary sclerosing cholangitis (PSC) is a progressive, chronic cholestatic liver disease characterized by duct destruction. We developed a standardized method of histologic evaluation for PSC and related histologic findings to clinical disease parameters.

Design: Study entry liver biopsies from the PSC-Ursodiol treatment trial (n=84) (Hepatology 50: 808; 2009) were stained with H&E, trichrome, reticulin, copper and cytokeratin 7 (CK7). Blinded semiquantitative evaluation of features of duct damage, inflammation, fibrosis, cholestasis and special stains were performed independently by 2 hepatopathologists. For each portal area on the CK7 stain, presence/absence of ducts and the degree of ductular reaction (DR) was recorded. A mean DR score and fraction of portal areas with ducts (DF) was calculated. The relationship between histologic and clinical features at baseline was assessed by Spearman rank correlation Rho, Chi-square or Mann-Whitney tests as appropriate.

Results: The study cohort had a mean age of 45 years and 47 (56%) were male. Alkaline phosphatase (AlkP) correlated strongly with histologic features of cholestasis, including duct injury, pseudoxanthomatous change (PXC), copper, periportal CK7 staining, DF and DR (all p<0.001) as well as with lobular inflammation and fibrosis. AST correlated with PXC, copper, DR and fibrosis (p<0.002). The Mayo PSC Risk Score was strongly correlated with PXC, copper, periportal CK7 staining and DR (p<0.0001) as well as fibro-obliterative duct lesions (p=0.001), and fibrosis (p=0.0001). The protocol defined composite outcome (including cirrhosis, varices, carcinoma, transplantation and death) was met in 31 (37%) of these patients during the study. The development of an adverse outcome was strongly associated with DF and DR (Mann-Whitney, p<0.0001) as well as copper (p=0.0006) and PXC (p=0.001) (Chi-square).

Conclusions: In a standardized evaluation of PSC biopsies from this clinical trial, features of chronic cholestasis showed a high degree of correlation with baseline measures of AlkP and AST as well as the calculated Mayo PSC Risk Score and the protocol defined composite outcome. These observations offer promise that standardized histologic evaluation of PSC can offer insights into the unique aspects of this cholestatic disease process and s methods of evaluating histologic response to therapeutic intervention.

1691 Idiopathic Post-Transplantation Hepatitis: Clinicopathologic Features

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Background: Idiopathic post-transplantation hepatitis (IPTH) has been described in orthotopic liver transplantation (OLT) recipients with variable reported incidence. The significance of IPTH and its relationship to de novo autoimmune hepatitis (DNAIH) is unclear. The aim of this study is to elucidate these features in our OLT population.

Design: We searched our database for chronic hepatitis following OLT. Patients transplanted for viral hepatitis, autoimmune hepatitis, PBC, or PSC were excluded, resulting in a total pool of 735 patients (1987 to 2008). Histologic features including ISHAK hepatic activity index (mHAI) of the first biopsy with IPTH were recorded. Previous and follow-up biopsies were also reviewed. Relevant clinical and laboratory data were recorded. Patients were scored using the international autoimmune hepatitis Group (IAHG) criteria; scores >15 were diagnostic of DNAIH. Graft loss, mortality, acute cellular rejection (ACR), and end-point fibrosis were compared with an age and OLT date-matched control group of 90 patients.

Results: Seventeen (2.3%) of 735 patients had histologically confirmed IPTH (10 males, 7 females, age: 2-62 years, 5 patients <18 years). Biopsies with IPTH occurred at an average of 850 ± 688 days after OLT. The clinical and histologic follow-up periods averaged 10.6 ± 4.6 and 6.3 ± 4.4 years, respectively. Viral hepatitis serology was negative in all patients except one with positive CMV-IgM. ANA and ASMA were positive in 9 (of 15) and 3 (of 13) patients, respectively. mHAI score averaged A:2.1 B:1.5 C:1.8 D:2.1. Plasma cell percentage averaged 20 ± 17%. Six patients (35%) with DNAIH had significantly higher plasma cell percentage (mean=33%) and lobular necroinflammatory activity (mean mHAI C=2.5) compared to the remaining IPTH patients (p=0.015 and 0.006, respectively). They also tended to have higher mortality (17%), graft loss rate (20%), fibrosis stage (mean=2.3 of 4), and a higher rate of previous ACR episodes (83%). Of all IPTH patients, 13 (76%) had previous episodes of ACR, significantly higher than 47% in the control group, p=0.02. IPTH patients also had significantly higher end-point fibrosis (mean=stage 2) and graft loss rate (13%) compared to the control group (mean stage=0.5 and graft loss rate=1.3%); p=0.0001 and 0.015, respectively. There was no difference in mortality between IPTH patients (12%) and the control group (13%); p=0.9.

Conclusions: IPTH is rare following OLT and is associated with increased fibrosis and graft loss. Association with ACR suggests alloimmune pathogenesis. DNAIH appears to be a more aggressive subset of IPTH.

1692 Altered Hepatic Vascular and Lobular Organization near Centrizonal Scars in Chronic Venous Outflow Obstruction

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Background: Chronic hepatic venous outflow obstruction (CVOO) is characterized by centrizonal (cz) hepatocyte ischemia, atrophy, necrosis, sinusoidal fibrosis and zone 3 scarring. Other conditions associated with cz scarring such as steatohepatitis often show aberrant cz arterialization and hepatocytic ductular metaplasia (DM). We have shown that cz scars in CVOO also undergo arterialization and ductular reaction (DR), which correlate with degree of fibrosis and may result in misinterpretation of CVOO as a biliary problem. However, consequences of the vascular alterations on functional lobular organization and hepatobiliary differentiation remain undefined.

Design: We studied 25 CVOO cases previously evaluated for cz arterialization, DR, and fibrosis. IHC was performed for CD34 to assess changes in cz sinusoidal staining as surrogate for vascular flow abnormalities (n=24) and for K7 and K19 to assess for DM or progenitor cell presence (n=25). Grading was semi-quantitative (scale 0-3). IHC for glutamine synthetase (GS) was performed to assess changes in normal lobular zonation (n=23). Cz fibrosis was staged using NASH criteria.

Results: Cz sinusoidal CD34 staining was present in 23 of 24(95.8%) cases; 13(54.2%) showed 2-3+ staining. Extent of staining correlated with cz microvessels (mv; p=0.001) but not cz arterialization (czA; p=1.00). CzA correlated with fibrosis stage (p=0.008); CD34 and mv did not (p=0.433 and p= 0.52). Four cases (16.7%) were CD34+ in absence of ductules with minimal (1b) fibrosis; all cases with cz ductules or stage 2-4 fibrosis were CD34+. Most cz ductules were K7+/K19-; 21 of 25(84%) cases were K7+ and 14(56%) were K19+ (p=0.025) with K19<K7 grade in 10(71.4%). Only 1(4%) case showed 2+ K19 staining compared to 12(48%) K7+ cases (p=0.001). CD34 staining correlated with cz K7+ but not K19+ ductules (p=0.004 v 0.561). K7+ but not K19+ ductules correlated with extent of fibrosis (p=0.002 v 0.067). Cz GS staining was decreased or absent in 21 of 23(91.7%) cases with periportal staining seen in 2(8.7%).

Conclusions: Cz sinusoidal CD34 staining and loss of cz GS zonation are common in CVOO. The associated cz ductules may represent DM rather than ingrowth of progenitor cells, evidenced by keratin profiling. CD34 staining may precede DM and higher fibrosis stages, further suggesting possible chronic ischemic etiology. Lastly, in addition to cz scarring, DM, and arterial ingrowth, the aberrant cz endothelialization and loss of GS zonation may further cause misinterpretation of central zones as portal tracts with resultant misdiagnosis as a biliary problem.

1693 Histopathologic Changes in Alcoholic Liver Disease Patients Treated with S-Adenosyl-L-Methionine: An In-Depth Look at Data from a Double-Blinded, Randomized, Placebo-Controlled Trial

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Background: S-adenosyl-L-methionine (SAMe) is a methyl donor for methyltransferase reactions that regulates the synthesis of glutathione, a main cellular antioxidant. SAMe is also involved in regulation of hepatocyte growth, differentiation, and death. Studies have shown that SAMe prevents alcohol-induced liver injury in rats by reducing liver lipid peroxidation and cell proliferation. We evaluated pre- and post-treatment liver biopsies in patients to assess any changes after SAMe treatment.

Design: Liver biopsies of thirteen randomized patients with ALD (six in the treatment arm and seven in the placebo arm) were evaluated at baseline and at 24 weeks following treatment with SAMe. Patients received 1.2 g of SAMe or placebo by mouth daily. Liver biopsies were histopathologically scored using accepted criteria for the following categories: fat, inflammation, necrosis, fibrosis, percent fibrosis per square field (morphometric fibrosis), tunnel formation, smooth muscle actin, Kupffer cells, polymorphonuclear leukocytes (PMN), lipogranules, lymphocytes, balloon cell formation (ghost cells), Mallory Denk bodies, and duct metaplasia.

Results: Although the treatment and placebo groups started at different baselines in some of the parameters, we observed that there was a statistically significant increase in the histopathologic score of morphometric fibrosis in the SAMe treated group. There was surprisingly a decrease in balloon cells and fibrosis in the placebo group but not the SAMe treated group. The scores of PMN infiltration, inflammation, and lipogranules trended up with treatment with SAMe, and the sores of necrosis, SMA, and Kupffer cells trended down in both the treated and placebo group, however, the p values were greater than 0.05.

Conclusions: In this study the treatment with SAMe caused an increase in morphometric fibrosis, whereas without treatment, the placebo group had a decrease in balloon cell formation and fibrosis. This highlights that stopping consumption of alcohol will also decrease balloon cell formation and fibrosis and differs from the previous human study that showed no significant difference in SAMe treated patients compared to placebo. Our study shows when alcohol consumption is stopped and SAMe is given, there may be a worsening of some liver pathology features.

1694 Expression of High Mobility Group AT-Hook 2 (HMGA2) in Intrahepatic Cholangiocarcinomas: An Independent Prognostic Marker Associated with Poor Prognosis

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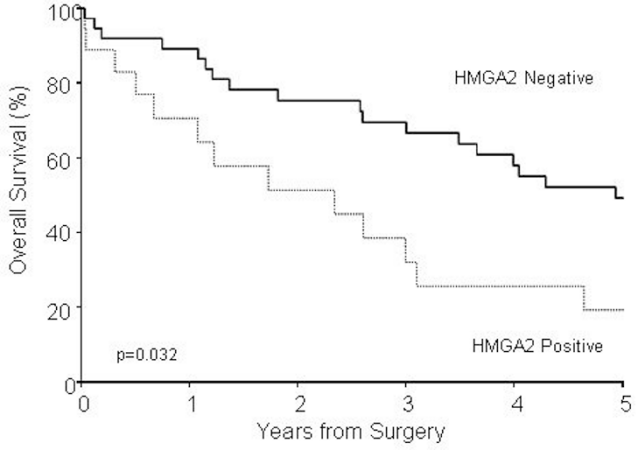
Background: High mobility group AT-hook 2 (HMGA2) is an important regulator for cell growth, differentiation, apoptosis, and neoplastic transformation. Previous studies have shown that malignant tumors expressing HMGA2 such as gastric, lung, and colorectal carcinomas usually had poor prognosis. HMGA2 expression and its clinical significance in intrahepatic cholangiocarcinomas have not been studied before.

Design: We identified 55 intrahepatic cholangiocarcinomas resected at our institute from 1994 to 2003. H&E slides from all cases were reviewed and the histopathological features of tumor size, mitotic count, tumor grade, presence of satellite nodules, desmoplasia, tumor necrosis, vascular and perineuronal invasion, lymph node metastasis, and margin status were recorded. By using immunohistochemical staining, we examined expression of HMGA2, P16, P53, Kit, AFP, and Ki-67 index. Associations of clinicopathologic features and immunohistochemical findings with patient survival were evaluated using Cox proportional hazards regression.

Results: The mean age of 55 patients (21 male; 34 female) was 60.9 years old. Twelve (23%) cases had positive lymph node metastasis. Expression of HMGA2, P16, P53, Kit, and AFP was observed in 18 (32%), 26 (47%), 37 (69%), 21 (38%), and 2 (4%) of the intrahepatic cholangiocarcinomas, respectively. The mean Ki-67 index was 9.1% (ranging from 0 – 90%). Univariate analysis showed that HMGA2 expression and lymph node metastasis were associated with shorter patient survival (p = 0.02 and 0.03, respectively). Higher Ki-67 index was associated poor survival although it did not reach statistical significance (p=0.09). The other histopathological features and the expression status of P16, P53, Kit, and AFP did not show associations with patient survival. Multivariable analysis showed that HMGA-2 expression (hazard ratio 2.10; p=0.03) and lymph node metastasis (hazard ratio 2.25; p=0.04) were independent prognostic factors associated with poor survival.



Conclusions: HMGA2 is expressed in a subset (32%) of intrahepatic cholangiocarcinomas and is an independent prognostic marker associated with poor survival.

1695 Sinusoidal Portal Hypertension in Non-Cirrhotic Patients: Description of a Post-Transplant Cohort with Conflicting Clinical/Radiologic Features and Highlight of Deficiencies in the Current Fibrosis Staging Systems

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Background: Cirrhosis produces sinusoidal portal hypertension (sPHTN) and often correlates with high corrected sinusoidal pressures (CSP). Current pathology staging recognizes cirrhosis as regenerating nodules, fibrous septae, and loss of normal micro-architecture. We here describe pathologic findings in a cohort of 30 post-transplant (postTX) patients in whom portal hypertension was clearly present but had no radiologic features of cirrhosis except increased CSP in some. These patients had extensive sinusoidal fibrosis but preserved underlying micro-architecture and absence of true nodules.

Design: Clinical and radiologic history of postTX patients biopsied with portal hypertension (PHTN) clinically believed to be non-cirrhotic because of absence of radiologic features are identified. These biopsies were pulled and their H&E, trichrome, and reticulin stains reviewed.

Results: Thirty patients between 2001 and July 2012 meet selection criteria once we excluded those with other clear morphologic explanations for portal hypertension such as NRH; outflow obstruction, and others. Time from TX to biopsy was 3.6 – 156 months (mean =54.6; median = 33.6). Of these 30 (24 male; 6 female), ascites was present in 15 (50.0%). CSP was elevated (higher than 8) in 7 of 7 who had this information. Imaging revealed "abnormal blood flow" in 3 cases; all 30 had normal synthetic function (INR <1.3). Indication for transplantation in the patients was HCV (20 or 67%) and others (autoimmune hepatitis; PBC; HBV; NASH = 10, 33%). One biopsy (3.33%) contained severe steatosis, but none had steatohepatitis. Overall 24/30 biopsies (80%) would ordinarily be staged as F 1-2 /4 but these as well as other 6 (F2-3) had moderate to severe sinusoidal fibrosis without nodules, real fibrous septae, or significant alteration of the hepatic micro-architecture. None of these 30 biopsies can be staged as cirrhosis by any existing criteria, yet appear to solely explain PHTN due to marked sinusoidal collagenization.

Conclusions: Diffuse, non-nodular sinusoidal fibrosis from various post-transplant injury, identified in our post-transplant cohort, have also been seen in non-transplant patients, produce the scenario for sinusoidal PHTN, but are difficult to diagnose radiologically and could potentially be under-staged by all of the current criteria. Review of existing criteria for "cirrhosis" is needed to better report non-nodular sPHTN in a uniform and easily communicated manner.

1696 Histology of Liver Injury Secondary to Chronic Passive Congestion in Heart Failure

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Background: Liver injury from chronic passive congestion from heart failure has been characterized based mostly on autopsy series. As a result, these series likely include agonal as well as autolytic changes in the liver parenchyma. Multiple reports of combined heart and liver transplant have been published from a surgical standpoint; however, no detailed descriptions of the histologic changes in livers seen in the context of combined transplant have been reported. We now describe the histologic findings observed in liver explants from patients receiving combined heart-liver transplants.

Design: We identified 6 cases of combined heart-liver transplants performed at our institution over a 10 year period from 2002-2012. For each case, the liver explant was examined by H&E, trichrome, reticulin, and elastic Van Gieson, and by immunohistochemistry for CD61. Clinical background and follow up was also obtained.

Results: The 6 patients identified all had heart failure related to either congenital heart disease or idiopathic dilated cardiomyopathy. All 6 livers showed changes that were felt secondary to cardiac dysfunction without other reasons for liver injury, including viral hepatitis. The changes included increased fibrosis, either in a bridging pattern, in a pericellular distribution, or both. Reticulin stains highlighted regenerative nodules in all cases. 3/6 cases showed patchy sinusoidal staining on CD61 stains, indicating platelet-fibrin deposition within sinusoids. 1/6 cases showed CD61 staining within blood vessels, and an additional case showed evidence of vessel obliteration on EVG with absence of CD61 staining, indicative of remote, organizing thrombosis. EVG stains also highlighted intimal thickening in 3 other cases, raising the possibility of resolved thrombosis. The liver injury also showed a patchy distribution; in all cases, the livers showed areas that appeared relatively uninvolved with no evidence of bridging fibrosis, sinusoidal dilation or architectural distortion.

Conclusions: In all cases examined, increased fibrosis and regenerative nodules were observed in all cases; however, the changes also showed a variable distribution, usually more abnormal in subcapsular areas. As every case showed uninvolved areas, none of the cases could be characterized as cirrhotic. Several cases showed areas of either remote or active thrombosis, suggesting a role for thrombosis in the development of fibrosis within cardiac livers. No significant hepatocellular necrosis was seen, suggesting that liver cell necrosis represents an agonal change that is not present in well compensated congestive heart failure.

1697 Sinusoidal Obstruction Syndrome Injury in Liver Biopsies after Hematopoietic Cell Transplantation

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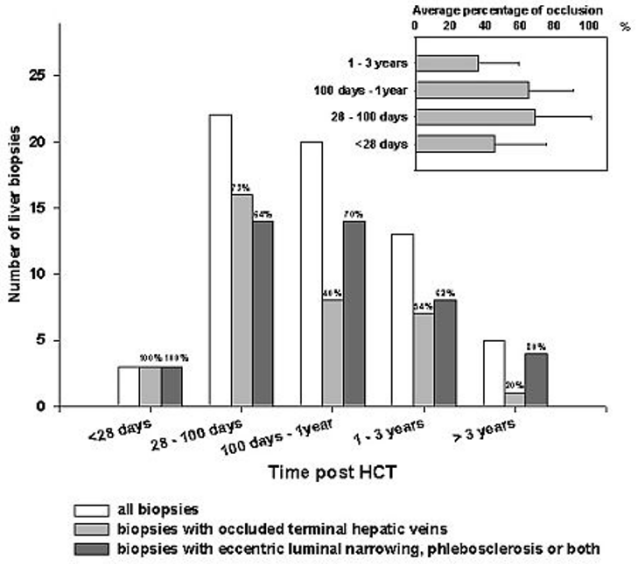
Background: The differential diagnosis of liver dysfunction after hematopoietic cell transplantation (HCT) is broad; early and severe findings favor sinusoidal obstruction syndrome (SOS) while later, graft-versus-host disease (GVHD), infection, drug toxicity, recrudescent or new viral hepatitis are likely. Although rarely discussed, post-HCT liver biopsies (Bxs) may show features of SOS injury. In this study we evaluated SOS injury in liver Bxs taken over a broad range of post-HCT period.

Design: Sixty-three consecutive liver Bxs for elevated liver tests (LT) with sufficient material were collected from 58 HCT patients. None had clinical parameters of SOS or hepatic/portal thrombosis on imaging. Hematoxylin & eosin, trichrome, reticulin, and Verhoeff-Van Gieson stained sections were scored for histologic lesions of SOS: occlusion, eccentric luminal narrowing, and/or phlebosclerosis of the terminal hepatic vein (THV), sinusoidal fibrosis, and centrilobular necrosis.

Results: The median number of days post-HCT for Bxs was 169 (range: 12 - 3304). Reported pathologic diagnoses were GVHD (75%), SOS without GVHD (5%), and "other" without GVHD or SOS (20%). Fifty-two (83%) Bxs had THV injuries. The median number of occluded THVs per Bx was 3 (range: 1-12); the average percentage of occlusion per Bx was 66%. Sinusoidal fibrosis and centrilobular necrosis were seen in 21 (33%) and 12 (19%), respectively. Stratified by time, 3 of 3 Bxs within 28 d of HCT, 20/22 (91%) between 28 - 100 d after HCT, 16/20 (80%) 100 d - 1 y, 9/13 (69%)

1 - 3 y, and 4/5 (80%) > 3 y after transplant had THV injuries. The frequencies of Bxs with occluded THV decreased from 100% within 28 d of HCT to 20% > 3 y after HCT. The frequencies of Bxs with THV narrowing and/or phlebosclerosis ranged from 100% to 80% (Figure 1). SOS injury ranged from 75% to 100% regardless of final diagnoses.



Conclusions: Our results demonstrate a high incidence and degree of SOS injury in Bxs of post-HCT patients with elevated LT regardless of time post-HCT, concurrent with other diagnoses. This high incidence likely reflects an aggregate of injuries pre- and post-HCT and the degree of injuries may adversely affect recovery. The presence and degree of injury to THV should be indicated when evaluating post-HCT Bxs for elevated LT.

1698 Liver Fibrosis Quantitation Via Image Analysis: Correlation with Pathologist Assessment and Clinical Parameters

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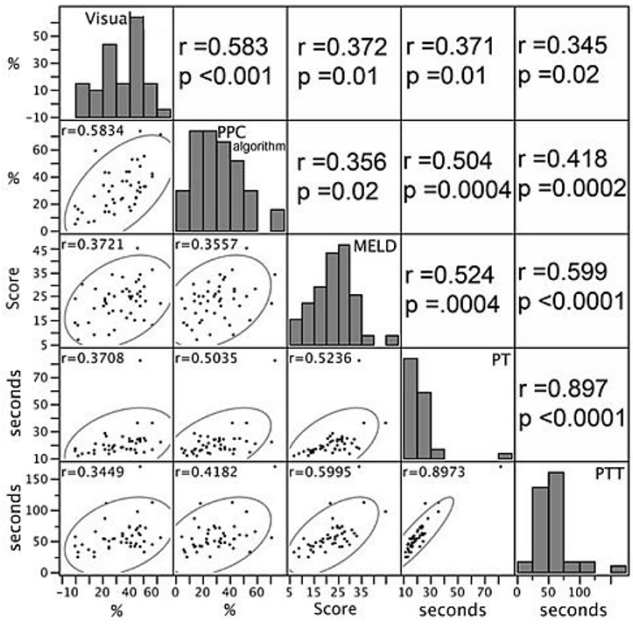
Background: The assessment of hepatic fibrosis is susceptible to sampling and pathologist observer variability, sometimes making consistent, objective fibrosis severity appraisal difficult. Image analysis tools have been used with varying success; however, technology limitations and lack of correlation with clinical parameters have prevented the application of potentially more objective image analysis methods.

Design: Transplant hepatectomy specimens were sectioned in the axial plane, and at least 5 sections were taken for histology from each hepatectomy. Whole slide images (WSIs) of trichrome-stained sections were obtained using a whole slide scanner. In sections containing the least and greatest fibrosis, %fibrosis was quantitated using a positive pixel count (PPC) algorithm tuned to detect fibrosis; and an average PPC measurement was obtained. Image analysis measurements were compared with pathologist assessments of %fibrosis and clinical parameters.

Results: All cases (n=46) were cirrhotic hepatectomies in patients with end stage liver disease from a variety of disorders. A wide range of %fibrosis was present (average±S.D. = 33.0±16.6 and 30.6±16.4 as determined by visual and PPC methods, respectively). There was a statistically significant correlation between the visual and PPC methods (r=0.58, p<0.0001). The visual and PPC methods also showed correlation with MELD score, PT, and PTT (r=0.37 and 0.36, 0.37 and 0.50, and 0.34 and 0.42, respectively with p = 0.02 to <0.0001). The relationships between the visual and PCC methods and total bilirubin, AST, ALT, GGT, and albumin were not statistically significant.



Conclusions: A wide range of %fibrosis was observed according to image analysis and visual assessment, and these measurement methods correlated with each other and some clinical parameters. These findings suggest that image analysis methods have the potential to provide an objective assessment of hepatic fibrosis. Future improvement in image analysis methods could improve correlation with clinical parameters, assisting pathologists in providing the best possible appraisal of hepatic fibrosis.

1699 S100P as a Marker for Poor Survival and Advanced Stage in Gallbladder Carcinoma

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Background: The outcome of gallbladder carcinoma remains dismal and identification of biomarkers for prognostic stratification and development of targeted therapeutic modalities is urgently needed. Overexpression of S100P has been shown in several tumors including biliary and pancreatic cancers. However, the association of S100P with the clinicopathological characteristics and clinical outcome of gallbladder carcinoma remains unclear.

Design: Tissue microarray was constructed from 91 surgically resected gallbladder carcinoma specimens. Immunohistochemistry of S100P was performed. The staining intensity was scored as 0 (no stain), 1 (weak), 2 (weak to moderate), 3(moderate to intense) and 4 (intense). Percentages of cells positively stained were semi-quantitatively scored as 0 (<10%), 1 (10-24%), 2 (25-49%), 3 (50-74%) and 4 (>74%). Immunoreactive score (IRS) was calculated by multiplying the intensity of stain with the score of positive cells, producing scores ranging from 0 to 16. Tumors were classified, graded, and staged according to current WHO and AJCC standards.

Results: Higher IRS was significantly associated with TNM staging (p=0.04). 68/91 (75%) of the cases had IRS score ≥3 when compared to 20/91(22%) cases with IRS<3. Cases of staining intensity ≥3 in ≥25% tumor cells were significantly increased in pathological stage T4 (p= 0.01). Staining intensity was significantly associated with poorer survival (p=0.006). Vascular invasion (p=0.01) and perineural invasion (p=0.04) were also predictors of poorer survival. Age, sex, histological type, histological grade, vascular invasion, perineural invasion and necrosis were not found to be associated with S100P expression.

Conclusions: Besides vascular invasion and perineural invasion, staining intensity of S100P is strongly associated with poorer survival in gallbladder carcinomas. Overexpression of S100P is also significantly associated with pathological stage T4 carcinoma. Our results suggest S100P may serve as a surrogate marker for prognosis in gallbladder carcinoma.

1700 Morphologic and Immunohistochemical Features of Sarcomatoid Hepatocellular Carcinoma

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Background: Sarcomatoid hepatocellular carcinoma (SHCC) is a rare histologic subtype of hepatocellular carcinoma. The expression of newly available epithelial, hepatocellular and progenitor cell-related markers in the sarcomatoid component is not known.

Design: Immunohistochemistry was done on 13 SHCC cases from 12 patients using the following markers:(a)Hep Par 1(Hep),polyclonal CEA (pCEA),glypican-3(GPC),arginase-1(Arg),alpha-fetoprotein(AFP) (b) Epithelial: Pankeratin (CK), MNF116, MOC31, CK7, CK19,EMA, (c)Putative progenitor cell markers: CD56,

CD117,(d)Mesenchymal: vimentin, S-100, smooth muscle actin (SMA), desmin, myogenin. The staining intensity was recorded on a scale of 0-3; 2+ or 3+ staining in >10% of tumor cells was considered positive.
Results: The age range was 46-85 years (mean 62); male-to-female ratio was 2.7:1. Cirrhosis was present in 6 (50%) cases (2 hepatitis C, 2 alcoholic, 2 nonalcoholic steatohepatitis). Hepatitis C without cirrhosis was present in 3 cases;no liver disease was seen in the remaining 3 cases. Serum AFP was elevated in 50% of cases. The outcome was available for 8 cases;all patients died within one year of diagnosis. All cases had typical HCC and sarcomatoid components.HCC component was poorly differentiated in 9 (69%) cases. Sarcomatoid component was spindle cell in 8 cases (4 low, 2 intermediate, 2 high-grade), epithelioid in 1 (high grade), mixed epithelioid and spindle in 4 (1 low, 1 intermediate, 2 high-grade). There was 1 rhabdomyosarcoma, 1 leiomyosarcoma, rest were undifferentiated sarcomas. Arg was positive in sarcomatoid area in 1 case; all other hepatocellular and progenitor cell-related markers were negative. CK (92%) and MNF116 (72%) were positive in majority of cases; MNF116 positivity was more diffuse compared to CK in most cases. Other epithelial markers were negative.
Conclusions: SHCC is an aggressive subtype of HCC. Most cases show undifferentiated spindle cell morphology. Hepatocellular and progenitor cell markers are negative except rare Arg positive cases. Vimentin, CK and MNF116 are positive in most cases. The more diffuse staining with MNF116 suggests that it can be useful addition to CK to demonstrate epithelial differentiation in SHCC in needle biopsies.

1701 Utility of Bile Salt Export Pump Transporter Immunohistochemistry Compared to Other Hepatocellular Markers for the Diagnosis of Hepatocellular Carcinoma

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Background: Bile salt export pump transporter (BSEP) is encoded by the ABCB11 gene and is expressed on the apical side of the bile canalicular membrane in hepatocytes. The role of BSEP for the diagnosis of hepatocellular carcinoma (HCC) has been suggested but not explored in detail.
Design: Immunohistochemistry for BSEP was performed on 71 HCC. The cases were stratified into well differentiated (WD, n=13), moderately differentiated (MD, n=35) and poorly differentiated (PD, n=23) HCC based on WHO criteria. More than one differentiation pattern was seen in 12 cases; these were scored separately yielding 83 observations. Canalicular staining pattern with BSEP was considered positive. The staining intensity was recorded on a scale of 0-3; 2+ or 3+ staining in >5% of tumor cells was considered positive. The results were compared with other hepatocellular markers that had been previously done in the same cases: Hep Par 1 (Hep), polyclonal CEA (pCEA), glypican-3 (GPC) and arginase-1 (Arg).
Results: When staining of >5% of tumor was considered positive, BSEP had a sensitivity of 76% (92% in WD-HCC, 95% in MD-HCC, and 45% in PD-HCC). When staining of >50% of tumor was considered positive, the overall sensitivity of BSEP decreased to 47% (69% in WD-HCC, 72% in MD-HC, and 6% in PD-HCC). Membrane staining with BSEP was seen in 8 (9.6%) HCCs, which obscured the canalicular staining pattern. BSEP was similar to Arg, Hep and pCEA in WD and MD HCC. For PD HCC, the sensitivity was lower compared to GPC and Arg. The addition of BSEP to other hepatocellular markers did not lead to increase in sensitivity for any differentiation.

Table 1

	BSEP	Arg	GPC	Hep	pCEA
WD	92/69	100/100	62/15	100/100	92/77
MD	95/39	100/98	82/59	95/82	87/67
PD	45/6	97/80	87/74	65/26	55/13

Numbers a/b reflect percentages; a-positivity in >5% of tumor, b-positivity in >50% of tumor

Table 2

	Arg+BSEP	GPC+BSEP	Hep+BSEP	pCEA+BSEP
WD HCC	100/100	100/69	100/100	100/85
MD HCC	100/97	100/95	100/85	97/90
PD HCC	97/81	97/74	68/32	71/19

Numbers a/b reflect percentages; a-positivity in >5% of tumor, b-positivity in >50% of tumor
Conclusions: BSEP can be used as a marker for hepatocellular differentiation and shows a crisp canalicular pattern of staining. It has high sensitivity in WD and MD HCC, which is comparable to Arg, Hep and pCEA. BSEP immunoreactivity is seen in less than half of the PD HCC, which is significantly lower compared to Arg and GPC. Although BSEP appears to have good overall sensitivity, its role in establishing hepatocellular differentiation is limited when added to a panel of Hep, GPC and Arg.

1702 Neonatal MSG Treatment in DIAR Mice Causes Macrovesicular Steatosis with Lobular Inflammation in the Liver

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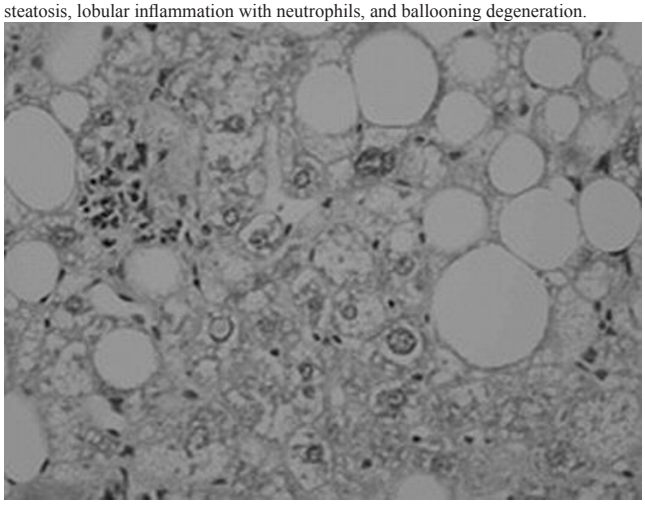
Background: The liver manifestations of metabolic syndrome include non-alcoholic fatty liver disease and its progressive variant, non-alcoholic steatohepatitis (NASH). Centrilobular macrovesicular steatosis is one of the typical pathological findings of NASH. We have previously reported that subcutaneous injection of monosodium glutamate (MSG) in neonatal ICR mice resulted in NASH-like pathology. However, its steatosis was microvesicular. DIAR mice are an inbred strain selected from *ddy* for their non-diabetic features. In a preliminary study, DIAR mice spontaneously developed sporadic macrovesicular steatosis. With an aim to develop a NASH mouse model with macrovesicular steatosis, we analyzed the liver pathology and other characteristic findings of DIAR mice following neonatal MSG treatment.
Design: Twenty-nine- and 54-week-old MSG-treated (DIAR-MSG) and MSG-untreated (DIAR-control) male mice were analyzed. Each group contained 5-6 mice. Liver was removed and fixed in 10% formalin. The specimens were evaluated by hematoxylin-eosin staining, silver staining, and Azan staining. NASH activity scores and the type of steatosis were evaluated. Measurement of body mass index (BMI) and blood glucose level, and oral glucose tolerance test (OGTT) were performed for mice aged 29 weeks.
Results: BMI and blood glucose levels of DIAR-MSG mice were significantly higher than those of DIAR-control mice. OGTT revealed a type 2 diabetes pattern in DIAR-MSG mice. The liver of 29-week-old DIAR-MSG mice showed macrovesicular steatosis, lobular inflammation with neutrophils, and ballooning degeneration.



At age 54 weeks, mild perivenular and pericellular fibrosis were observed in 83% of DIAR-MSG mice. Some mice exhibited cellular and structural atypia, mimicking human hepatocellular carcinoma.
Conclusions: DIAR-MSG mice exhibited mild obesity and type 2 diabetes. In addition, these mice exhibited macrovesicular steatosis, lobular inflammation, ballooning degeneration, and mild perivenular fibrosis of the liver. In 54-week-old mice, atypical liver nodules were also observed frequently. These findings are quite similar to those of human NASH. In conclusion, DIAR-MSG mice are a valuable animal model to evaluate NASH pathogenesis and carcinogenesis.

1703 Association between Liver Biopsy Length and the Diagnosis of Non-Alcoholic Steatohepatitis

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Background: Adequacy assessment is a critical part of the evaluation of liver biopsies performed for non-focal liver diseases. A small number of studies using chronic viral hepatitis as a model have examined the minimum amount of liver that must be examined to ensure an accurate diagnosis. No study has yet examined adequacy criteria in NASH, a disease in which the patterns of liver injury and fibrosis vary from chronic viral hepatitis. In this study, we examined the association between biopsy length and the diagnosis of steatohepatitis.
Design: Thirty 18G liver biopsies of at least 2.5 cm length performed for clinical suspicion of NASH were identified. Removable tape was used to mask the biopsies (1 H&E and 1 trichrome) so that 0.5 cm increments were added to each review, resulting in biopsies of 0.5 cm, 1.0 cm, 1.5 cm, and 2.0 cm lengths, and full length. The biopsies were randomized before each length was scored and reviewed without knowledge of prior score. Biopsies were scored as "not steatohepatitis", "steatosis with borderline features of steatohepatitis", and "definitely steatohepatitis" using the NASH-CRN system.
Results: There was an association between biopsy length and the probability that a biopsy would be diagnosed as "definitely steatohepatitis." 55% of the full-length biopsies were diagnosed as "definitely steatohepatitis", as compared to 37% of 0.5 cm, 42% of 1.0 cm, 45% of 1.5 cm, and 47% of 2.0 cm biopsies. This difference was statistically significant when compared to the full-length biopsy for the 0.5 and 1.0 cm biopsies (p=0.004 and p=0.037, respectively). When the diagnoses of the shortened biopsies were compared to the full-length, 48% showed no discordant diagnoses at any length (i.e. the same diagnosis was rendered at every biopsy length). 27% of the 0.5 cm biopsies, 38% of the 1.0 cm biopsies, 28% of the 1.5 cm biopsies, and 18% of the 2.0 cm biopsies had diagnoses that differed from the full-length biopsy.
Conclusions: Short liver biopsies (0.5 and 1.0 cm) are more likely to be diagnosed as "not steatohepatitis" or "steatosis with borderline features of steatohepatitis" relative to biopsies of 1.5 cm length or longer. 2.0 cm biopsy length resulted in the fewest discordant diagnoses as compared to the full-length biopsy. We recommend that biopsies performed for clinical suspicion of NASH should be of at least 2.0 cm length. Future analyses will focus on the effects of biopsy length on individual NAS components and fibrosis.

1704 Adenomatous (Dysplastic) Transformation in Cholesterol Polyps (CPs) of the Gallbladder (GB)

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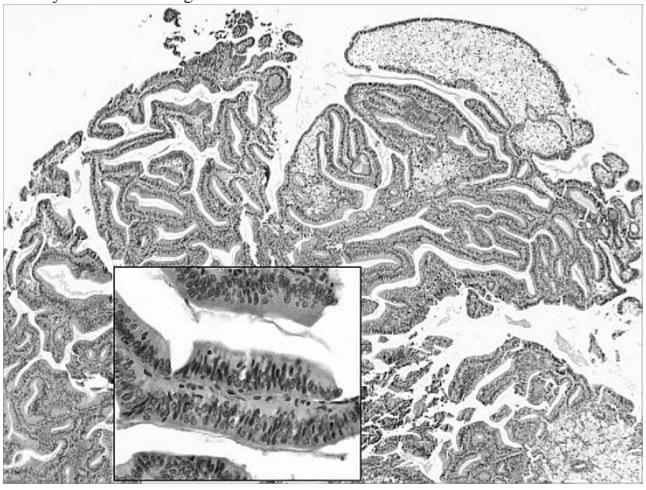
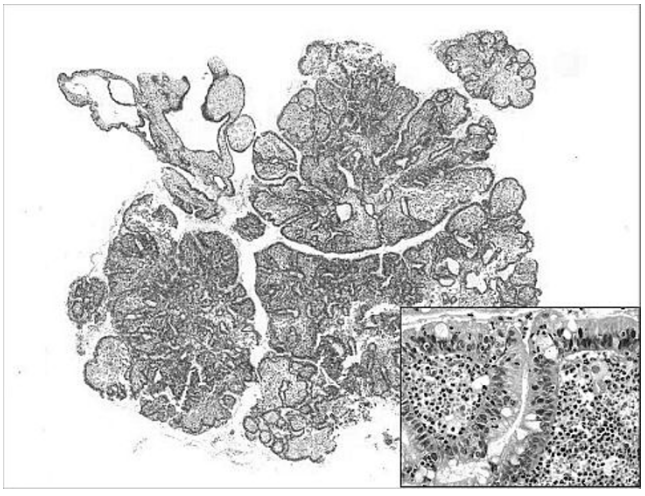
Background: CPs of the GB are common incidental findings, and regarded as innocuous lesions with no significance. In fact, it has been speculated that cholesterolosis may be

protective against neoplastic change; numerous studies have found that cholesterolosis correlate inversely with carcinoma in the GB.
Design: Histology of 394 polypoid lesions of the GB were reviewed.
Results: 13 cases of CP with adenomatous (dysplastic) transformation were identified, all showing dysplastic transformation almost exclusively within the polyp. Male to female ratio was 6:7, with a mean polyp size of 1.14 cm (0.2-5), and 9 were ≥1 cm. The mean age was 61(as opposed to 49 yrs for those CPs without neoplastic change). In 4, the dysplastic changes were focal (<25% of the polyp), in 1, substantial (25-75%) and in 8, diffuse. All lesions were recognizable by the distinctive architecture characteristic of CPs, in addition to clusters of cholesterol laden macrophages within the polyp stroma. Uninvolved GB revealed cholesterolosis in only 3/13. Only 1 had any significant cholecystitis in the background. 3 were associated with invasive ca in the same GB.



A. Bulk of the lesion was otherwise classical CP but there were foci of dysplastic transformation within the lesion.



B. Bulk of the lesion was ordinary neoplastic polyp (intracholecystic papillary tubular neoplasm) but, in some foci, the underlying CP was evident.
Conclusions: This study reveals a hitherto unrecognized phenomenon of neoplastic transformation in CPs. This appears to be an age-related progression phenomenon. Also, in all cases with diffuse dysplasia, CPs were ≥1 cm, supporting the current practice of 1 cm criteria for cholecystectomy. These cases further illustrate the propensity of the proliferative GB epithelium to develop into neoplasia, thus lends further support to the well-known injury-cancer association in the GB.

1705 Mucinous Hepatocelluar Carcinoma: A Previously Undescribed Variant of Hepatocellular Carcinoma

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Background: Mucin production in a primary liver cancer generally provides evidence for a diagnosis of cholangiocarcinoma or a biphenotypic carcinoma with mixed hepatocellular and cholangiocarcinoma differentiation. We describe four cases of a unique subtype of hepatocellular carcinoma, one that shows unequivocal hepatocellular differentiation, but produces pools of extracellular mucin and has no evidence for glandular or biliary differentiation.
Design: The surgical pathology files were searched for cases of hepatocellular carcinoma with extracellular mucin production. All cases of cholangicocarcinoma and all cases of biphenotypic hepatocellular/cholangiocarcinoma were excluded.
Results: Four cases were identified (three resections, one biopsy). Three were consult cases submitted because of the unusual extracellular mucin production. All were male patients and two had chronic hepatitis C, one had no known liver disease, and information was not available in the fourth case. The median age was 49 years (range 34-83 years). Three of the patients (75%) were Caucasian and one was Middle Eastern in ethnicity. The median tumor size was 5.8 cm (range 3.3-12 cm) and tumors were single in two cases and multifocal in one case; one case did not have information available. The tumors were well differentiated in all cases, with cells growing in a trabecular architecture and showing typical hepatocellular morphology with abundant eosinophilic cytoplasm and only mild cytological atypia. However, the tumors were also striking for large pools of extracellular mucin that separated the trabecular plates. No intracellular mucin was seen. No gland formation or psuedogland formation was seen. The mucin was alcian blue positive in all cases and mucicarmine positive in 2 of 4 cases. All cases were negative for lymphovascular invasion. By immunohistochemistry, the tumors were Hep Par positive and showed a typical canalicular staining pattern for CD10 or pCEA staining. Ki-67 immunostains showed mildly increased proliferative rates. CK19 immunostains (typically positive in cholangiocarcinomas) were negative. The background livers in the resected specimens showed portal fibrosis (N=2) and cirrhosis (1).
Conclusions: We report a previously undescribed subtype of hepatocellular carcinoma: mucinous hepatocullar carcinoma. These hepatocellular carcinomas show striking extracellular mucinous production, but lack glandular or biliary differentiation. Recognition of the unique histopathological findings will allow pathologists to properly diagnosis this unique variant of hepatocellular carcinoma.

1706 Fibrosing Cholestatic Hepatitis C Versus Biliary Obstruction: Distinguishing Histopathologic Features

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Background: The histopathologic distinction between posttransplantation fibrosing cholestatic hepatitis C (FCH-C) and biliary obstruction is challenging. We sought to identify histopathologic features that could be useful in the differential diagnosis between these two entities.
Design: Thirty eight cases of HCV-negative, cholangiography-proven biliary obstruction (including 16 post-transplant and 22 non-transplant patients [M:16, F:22; mean age 46.3 [13-81 yrs]), and 13 patients with posttransplantation FCH-C (M=9, F=4, mean age 57.3 [32-72 yrs]) were included. FCH-C patients were characterized by cholestatic disease (bilirubin >2 mg/dL), high HCV viral load, no evidence of biliary tract obstruction on imaging, and typical histopathologic findings (≥3 of the following: prominent ductular reaction, hepatocyte ballooning, periportal sinusoidal fibrosis and cholestasis). Biopsies were evaluated with H&E, trichrome, Victoria Blue, and rhodanine stains as well as CK7 immunohistochemistry. A "biliary" CK7 pattern was defined by abundant CK7+ ("biliary" or "metaplastic") hepatocytes in the periportal area, while "FCH" pattern was characterized by few or no CK7+ hepatocytes in spite of prominent ductular reaction.
Results:

	Biliary obstruction n=38	FCH n=13	p value
Bile duct dilatation	26.3% (10/38)	0% (0/13)	0.0003
Neutrophils in ductular reaction	94.7% (36/38)	100% (13/13)	NS
Portal edema	63.1% (24/38)	7.6% (1/13)	<0.0001
Ductular cholestasis	21% (8/38)	7.6% (1/13)	0.18
Hepatocyte swelling with lobular disarray	5.2% (2/38)	84.6% (11/13)	<0.0001
Lobular inflammation (Hepatitis Activity Index, score)	1 (0-2)	2 (1-3)	NS
Cholestasis	65.7% (25/38)	76.9% (10/13)	0.43
Periportal sinusoidal fibrosis	34.2% (13/38)	100% (13/13)	<0.0001
Copper (rhodanine)	60.5% (23/38)	15.3% (2/13)	0.0006
Copper-binding protein (Victoria blue)	47.3% (18/38)	0% (0/13)	<0.0001
CK7 expression	•FCH pattern: 26.4% (10/38) •Biliary pattern: 73.6% (28/38)	•FCH pattern: 92.3% (12/13) •Biliary pattern: 7.7% (1/13)	<0.0001

NS: Not significant (p>0.05)
Conclusions:

	Favors biliary obstruction:	Favors FCH:
H&E and trichrome stains	•Bile duct dilatatio•Portal edema •Acute cholangitis•Bile infarcts •Periductal fibrosis	•Hepatocyte swelling w/ lobular disarray •Periportal sinusoidal fibrosis
Copper/copper-binding protein stains	Present, especially if abundant	Absent, despite pronounced ductular reaction
CK7 pattern	Abundant CK-7+ periportal hepatocytes	No/few CK7+ hepatocytes despite pronounced ductular reaction

1707 Infiltration of Inflammatory Cells Expressing Mitochondrial Proteins around Bile Ducts and Intraepithelial Layer May Be Involved to the Pathogenesis in Primary Biliary Cirrhosis

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Background: Serum anti-mitochondrial antibodies (AMAs) are characteristics in most patients with primary biliary cirrhosis (PBC); however, the significance of AMAs in the pathogenesis of PBC has not been fully clarified, so far. We have reported the deregulated autophagy of mitochondria in biliary epithelial lesions in PBC and noticed a peculiar accumulation of mitochondrial protein-expressing inflammatory cells around bile ducts. In this study, we examined an extent, distribution and types of mitochondrial protein-expressing inflammatory cells and its association with biliary epithelial lesions in PBC.
Design: We examined the expression of pyruvate dehydrgenase complex-E2 component (PDC-E2), a major target of AMAs, and a mitochondrial protein cytochrome c oxidase, subunit I (CCO) in inflammatory cells in livers taken from patients with PBC (n=37), primary sclerosing cholangitis (PSC) (n=13), extrahepatic biliary obstruction (EBO, n=10), chronic viral hepatitis (CVH, n=25) and control normal livers (n=16). Mitochondrial protein-expressing inflammatory cells were characterized by double

immunofluorescence with CD3, CD4, CD8, CD20, CD38, CD56, CD68, CD79a, CD138 or myeloperoxidase (MPO).
Results: Infiltration of mitochondrial protein-expressing inflammatory cells was mainly observed in portal tracts and around the damaged small bile ducts and in the intraepithelial layer in PBC. The extent of infiltration in portal tracts was significantly higher in PBC and early stage of CVH than normal livers ($p<0.01$). The extent of infiltration around bile ducts and/or intraepithelial layer was significantly higher in early stage of PBC than PSC, CVH, EBO and normal livers ($p<0.01$). Mitochondrial proteins-expressing inflammatory cells included the following 2 types; 1) CD68 and/or MPO-positive monocytes, macrophages or epithelioid cells and 2) CD79a, CD38 and/or CD138-positive plasmablasts and plasma cells in double fluorescence. There was no CD3-positive cells with expression of mitochondrial proteins.
Conclusions: Infiltration of mitochondrial proteins-expressing inflammatory cells was frequently observed around damaged bile ducts and intraepithelial layers in PBC. These mitochondrial proteins-expressing inflammatory cells may be closely associated in the pathogenesis of bile duct lesion in PBC.

1708 Clinicopathological Characteristics of Serum Amyloid A-Positive Hepatocellular Neoplasms Arising in Advanced Alcoholic Liver Disease

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Background: Hypervascular hepatocellular nodular lesions resembling hepatocellular carcinoma are sometimes detected by imaging modality in patients with alcoholic cirrhosis. Herein, forty-eight hepatocellular nodules were characterized in 19 patients (2 women and 17 men, age ranged 40-67 yrs) with alcoholic cirrhosis.
Design: Nineteen patients were retrieved from our pathological files (1997-2012). The hepatocellular nodules were multiple (>3) in 15 patients. The immunoreactivity for serum amyloid A, glutamine synthetase (GS) and glypican-3 was examined in 48 hypervascular hepatocellular nodules. Fourteen hepatocellular nodules were examined on the magnetic resonance (MR) imaging with gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB) enhancement.
Results: Thirty-two nodules (4-35mm in diameter, mean±SD, 13.0± 7.5mm) in 14 patients (2 women and 12 men, age ranged 40-67 yrs) were diagnosed as serum amyloid A-positive hepatocellular neoplasm, which shares features with inflammatory hepatocellular adenoma (Sasaki M, et al. Modern Pathol 2012). The remaining sixteen nodules (5-25mm, mean±SD, 10.2± 4.3mm) in 7 patients (a woman and 6 men, age ranged 41-62 yrs) were focal nodular hyperplasia (FNH)-like nodules. The FNH-like nodules showed no immunoreactivty for serum amyloid A and a map-like staining pattern of GS. Two patients had both serum amyloid A-positive hepatocellular neoplasms and FNH-like nodules. The serum amyloid A -positive hepatocellular neoplasms showed increased cellular density, sinusoidal dilatation, inflammatory infiltrate and ductular reaction to various degrees. These histologic features tended to be less extensive in FNH-like nodules. The serum amyloid A -positive hepatocellular neoplasms and FNH-like nodules did not show an overexpression of GS and the immunoreactivity for glypican-3. Seven of 11 serum amyloid A-positive hepatocellular neoplasms showed hypointensity in the hepatobiliary phase on the MRI with Gd-EOB enhancement, similarly to hepatocellular carcinoma. In contrast, 3 FNH-like nodules showed iso-intensity in the hepatobiliary phase.
Conclusions: This study further confirmed characteristics of serum amyloid A-positive hepatocellular neoplasm arising in alcoholic cirrhosis that share features with inflammatory hepatocellular adenomas. Serum amyloid A-positive hepatocellular neoplasms sometimes co-exist with FNH-like nodules and may show different findings on Gd-EOB enhanced MR imaging.

1709 Prevalence and Significance of "Subtypes with Stem-Cell Feature" in Combined Hepatocellular-Cholangiocarcinoma and Hepatocellular Carcinoma

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Background: Combined hepatocellular-cholangiocarcinoma (cHC-CC), a malignant liver tumor with poor prognosis, is composed of hepatocellular carcinoma (HCC), cholangiocarcinoma (CC) and diverse components with intermediate features between HCC and CC. According to the WHO classification 2010, we surveyed the prevalence and clinicopathological significance of "subtypes with stem cell features (SC subtype)"; typical subtype (TS), intermediate cell subtype (Int) and cholangiolocellular type (CLC) in cHC-CC and HCC.
Design: Thirty-nine patients with cHC-CC (12 women and 27 men, age ranged 44-77 yrs) and 26 patients with HCC (all men, age ranged 52-86 yrs) were retrieved from our pathological files (1987-2012). The background diseases were hepatitis B (n=15 and 6), hepatitis C (12 and 11), chronic alcoholism (3 and 6) and cryptogenic (9 and 3) in cHC-CC and HCC, respectively. The prevalence of each component (HCC, TS, INT, CLC and CC) was histologically assessed with assistance of mucin staining and immunohistochemical staining for CK7, CK19, EMA, EpCAM, NCAM, AFP and HepPar1. Histological grading of HCC and the extent of stromal fibrosis and inflammation in tumor tissues were also evaluated.
Results: Mucin production was detected in 14 cHC-CCs. SC subtypes were observed in all cHC-CCs in various amount and combination. The prevalence of each SC subtype in cHC-CC was as follows; TS, 7 (17.9%); INT, 33 (84.6%); CLC, 22 (56.4%). The proportion of TS was significantly associated with lower histological grade of coexistent HCC ($p<0.01$). In contrast, the proportion of INT was associated with higher histological grade of coexistent HCC ($p<0.01$). The proportion of INT was correlated with tumor size ($p<0.01$), while the proportion of CLC was inversely correlated with tumor size ($p<0.01$). The proportion of CLC was associated with AFP expression and the extent of inflammation ($p<0.01$). The components of TS and CLC were also observed in 6 (23.1%) and 2 (7.7%; all coexist with TS) in HCC, respectively. The proportion of TS in HCC was significantly associated with the extent of stromal fibrosis and inflammation ($p<0.01$).
Conclusions: The TS was associated with lower histological grade of HCC in cHC-CC. In contrast, the INT was associated with higher histological grade of HCC and bigger tumor size in cHC-CC. The CLC was significantly associated with smaller size, AFP expression and the extent of inflammation. Each SC subtype may have different clinicopathological significances in cHC-CC.

1710 Disturbances of Intrahepatic Venous and Arterial Microcirculation in Idiopathic Portal Hypertension

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Background: Idiopathic portal hypertension (IPH) is a condition of non-cirrhotic portal hypertension without a known cause of liver disease, and o[/underline]bliterative portal venopathy is regarded as the primary lesion for the development of IPH. The obliteration of portal venules results in disturbed intrahepatic microcirculation, where its histological characteristics have not been fully clarified.
Design: Paraffin-embedded tissue sections of the livers of IPH (n = 27) and normal/subnormal livers (n = 20) were used. For the sections, triple immunohistochemical staining of glutamine synthetase (GS), alpha-smooth muscle actin (SMA), and cytokeratin (CK)7 was performed. GS, alpha-SMA, and CK7 were used to identify hepatic venules, muscular arteries, and bile duct/ductular cells, respectively.
Results: In normal/subnormal livers, the expression of GS was confined to a few layers of hepatocytes surrounding the central veins and small hepatic veins, showing normal liver zonation. [/underline]Dilated portal veins herniating into the surrounding parenchyma (paraportal shunt vessels) were observed in 18 cases (67%) of IPH, and among the 18 cases, hepatocytes around the dilated portal veins showed positive immunohistochemical staining of GS in 7 cases. Isolated arteries in the hepatic lobules were seen in 20 cases (74%) of IPH, and they were located around the central vein in 6 cases (22%), corresponding to centrizonal arteries. In 2 cases (7%) of IPH, the centrizonal arteries were accompanied by ductular reaction, and the histological appearance mimicked the anatomy of a portal area. Isolated arteries were also observed in 5 cases (25%) of normal/subnormal livers, although their number was small and none of them were located in the centrizonal area. Broad, anastomosing hepatocellular expression of GS, which was similar to that seen in focal nodular hyperplasia, was observed in 5 cases (19%) of IPH, while such staining areas were not seen in normal/subnormal livers.
Conclusions: Intrahepatic microcirculatory disturbances in IPH were associated with abnormalities in both venous and arterial vessels. Several cases of IPH were accompanied by hyperplastic response of hepatocytes, which might relate to abundant blood supply due to the abnormal arteries. The vascular lesions were heterogenous, and differed from case to case of IPH.

1711 Detecting C4d in Liver Allografts: Immunohistochemistry and Immunofluorescence Show Equivalent Staining

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Background: Endothelial deposition of C4d, detected by immunofluorescent staining (IF), is the gold standard for the diagnosis of antibody-mediated rejection (AMR) in renal allografts. In contrast, reliability of C4d stains in liver allografts has yet to be definitively established. The aims of this study are to compare the sensitivity of C4d stains in liver biopsies by IF and immunohistochemistry (IHC) and to correlate endothelial deposition of C4d with results of serologic tests for AMR.
Design: Our database was searched for biopsies of allograft and native livers for evaluation of rejection or chronic/recurrent hepatitis C (HCV). Serial allograft biopsies from individual patients were included. C4d stains were performed by IHC on formalin fixed and by IF on frozen tissue. Positive staining was defined as strong linear endothelial staining. C4d positivity was correlated with tests for donor serum antibodies (DSA), treatment and clinical response.
Results: As in prior studies, endothelial C4d deposition was demonstrated in inflammatory conditions: C4d staining was seen in 3/11 (27%) of native livers biopsied for HCV staging, 3/15 (20%) of allografts with recurrent HCV, and 2/12 (16%) with acute rejection. Comparison of C4d staining by IF and IHC was done for 17 biopsies taken from 10 patients. Staining patterns in portal and sinusoidal endothelium were concordant between methods in 12 of 17 biopsies (71%). DSA tests were performed in 10 patients, with 19 corresponding biopsies; see Table 1.

Table 1

PT	DSA	IF	IHC	TREATED FOR	RESPONSE
1	POS	POS	-	AR	+
2	-	-	-	RAIH	+
2	-	-	-	RAIH	+
3	POS*	POS	POS	AMR	+
4	-	-	-	AC	+
5	POS	-	POS	AMR	-
5	POS	-	POS	AMR	+/-
5	POS	POS	POS	AMR	+
5	POS	POS	POS	Drug injury	-
5	POS	POS	POS	AMR	+/-
5	POS	N/A	-	AMR	-
6	-	POS	-	AR	-
6	POS†	-	-	AMR	-
6	-	-	-	AR	+
6	-	N/A	-	AR	-
7	POS	-	-	AMR	+/-
8	-	-	-	RHCV	+
9	WEAK POS	N/A	-	Drug injury	+
10	-	N/A	-	AR	+
	% POS DSA	% STAINING IN POS DSA§	% STAINING IN POS DSA		
	11/19 55%	5/10 50%	6/11 55%		

*anti-B, †anti-endothelial, AR=acute rejection, AMR=antibody mediated rejection, RAIH=recurrent autoimmune hepatitis, RHV=recurrent HCV, §in subset with IF

Conclusions: In this series, IHC and IF are equally sensitive methods for C4d detection. Staining was concordant with DSA in 15/19 biopsies, representing 8/10 patients, when both IHC and IF were employed. Discordance between DSA and C4d can occur with either staining method. Finally, a diagnosis of AMR made on the basis of either DSA or C4d tests does not predict therapeutic response. Larger studies are needed to validate AMR diagnostic methods.

1712 Arginase-1: A New Rabbit Monoclonal Antibody Is a Superior Marker in Differentiating Primary Hepatocellular Carcinoma vs. Tumors Metastatic to the Liver

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Background: Identification of a more sensitive and specific diagnostic marker delineating primary HCC from tumors metastatic to the liver is of immense clinical significance. Arginase-1 (ARG-1), a urea cycle metalloenzyme found in liver, is now a key target for the differential diagnosis of HCC from metastatic tumors to the liver. An ARG-1 rabbit polyclonal antibody (Sigma) is commercially available for immunohistochemistry (IHC); however, only limited studies on liver cancers and cancers metastatic to the liver have been published. In a comparison IHC study, we will evaluate the efficacy of several commercially available ARG-1 antibodies in HCC.

Design: Sensitivity and specificity of 6 monoclonal/polyclonal antibodies to ARG-1 were determined using tissue microarrays (TMAs). A total of 957 neoplastic and normal tissues were examined in order to determine their suitability in differential diagnosis in liver tumors. For a direct IHC comparison, the referenced ARG-1 rabbit polyclonal antibody, Hep Par1, and TTF-1 antibodies were evaluated in 209 cases of HCC.

Results: Only a rabbit monoclonal antibody (RMab) ARG-1 was suitable for comparison to the referenced ARG-1. Staining patterns that consist of both cytoplasmic and nuclear staining were similar with both ARG-1 antibodies; however the ARG-1 RMab staining sensitivity was improved in grades II and III HCC [Table 1]. Staining sensitivity of ARG-1 RMab was also superior to TTF-1 ($p<0.0001$) and HepPar-1 ($p<0.0015$) [Table 2]. None of the studied neoplasms commonly metastatic to the liver were found to be immunoreactive to ARG-1 RMab, except in a very low percentage of pancreas and prostate malignancies. ARG-1 RMab stained 7/14 of cholangiocarcinomas; and in some HCC, staining of inflammatory cells was observed.

Table 1: Comparison of sensitivity and specificity of antibodies to ARG-1 (n=56)

ARG-1 antibody	Grade I	Grade II	Grade III
RMab	100% (15/15)	96.6% (28/29)	75.0% (9/12)
Reference Antibody	100% (15/15)	86.2% (25/ 29)	66.7% (8/12)

Table 2: Comparison of sensitivity of ARG-1 with Hep Par-1 and TTF-1 (n=209)

Tumor Grade	ARG-1	Hep Par-1	TTF-1
Grade I	95%	85%	60%
Grade II	88%	72%	59%
Grade III	70%	50%	50%

Conclusions: The ARG-1 RMab shows superior sensitivity and specificity in identifying HCC when compared to other ARG-1 antibodies. ARG-1 RMab was also superior to HepPar-1 and TTF-1 in distinguishing HCC versus metastatic liver lesions.

1713 TTF-1 and Napsin-A Are Expressed in a Subset of Cholangiocarcinomas Arising from the Gallbladder and Hepatic Ducts: Continued Caveats for Utilization of Immunohistochemisry Panels

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Background: Thyroid transcription factor-1 (TTF-1) and Napsin-A (NapA) are frequently used to classify a tumor of unknown origin as lung primary. Multiple studies have shown that TTF-1 positivity can occasionally occur in adenocarcinoma of non-pulmonary origin with different antibody clones. Currently, TTF-1 has been reported as negative or infrequently positive in tumors of biliary origin. Based on an index case of cholangiocarcinoma (cholangioCA) expressing TTF-1, we were prompted to study TTF-1 and NapA positivity in a cohort of cholangioCA.

Design: Archived paraffin embedded tissue blocks from liver, gallbladder, and pancreato-biliary resections from 2005-2012 were chosen for cholangioCA (n=33) and non-neoplastic intra- and extra-hepatic biliary epithelium (NNBE) control tissue (n=26). Immunohistochemistry for TTF-1 (SPT24 clone) and NapA (KCG1.1 clone) was performed. TTF-1 nuclear staining was graded for intensity on a scale of 0 to 3 (with 2+ and 3+ considered positive). The quantity of positive tumor was scored as follows: 0= 0%, 1=1-30%, 2=31-66%, or 3=67-100%. For NapA diffuse granular cytoplasmic staining was considered positive. Statistical analysis was performed using the two-sided Fischer exact test.

Results: TTF-1 was negative in NNBE but positive in 24.2% of cholangioCA. Interestingly, all TTF-1 positive cases (n=8) were extrahepatic (n=19, p=0.01) and arose from the upper biliary tract (gallbladder and hepatic ducts, n=13). TTF-1 positivity was associated with age ≥60 (p=0.01) but was not associated with gender (p=0.43). Among positive TTF-1 cases, the average intensity and quantity score was 2.9 and 1.9, respectively. The expression was not uniform in a tumor and showed patches of positivity. Three TTF-1 positive cases were also NapA positive (9% of total). NapA staining showed non-specific apical granular staining in 7 cholangioCA (21.8%).

Conclusions: In summary, 42.1% of extrahepatic cholangioCA expressed TTF-1, 37.5% of which also co-expressed NapA. No TTF-1 reactivity was detected in any NNBE. TTF-1 reactivity was more common in patients ≥60 years of age (47%). CholangioCA should be considered in the differential when evaluating a TTF-1 positive tumor of unknown primary, especially when using the SPT24 clone. As TTF-1 is not known for biliary system development and not detected in NNBE, the biologic significance of this "pulmonary" phenotype (TTF-1 and NapA expression) in a subset of cholangioCA is unknown and needs further investigation.

1714 Liver Transplant Biopsies (LTx) with Sinusoidal Dilatation, Congestion and/or Hemorrhage (SDC/H): A Retrospective Review and Prospective Follow Up in 60 of 665 Liver Transplant Patients in a Tertiary Care Transplant Center

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Background: Sinusoidal dilatation, Congestion and/or Hemorrhage (SDH/C) indicate venous outflow obstruction and ischemia in the liver. However, this has not been studied in the context of transplanted livers. The latter with the multiple vascular anastomoses, post operative complications and patient comorbidities present unusual and challenging situations which are different from the native livers. To our knowledge this is the first series to analyze the etiologies and follow up the clinical course of the transplanted liver with SDC/H.

Design: All the transplant liver biopsies from a transplant center with the diagnosis of SDC/ H were retrieved from Jan 2006 to April 2012. Slides were reviewed by three GI pathologists to assess the severity of the sinusoidal dilatation, congestion, centrilobular hemorrhage. Electronic medical records were reviewed to compile the possible etiology like congestive heart failure (CHF),Doppler confirmed vascular pathology like hepatic artery stenosis/thrombosis, Inferior venacava obstruction and perihilar hematoma. Prospective follow up included graft survival/ loss, complications and related deaths. Duration of follow up ranged from 6 months to 6 years.

Results: SDC/H was diagnosed in 60/665 (9%) transplanted Livers. Dilatation was mild in 61.66%, moderate in 15.51% and severe in 23.33%. Congestion and hemorrhage was mild in 60%, moderate in 20% and severe in 20%. Nine out of 60 patients (15%) lost the graft.

Etiology	Graft lost (9 cases)	Graft survived (51 cases)
Anastomotic complication/Hepatic artery stenosis/ Thrombosis	7	5
Inferior venacava obstruction	1	8
Perihilar hematoma	1	3
Congestive heart failure	0	15

No relevant etiology was found in 12/60 cases. Three patients expired during the followup period. Autopsy was performed in one of three expired. Autopsy confirmed dilated cardiomegaly and sequele of prolonged CHF. Budd Chiari malformation and Angiosarcoma was diagnosed in one case.

Conclusions: SDC/H is diagnosed frequently in LTx. In this special setting the etiologic factors are more diverse as compared with non transplant livers. Graft losses occur with devastating outcomes, more frequently in arterial anastomotic complications related SDC/H. It is not only CHF and/or venous outflow obstruction responsible for SDC/H but other etiologies like vascular anastomotic complications and perihilar hematoma can also manifest itself as SDC/H on biopsy, as seen by our results.

1715 A Triple Stain of Reticulin, Glypican-3, and Glutamine Synthetase Is Useful for the Diagnosis of Liver Lesions

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Background: The histologic diagnosis of mass lesions of the liver can be difficult, especially when there is limited material in a biopsy. Here, we evaluated the usefulness of a triple stain of reticulin, glypican-3 (Gly3) and glutamine synthetase (GS) in whole tissue slides (WTS) and tissue microarrays (TMA) of hepatocellular carcinoma (HCC), hepatic adenoma (HA), non-neoplastic liver tissue adjacent to hepatocellular carcinoma (Liv), and focal nodular hyperplasia (FNH).

Design: WTS of liver masses were retrieved from the archives including HCC (n=16), HA (n=10) and FNH (n=13). In addition, TMA were constructed to mimic a small biopsy of HCC (n=19), HA (n=16), Liv (n=20) and FNH (n=13). A triple stain of reticulin followed sequentially by immunostains for Gly3 (alkaline phosphatase red chromogen) and GS (diaminobenzidine chromogen) was performed on all WTS and TMA. Cases were evaluated for reticulin (intact, lost), Gly3 (positive if >10% or negative) and GS (perivenular, map-like, diffuse if >50% or negative). Sensitivity and specificity in TMA cases were determined using known diagnoses from the resection specimen.

Results: Expression of reticulin, Gly3 and GS in both WTS and TMA cases is shown.

Reticulin, Gly3 and GS expression in Liver Lesions

	Reticulin		Gly3		GS		
	Intact	Lost	Positive	Negative	Perivenular	Map-like	Diffuse
WTS HA	10/10 (100%)	0	0	10/10 (100%)	7/10 (70%)	0	1/10 (10%)
TMA HA	15/16 (94%)	1/16 (6%)	0	16/16 (100%)	8/16 (50%)	0	1/16 (6%)
WTS FNH	13/13 (100%)	0	0	13/13 (100%)	0	13/13 (100%)	0
TMA FNH	13/13 (100%)	0	0	13/13 (100%)	0	11/13 (85%)	2/13 (15%)
WTS HCC	1/16 (6%)	15/16 (94%)	8/16 (50%)	8/16 (50%)	1/16 (6%)	0	9/16 (56%)
TMA HCC	2/19 (10%)	17/19 (90%)	11/19 (58%)	8/19 (42%)	0	0	15/19 (79%)
TMA Liv	20/20 (100%)	0	0	20/20 (100%)	15/20 (75%)	0	0

The results in WTS and TMA are similar. However, map-like and perivenular GS positivity were decreased in TMA FNH and HA as compared to WTS, respectively, likely due to sampling error. Sensitivity and specificity in TMA HCC was compared to HA. Loss of reticulin was 94% sensitive and 94% specific for HCC. Gly3 positivity was 58% sensitive and 100% specific for HCC. Diffuse GS positivity was 79% sensitive and 94% specific for HCC. The sensitivity and specificity in TMA FNH was compared to HA. Intact reticulin was 100% sensitive and 6% specific for FNH. Gly3 negativity was 100% sensitive and 0% specific for FNH. A map-like GS positivity was 85% sensitive and 100% specific for FNH.

Conclusions: These results support the use of this triple stain in the differential diagnosis of HCC, HA and FNH in both WTS and biopsies.

1716 The "Almost Normal" Liver Biopsy: A Differential for a Problematic Area of Liver Pathology

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Background: A persistently challenging area of liver pathology is when biopsies are performed for chronic elevations in liver enzymes or for unexplained ascites, yet the liver biopsy appears almost normal. In these cases, generating a differential is very difficult, much to the disappointment of the clinical team and patients. There is to date essentially no information on the differential or natural history for the "almost normal" liver biopsy.

Design: All liver biopsies signed out by a single liver pathologist over a 5-year period were searched for cases in which a biopsy was performed for elevated liver enzymes or unexplained ascites, but the biopsy was essentially normal and no specific histological diagnosis could be made. All cases had no significant inflammation, fatty change, biliary tract disease, vascular disease, nodular regenerative hyperplasia, iron overload, metabolic disorders, or fibrosis. None had viral hepatitis or evidence for a drug effect. We also excluded all liver transplant biopsies, all mass-directed biopsies, and all biopsies for specific indication such as pre-transplant biopsies or evaluation of methotrextate toxicity.

Results: Over this 5-year time period, 94/2528 (4%) liver biopsies met the inclusion criteria of minimal nonspecific histological changes; 26 cases were then excluded for lack of follow-up, leaving 68 study cases. The most common clinical indications for biopsy were chronic enzyme elevations (74%) and unexplained ascites, splenomegaly, or gastroesophageal varices (18%). For the 68 study cases, subsequent clinicopathological follow-up identified a cause in 66% of cases. The top three causes were systemic autoimmune disorders such as lupus or rheumatoid arthritis (16% of cases); vascular abnormalities including thromboses or unusual vascular shunts (13%); and the metabolic syndrome (10%), even though no fat was present on biopsy. In the remaining cases, 9% eventually went on to develop a typical autoimmune hepatitis or primary biliary cirrhosis, 5% were associated with gastric inflammation such as Crohn's disease, 5% were associated with low grade liver ischemia, and 9% had a variety of miscellaneous conditions. In 23 cases (34%), no cause was identified, and liver enzymes eventually self-normalized in 1/3 of cases but persisted in the remaining 2/3.

Conclusions: This study provides a differential for the "almost normal" liver biopsy. Knowing this differential will allow pathologists to help direct subsequent clinical and laboratory work up in efforts to identify an etiology. An etiology can be identified in the majority (66%) of cases.

1717 Histopathological Features of Hepatic Venous Outflow Obstruction in Transplant Liver Biopsies

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Background: Hepatic venous outflow obstruction (HVOO) is a clinically significant complication of orthotopic liver transplantation. Because its histological features often overlap with other conditions, definitive diagnosis is occasionally problematic, in part because these features have not been systematically evaluated in the context of radiologic findings. We analyzed histopathological changes in liver allograft biopsies from patients with concurrent radiological evidence of HVOO.

Design: 28 post-transplant orthotopic liver allograft biopsies with clinical suspicion for hepatic venous outflow obstruction and with no histological evidence of rejection were selected for study. 15 cases had imaging evidence of HVOO (HVOO group) while 13 cases did not (control group). Clinical and laboratory data were also reviewed.

Results: 97% of imaging proven HVOO cases occurred within the first year post transplant (median=16 weeks; range 1-104 weeks). The most common clinical presentation included ascites and elevated LFTs. Perivenular hepatocyte dropout and perivenular congestion were present in the vast majority of HVOO cases (100% and 80%, respectively) but only in 23% (p=0.001) and 30% (p=0.02) of controls, respectively. Perivenular fibrosis was significantly more frequent in HVOO compared to controls (93% and 46%, respectively; p=0.01). Diffuse sinusoidal dilation was more commonly seen in HVOO but this feature did not reach statistical significance. Perivenular collapse and edema were observed only in HVOO, but were not commonly identified (13 %).

Histologic features of HVOO

	Perivenular dropout	Perivenular congestion	Sinusoidal dilation (>focal)	Perivenular fibrosis	Hepatocytic atrophy	Perivenular edema	Perivenular inflammation
HVOO (n=15)	15 (100%)	12 (80%)	8 (53%)	14 (93%)	6 (40%)	2 (13%)	2 (13%)
Control (n=13)	3 (23%)	4 (30%)	2 (15%)	6 (46%)	5 (38%)	0	0
P value	0.0001	0.0200	0.0546	0.0108	1.0000	0.4841	0.4841

Conclusions: Based on systematic review of histological features associated with imaging proven hepatic venous outflow obstruction (HVOO) in allograft liver biopsies, we conclude that the most reliable among them are perivenular hepatocyte dropout, perivenular sinusoidal congestion and perivenular fibrosis. Perivenular collapse and edema, though specific, are not sensitive markers of HVOO. These findings may aid in the identification and proper management of patients with HVOO.

1718 Reevaluation of the Diagnostic Utility of Villin and Mammaglobin in the Differential Diagnosis between Metastatic Breast Ductal Carcinoma and Intrahepatic Cholangiocarcinoma in the Liver

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Background: Liver is a common metastatic site for breast cancer; differentiation of metastasis from intrahepatic cholangiocarcinoma (ICC) is crucial for patient management. We recently encountered a patient with a history of ER-negative microinvasive breast cancer who presented with a liver mass; a definite diagnosis cannot be made due to similar morphology and lack of specific markers. Villin and mammaglobin are markers of gastrointestinal and breast tissue, respectively; however, they were considered not useful in cholangiocarcinoma for various reasons. We decided to reevaluate these two markers in the differential diagnosis between metastatic breast ductal carcinoma and ICC.

Design: Fifty-two cases of breast ductal carcinoma (26 ER-positive, 26 ER-negative), 27 cases of ICC, and 19 cases of extrahepatic bile duct adenocarcinoma (EBC) were retrieved from the pathology archive. Available lymph node metastases (LNM) were included in all breast cases. Immunohistochemical staining for villin was performed on all cases; mammaglobin was performed on the breast and ICC cases. Villin was interpreted as positive with any luminal staining, mammaglobin was interpreted as positive with at least 1% of the cells showing cytoplasmic staining. Fisher's exact test was used for statistical analysis.

Results: Villin was negative in all ER-positive (23 invasive ductal carcinomas [IDC], 18 ductal carcinoma in situ [DCIS], 24 LNM) and ER-negative (23 IDC, 12 DCIS, 11 LNM) cases of breast carcinoma. It was positive in all 27 cases of ICC (6 surgical resections, 9 resections with matched prior biopsies, 12 biopsies) and 12 of 19 cases of EBC (63%). Mammaglobin was positive in 6 of 46 IDC (13%), 7 of 30 DCIS (23%), and 12 of 35 LNM (34%), with no significant difference between ER-positive and negative cases. Notably, discrepancy of mammaglobin staining in matched IDC, DCIS and LNM was common. All ICCs were negative for mammaglobin staining, when caution was taken not to misinterpret nonspecific staining in the interspersed hepatocytes as positive.

Conclusions: Contrary to earlier belief, villin expression is highly accurate in the differential diagnosis between ICC and metastatic breast ductal carcinoma, which is particularly useful for ER-negative cases. Mammaglobin is useful when it is positive (in about a third of breast cancer cases). The same conclusion is expected to apply to microinvasive carcinoma based on staining in DCIS and IDC.

1719 Protein Expression of ARID2, PIK3CA, p53 and ß-Catenin in Hepatocellular Carcinoma (HCC) and Background Cirrhotic Liver

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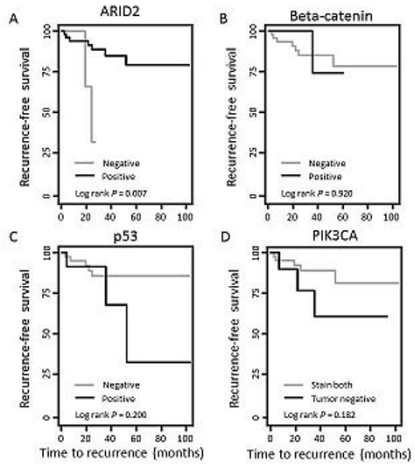
Background: Available evidence suggests that HCCs are genetically heterogeneous tumors, yet the genetic events are not clearly understood. Recent molecular studies have detected *ARID2* mutations in HCC and others have shown a possible association with viral etiology and cancer mutations in *PIK3CA*, *p53* and β-catenin. However, studies evaluating these genetic events through protein expression are lacking.

Design: Immunohistochemistry was performed using ARID2, PIK3CA, p53, and β-catenin antibodies on HCC and background cirrhotic liver from 58 explanted livers.

Results: Diffuse loss of nuclear expression of ARID2 was observed in 4 of 58 (6.9%) HCCs and 13 of 57 (22.4%) HCCs showed nuclear expression of p53. β-catenin nuclear expression was observed in 5 of 57 (8.6%) HCCs. While PIK3CA expression was seen in all non-neoplastic cirrhotic livers at dilution of 1:200, 10 of 57 (17.2%) HCCs had complete loss of PIK3CA expression; the remaining 47 cases showed PIK3CA expression in both neoplastic and non-neoplastic tissue. Statistical analysis showed no association between the expression of the four proteins in HCC and the etiology of cirrhosis (all $p>0.05$). Protein expression was independent of each other ($r^2 \leq 0.72$). ARID2 inactivation had a significant association with cancer recurrence (p=0.042 multivariate adjusted) [figure 1] and occurred more frequently in non-Caucasians (P=0.049). p53 nuclear expression had a strong association with poor differentiation ($P<0.0001$) and tumor number (p=0.031). PIK3CA loss of expression in tumor was more common in patients with tumors that did not meet the Milan criteria at time of liver transplantation (P=0.049) and more common in non-Caucasians (P=0.033).

Conclusions: An association with viral etiology and protein expression was not observed. Protein expression was found to be independent of each other. This is the first study to show that loss of ARID2 expression in HCC is associated with cancer recurrence. In support of previous studies, p53 nuclear expression had a high association with poor differentiation and tumor number. Diffuse loss of expression of the oncoprotein

PIK3CA in HCC is a novel finding and further investigations may determine if this represents feedback inactivation of the mTOR pathway.



1720 Aberrant von Willebrand Factor (vWF) Expression of Sinusoidal Endothelial Cells in Nodular Regenerative Hyperplasia and Obliterative Portal Venopathy

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Background: Nodular regenerative hyperplasia (NRH) and obliterative portal venopathy (OPV) are under-recognized diseases of uncertain etiology that result in noncirrhotic portal hypertension (NCPH). The diagnosis can be easily missed on needle liver biopsy. CD34 and vWF are commonly used endothelial markers. vWF is released by activated endothelial cells and plays a crucial role in primary hemostasis and in the development of thrombotic vascular obliteration. Liver sinusoidal endothelial cells (LSEC) are unique in that the expression of CD34 and vWF are confined only to periportal areas in the normal liver. We sought to investigate the potential utility of these two immunomarkers in helping make the diagnosis of NRH and OPV. Additionally, the immunoexpression pattern may further elucidate the pathogenesis of these conditions.

Design: Re-review of the histology of liver wedge and needle biopsies of clinically proven NCPH cases was undertaken. NRH is defined as small hyperplastic nodules centered around portal tracts compressing adjacent atrophic hepatocytes and sinusoids whereas OPV, although having heterogeneous histology, commonly demonstrates different degrees of phlebosclerosis and dense portal fibrosis. Cases with combined OPV and NRH on biopsy were also noted. Immunohistochemical staining for CD34 and vWF (DAKO, Carpinteria, CA) was performed using standard methods.

Results: There were 15 NRH, 25 OPV and 5 normal liver biopsies (acting as controls). Among the 25 OPV, 20 had concurrent features of NRH (80%). CD34 (+) staining was mainly confined to small vessels in the portal tracts as well as LSECs in periportal areas in both NRH and OPV, similar to that in the normal control biopsies. Unlike CD34, expression of vWF in LSECs was (+) along the dilated sinusoids of NRH, and in a patchy or geographic pattern, particularly prominent in the perivenular areas of OPV as opposed to vWF expression being confined to periportal areas in the controls.

Conclusions: NRH and OPV are commonly seen together in the same liver biopsy. The aberrant expression of vWF in NRH and OPV suggest that LSEC activation is involved in their pathogenesis and that NRH and OPV may share a common pathway of vascular injury. The aberrant expression pattern of vWF may also aid in the histologic diagnosis and recognition of NRH and OPV on liver biopsy.

1721 The p53 Negative Regulator, MDM4 but Not MDM2, Is Frequently Activated in Hepatocellular Carcinoma

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Background: The p53 tumor suppressor pathway is frequently inactivated in human cancers including hepatocellular carcinoma (HCC). MDM2 and MDM4 are the primary negative regulators of p53. Amplification or over-expression of MDM2 and MDM4 abolish the p53 mediated response by inactivating the wild-type p53 protein. A functional single nucleotide polymorphism of the *MDM2* (SNP-309 T/G) enhances the Sp1 binding to *MDM2* promoter and MDM2 expression resulting in attenuation of p53 and has been associated with the development and prognosis of a number of tumors. We hypothesized that over-expression of MDM2 and MDM4 may be the common mechanism of p53 inactivation in HCC and thus a potential therapeutic target.

Design: Tissue microarrays of HCC were constructed and immunohistochemically stained for MDM2, MDM4 and p53. Expression intensity was scored as 0 (absent), 1+ (modest) or 2+ (high). Genotyping of *MDM2* SNP-309 was performed on genomic DNA extracted from tumor by PCR amplification flanking the corresponding promoter region followed by temperature gradient capillary electrophoresis and direct sequencing. We evaluated the association between *MDM2* SNP-309 and the risk of HCC by comparing the genotype frequency with that of controls. We also investigated the relationships between *MDM2* SNP-309 genotype, MDM2, MDM4 and p53 expression and median overall survival time.

Results: MDM4 expression was detected in 42 of 93 HCC (45%; 1+ in 33, 2+ in 9), p53 was detected in 6 (6%; 1+ in 4, 2+ in 2), and no MDM2 immunoreactivity was found. The *MDM2* SNP-309 genotypes of HCC were not statistically different from those of 100 controls.

MDM2 SNP-309 Genotypes in HCC and Controls

	HCC (n = 69)	Control (n = 100)
G/G	7 (10%)	12 (12%)
T/G	30 (43.5%)	40 (40%)
T/T	32 (46.4%)	48 (48%)

p = 0.981

No correlation was observed between *MDM2* SNP-309 genotype, MDM4 and p53 expression level and median overall survival time.

Conclusions: Aberrant activation of MDM4 is frequently present in HCC and could represent a common mechanism by which wild-type p53 is inactivated. It is unlikely that *MDM2* SNP-309 or over-expression of MDM2 contribute to p53 inactivation. We are currently evaluating the potential mechanism of MDM4 over-expression and the correlation with p53 mutation status.

Neuropathology

1722 Altered Telomeres with Loss of *ATRX* Protein Are Frequently Seen in High-Grade Pediatric Gliomas

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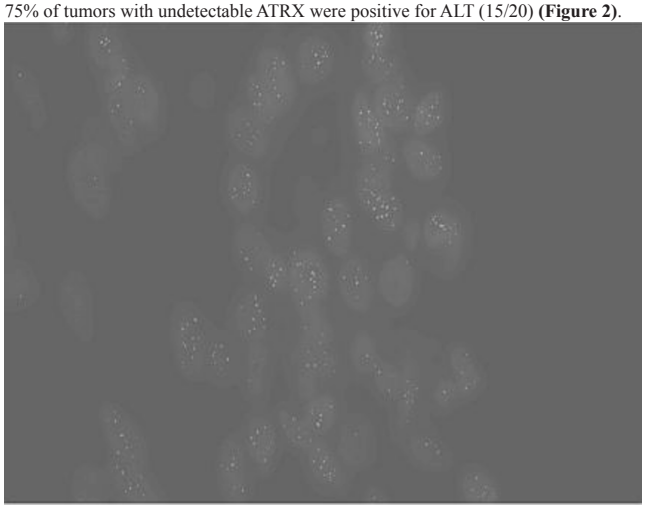
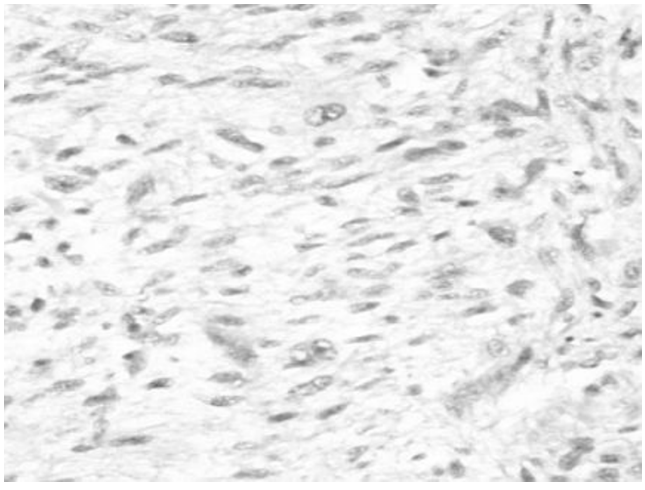
Background: Loss of function of alpha thalassemia/mental retardation syndrome X-linked (ATRX) protein leads to a phenotype called alternative lengthening of telomeres (ALT). Mutations that inactivate these genes are common in human pancreatic neuroendocrine tumors (PanNETs) and CNS tumors.

Design: We examined 60 cases of high-grade pediatric gliomas of various histological types and looked for loss of ATRX with immunocytochemistry and the presence of ALT with telomere-specific fluorescence in situ hybridization.

Results: Using a large cohort from multiple institution of high-grade pediatric gliomas (n = 60) we found that 33.33% of tumors were ALT positive (20/60) **(Figure 1)**, and 75% of tumors with undetectable ATRX were positive for ALT (15/20) **(Figure 2)**.





Conclusions: Further understanding of the role of ATRX/DAXX and histone H3.3 in GBM pathogenesis may lead to more accurate prognosis and stratification of patients to the most appropriate therapies. ALT/ATRX may serve as a potential screening and prognostic marker in patients with pediatric gliomas. Our results show that telomere-