increased 77.6% and 144.6% in RV and RV+ARB, while there were no change in R and R+ARB. Capillary length increased 18.5% in RV and 57.8% in RV+ARB, compared to 23.8% in R and 36.7% in R+ARB.
Conclusions: We conclude that ARB reduces glomerular matrix accumulation, and restoring VEGF in sclerotic glomeruli induces more new capillary branches, both of which contribute to ameliorate glomerulosclerosis.

1653 Histopathologic Evidence of Contrast-Induced Nephropathy

Cynthia Zhao, Luyu Yao, Wayne Zhang, Xin Gu. Louisiana State University Health Sciences Center, Shreveport, LA.
Background: Contrast-induced nephropathy (CIN) is the third leading cause of acute renal failure in hospitalized patients. The mechanisms of CIN are not well understood. Direct renal tubular cell damage is hypothesized as one of the major causes. However, there is limited histopathologic evidence supporting it. Proximal tubules are very vulnerable to renal toxic medications or chemicals. We hypothesize that CIN may result from direct structural damage of proximal tubules caused by contrast media (CM). The objective of this study is to investigate the histomorphologic changes of CIN.
Design: Our CIN mouse model is created by inhibiting prostaglandin and nitric oxide syntheses followed by administration of Iodixanol, one of the most commonly used CM. This model mimics the clinical CIN scenario because the hospitalized patients likely have underlining renal dysfunction with low prostaglandin and nitric oxide levels. Two dosages of Iodixanol, 6.24 gI/kg and 12.48 gI/kg, were given based on body weight. C57B1/6J mice received indomethacin (a prostaglandin synthesis inhibitor, 10 mg/kg) and Nω-Nitro-L-arginine methyl ester (L-NAME, a nitric oxide synthase inhibitor, 10mg/kg) intraperitoneally before injection of Iodixanol. The mice in control group received indomethacin and L-NAME followed by normal saline instead of Iodixanol. Kidneys were harvested after 24 hours. The specimens were fixed with 10% formalin, embedded in paraffin, and stained with Hematoxylin and Eosin (H&E) and Periodic Acid-Schiff (PAS) for histopathologic evaluation.
Results: The histopathologic changes were mainly identified in the proximal tubular epithelial cells. The glomeruli and medullary areas showed no significant abnormalities. The kidney in low dose group revealed mild acute tubular injury manifested with cellular edema and prominent vacuolar degeneration. The kidney in high dose group presented with moderate acute tubular injury with extensive cellular edema and prominent vacuolar degeneration. The PAS stain in high dose group also showed segmental brush border loss of the tubular epithelial cells. The control group revealed no significant tubular injury.
Conclusions: Our data showed clear histopathologic evidence of renal proximal tubular epithelial cell injury caused by CM with dosage-dependent severity. There were no significant medullary changes. Direct toxicity-related renal tubular cell damage is likely to be one of the mechanisms of CIN. Further investigation of protective agents against CIN is planned.

Liver

1654 Nuclear Forkhead Box O3a Expression in Hepatocellular Carcinoma: Correlation With Clinicopathologic Features and Survival

Hyein Ahn, Jongmin Sim, Hyunsung Kim, Kijong Yi, Yumin Chung, Abdul Rehman, Seung Sam Paik, Dong Ho Choi, Kiseok Jang. Hanyang University Hospital, Seoul, Republic of Korea.
Background: Forkhead box O3a (FoxO3a) is a transcription factor belonging to the subfamily of winged-helix forkhead box family which plays a critical role in the regulation of a wide spectrum of biological processes. FoxO3a is known as a tumor suppressor that regulates a variety of proapoptotic genes, and inactivates the PI3k-Akt oncogenic pathway. A recent study has demonstrated that FoxO3a with nuclear β-catenin promotes the survival of cancer cells, tumor expansion, and metastasis.
Design: A total of 223 cases of hepatocellular carcinoma (HCC) with adequate paraffin-embedded tissue samples were collected and reviewed. Expression of FoxO3a, β-catenin, and Ki-67 was analyzed by immunohistochemical staining on tissue microarrays. We evaluated the relation between FoxO3a overexpression and various clinicopathologic features. In addition, we investigated the correlations between FoxO3a overexpression and expression of β-catenin and Ki-67.
Results: The nuclear FoxO3a overexpression was correlated with aggressive phenotypes of HCC, such as advanced AJCC stage ($p = 0.002$), vascular invasion ($p < 0.001$), and higher histologic grade ($p < 0.001$). The Kaplan-Meier survival curves revealed that FoxO3a overexpression was significantly associated with poor disease free survival ($p = 0.042$, log-rank test). FoxO3a overexpression was associated with higher Ki-67 labeling index ($p < 0.001$).
Conclusions: Our results demonstrate that FoxO3a overexpression is associated with poor prognostic factor in HCC, and correlates with higher Ki-67 labeling index. These controversial findings should be clarified with further investigation, which can provide opportunities for the development of biomarker or potential targeted therapy.

1655 Cystadenomas of the Liver and Extrahepatic Bile Ducts. Morphologic and Immunohistochemical Characterization of the Biliary and Intestinal Variants

Jorge Albores-Saavedra, Juan Cordova-Ramon, Fredy Chable-Montero, Rita Dorantes-Heredia, Donald Henson. Medica Sur Clinic and Foundation, Mexico, DF, Mexico; Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico, DF, Mexico; Uniformed Services University of the Health Sciences, Bethesda, MD.
Background: Cystadenomas of the liver and extrahepatic bile ducts (EHBD) are uncommon neoplasms whose terminology and epithelial phenotype has been a source of controversy. The generic term "mucinous cystic neoplasm" has been recommended by the World Health Organization (WHO).
Design: We identified 20 cystadenomas of which 16 originated in the liver and 4 in the EHBD. Clinical and follow-up information were obtained from the medical records. Gross findings were obtained from the surgical pathology reports. The percentage of the epithelial lining cells: biliary, intestinal and foveolar, was estimated for each tumor. Multiple H&E stained sections were available for review in all 20 cases. From selected paraffin blocks additional slides were prepared for immunohistochemical analysis.
Results: Eighteen patients were women, with a mean age of 36.5 years. The tumor size ranged from 4 to 29 cm (average 11 cm). The cyst fluid in 13 tumors was described as serous, in two as clear, in two others as hemorrhagic, and in one as serous and mucinous. Only in 2 tumors was the fluid described as mucinous. In 18 cystadenomas the predominant epithelial lining consisted of a single layer of cuboidal or low-columnar non-dysplastic cells similar to those of the gallbladder and bile ducts. These cells expressed cytokeratin (CK) 7 and 19, and focally MUC1. Only two cystadenomas showed predominant intestinal differentiation characterized by mature goblet cells and columnar absorptive cells. These cells expressed CDX2, MUC2 and CK20. These 2 tumors showed areas of high-grade dysplasia and invasive adenocarcinoma with intestinal phenotype. A subepithelial ovarian-like stroma was present in all tumors. None of the patients died as a result of the tumors.
Conclusions: Our findings indicate that there are two types of cystadenomas in the liver and EHBD. The most common (80%), lined predominantly by non-dysplastic biliary epithelium appears to lack malignant potential, and the second showing predominantly intestinal differentiation, may progress to high-grade dysplasia and invasive adenocarcinoma. We believe that the term "mucinous cystic tumor" recommended by the WHO for all cystadenomas of the liver and EHBD is a misnomer.

1656 Autoimmune Hepatitis: Review of Validity of Histologic Features Included in the Simplified Criteria Proposed By the International Autoimmune Hepatitis Group (IAIHG)

Dana Balitzer, Nafis Shafizadeh, Najeeb Alshak, Sanjay Kakar. University of California, San Francisco, CA; Kaiser Permanente, Los Angeles, CA.
Background: Histologic features, autoantibodies, serum IgG and negative viral serology are part of Simplified Criteria adopted by IAIHG, which regard diagnosis of autoimmune hepatitis(AIH) as definite(≥7 points) or probable(6 points). Histologic features in these criteria are(1)interface hepatitis with portal lymphocytic/lymphoplasmacytic cells extending into lobule (2)emperipolesis (3)rosettes. Presence of all 3 features is typical of AIH(2 points), while a chronic hepatitis picture without all 3 features is compatible with AIH(1 point). The validity of these histologic features for AIH has not been examined.
Design: Clinical data and liver biopsies were reviewed for 89 AIH, 23 primary biliary cirrhosis(PBC) and 5 non-AIH acute hepatitis. The Simplified Criteria score was calculated.Copper and CK7 stains were done in 66 cases.
Results: Emperipolesis and rosettes were seen in 78% and 39% AIH, and 16% and 61% of non-AIH cases. Both features were present in 26% AIH and 17% non-AIH. Copper and CK7 stains were positive in 20% and 43% AIH, all of which had at least bridging fibrosis. Using features of Simplified Criteria, 26% AIH received 2 histologic points(typical AIH), and 60% received 1 histologic point(compatible with AIH). Using our proposed histologic features, 80% and 11% AIH received 2 and 1 histologic points. The proposed histologic features led to increase in Simplified Criteria score of AIH cases from 6(probable AIH) to 7(definite AIH) in 8%, and 5(no AIH) to 6(probable AIH) in 10% cases. There was no increase in score in PBC or non-AIH acute hepatitis.

Histologic Score	Proposed histologic Features
1	Hepatitis with mild or moderate necroinflammatory activity (at least Ishak A2, B1, and/orC2).
2	Any one of the following additional features: (a)Plasma cells: numerous or in clusters (b)CK7 and copper stains negative (for chronic cases with Ishak fibrosis score 3, not applicable toacute cases) (c)High necroinflammatory activity (Ishak >A3, B2 and/or C3).

Conclusions: The requirement of rosettes and emperipolesis in Simplified Criteria leads to a low histologic score even in typical AIH. These features are not specific for AIH and are present in a few PBC and majority of non-AIH acute hepatitis. We propose new histologic features that increase histologic and total scores in AIH, leading to increase in sensitivity of Simplified Criteria for diagnosis of AIH without misclassification of PBC or non-AIH hepatitis cases.

1657 Expression of PEG10 Is Associated With Poor Survival and Tumor Recurrence in Hepatocellular Carcinoma

Heejin Bang, Sang Yun Ha, Soo Hyun Hwang, Cheol-Keun Park. Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.

Background: Paternally expressed gene 10 (PEG10) was first identified as an imprinted gene that is paternally expressed and maternally silenced. In hepatocellular carcinoma (HCC), PEG10 has been identified as a potential target gene located within the amplified 7q21 locus. However, the prognostic significance of PEG10 protein expression in HCC has not yet been elucidated. The purpose of this study was to investigate the expression of PEG10 protein in HCC and evaluate its prognostic significance.

Design: PEG10 protein expression was examined by immunohistochemistry in tumor tissue from 218 HCC patients undergoing curative resection. The median follow-up period was 119.8 months for survivors.

Results: PEG10 expression was observed in 148 (67.9%) of the 218 HCCs and was significantly correlated with younger age, female, higher Edmondson grade, microvascular invasion, intrahepatic metastasis, higher AJCC T-stage, and higher α-fetoprotein level. PEG10 expression was independent predictor of early recurrence (*P*=0.013). PEG10 expression showed an unfavorable influence on recurrence-free survival (RFS) (*P*<0.001). Subgroup analysis showed that among patients with α-fetoprotein £20 ng/mL (80 patients), the PEG10-positive group also showed an unfavorable influence on RFS (*P*=0.002). Further analysis revealed that among patients with tumor size ≤5.0cm (134 patients) and patients at AJCC T-stage 1 (91 patients), the PEG10-positive groups tended to show unfavorable influences on RFS (*P*=0.072 and *P*=0.079, respectively).

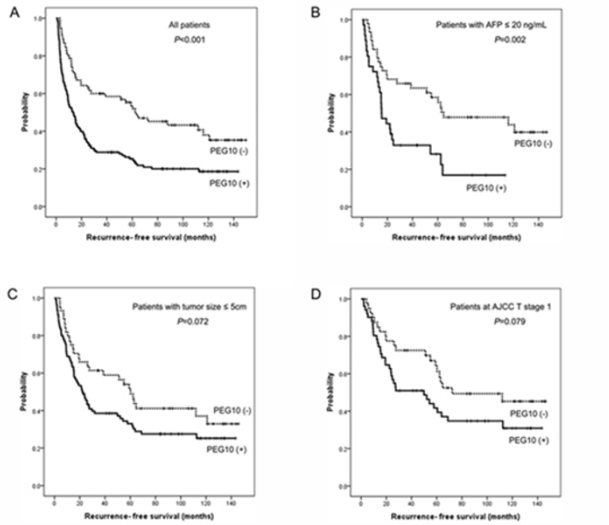


Fig. 1. Kaplan-Meier survival curves showing RFS among all patients (A), patients with α-fetoprotein ≤ 20 ng/mL (B), patients with tumor size ≤5.0 cm (C), and patients at AJCC T-stage 1 (D) according to the PEG10 expression.

Moreover, multivariate survival analysis identified PEG10 as an independent predictor of shorter RFS (*P*=0.005).

Conclusions: PEG10 protein could be a potential biomarker to predict early recurrence and RFS in HCC patients after curative resection, even in those with normal serum α-fetoprotein levels. These findings also indicate possible new lines of research for the development of therapeutic approaches targeting PEG10.

1658 C-MYC Over-Expression Is Rare in Hepatic Small Vessel Hemangioma and Diffuse C-Myc Staining Is Restricted To Hepatic Angiosarcoma

Ben Buelow, Thiago Amancio, Elizabeth Brunt, Ta-Chiang Lu, Gretta Jacobs, Hala Makhlouf, Celia Martginean, Ilke Nalbantoglu, Christine Sempoux, Dale Snover, Swan Thung, Matthew Yeh, Linda Ferrell, Ryan Gill. University of California, San Francisco, CA; Washington University, St. Louis, MO; University of Minnesota, Minneapolis, MN; Ottowa Hospital, Ottawa, ON, Canada; University of Washington, Seattle, WA; University Hospitals of Cleveland, Cleveland, OH; Universite Catholique de Louvain, Brussels, Belgium; National Institutes of Health, Franklin, MD; Universidade de São Paulo, São Paulo, Brazil; Mount Sinai Beth Israel Medical Center, New York, NY.

Background: Hepatic vascular neoplasms (HVN) are common lesions that span a spectrum from benign to malignant. With recognition of a small vessel hemangioma (SVH) variant as a mimic of angiosarcoma (AS), IHC markers of malignant potential in HVN are needed. Our group and others have shown that strong p53 and GLUT-1 labeling are largely restricted to malignant HVN. Although both markers are quite specific for EHE and AS, neither is very sensitive. Thus, novel markers that differentially stain benign and malignant HVNs are desirable. Cutaneous AS can show c-Myc overexpression and a recent USCAP abstract reported high sensitivity and moderate specificity for positive c-Myc staining in hepatic AS. Our aim is to characterize c-Myc staining among SVH as compared to hepatic AS.

Design: Representative sections from 14 SVH (4 biopsies, 9 resections, and 1 autopsy) and 9 AS (4 biopsies and 5 resections) cases were randomized, characterized histologically, and stained for c-Myc overexpression. Staining intensity/frequency was scored by 2 independent observers.

Results: 0/14 (0%) SVH and 2/9 (22%) AS showed diffuse (>50% of cells) nuclear c-Myc positivity in tumor cells. Additionally, 2/14 (14%) SVH and 1/9 (11%) AS cases showed focal tumor cell c-Myc staining (5-50% of cells). C-Myc positivity was not significantly correlated with SVH or AS by Fisher's exact test (diffuse c-Myc, p=0.14; focal or diffuse c-Myc, p=0.28).

Conclusions: Diffuse c-Myc staining was specific (100%) but not sensitive (22%) for AS. Although not a significant discriminator on its own, diffuse c-Myc staining adds support for AS and is recommended, in addition to Ki-67 and p53 staining, when considering this differential diagnosis, especially on core biopsy. No SVH patients in our study have had evidence of recurrent or metastatic disease; however, given its apparent infiltrative growth, increased proliferative index, and occasional p53 and focal c-Myc expression, we recommend complete resection and close follow up.

1659 Histologic Features in Biopsies of Donation After Cardiac Death (DCD) in Liver Transplant Recipients

Kathleen Byrnes, Neeta Vachharajani, Maria Doyle, Elizabeth Brunt, Ilke Nalbantoglu. Washington University, St. Louis, MO.

Background: Clinical outcomes of DCD liver transplant (OLT) have been previously described. The histologic features are not well characterized.

Design: Liver biopsies (n=131) from age matched DCD (n=60) and non-DCD (n=71) recipients with Hepatitis C virus were compared. Histologic features were studied in a blinded fashion and subgrouped into time 0, 0-6 months (m), and >6 m.

Results: In time 0 biopsies, ductular reaction (DR) with neutrophils (PMN) was more common in non-DCD (p=0.04). Although not statistically significant, more DCD cases had zone 3 drop-out (43.8% vs 29%) and bridging necrosis (19% vs 0%). Small droplet steatosis was more common in non-DCD (p=0.04).

At 0-6 m, more DCD cases had portal edema (p=0.01). Pericholangitis (30.4% vs 18.8%) and acute cholestasis (21.7% vs 12.5%) were more common in DCD, but not statistically significant. Indefinite for rejection was seen more in DCD (8.7% vs 0%) whereas non-DCD had more mild acute cellular rejection (6.3% vs 4.3%).

At >6 m, pericholangitis (19% vs 4.5%) was more common in DCD, though not statistically significant. Cholangitis, DR with PMN, and acute cholestasis were similar in the two cohorts (table 1). Overall, both groups had similar portal inflammation and fibrosis. Post-operative biliary complications were more common in DCD (19% vs 0%). 90 day and 1 year graft survival and patient outcomes were similar in both cohorts.

Table 1

	Time 0		0-6 months		>6 months	
	DCD/ Non-DCD	p-value	DCD/ Non-DCD	p-value	DCD/ Non-DCD	p-value
Total Biopsies	16 / 17	-	23 / 32	-	21 / 22	-
Portal Edema (%)	0 / 0	-	17.4 / 0	0.01*	4.8 / 0	0.3
Pericholangitis (%)	0 / 5.9	0.32	30.4 / 18.8	0.31	19 /4.5	0.13
Cholangitis (%)	0 / 11.8	0.15	13 / 9.4	0.66	14.3 / 18.2	0.72
DR with PMN (%)	18.8 / 52.9	0.04*	34.8 / 53.1	0.17	38.1 / 40.9	0.85
Acute Cholestasis (%)	0 / 5.9	0.32	21.7 / 12.5	0.36	8.7 / 9.1	0.96
Small Droplet Steatosis (%)	18.8 / 52.9	0.04*	13 / 12.5	0.95	28.6 / 13.6	0.22

Conclusions: Biliary alterations were more prevalent in the 0-6 m DCD biopsies reflecting increased vulnerability of this group to biliary complications in the early post-OLT period. This finding may suggest poor graft perfusion despite comparable cold ischemia times.

1660 Steatohepatitic Hepatocellular Carcinoma: An Uncommon Variant of Hepatocellular Carcinoma Associated With Metabolic Risk Factors and Late Tumour Relapse

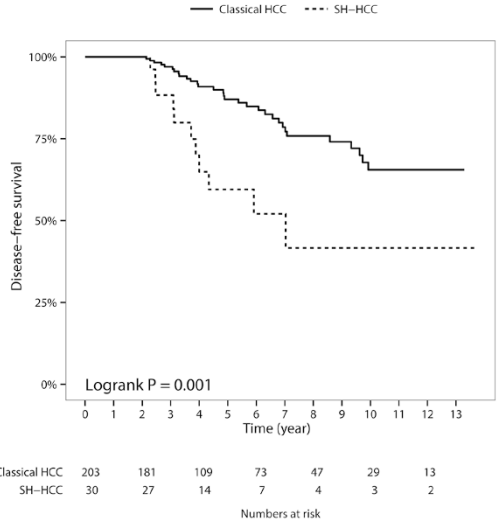
Anthony Chan, Joanna Tong, Stephen Chan, Paul Lai, KF To. The Chinese University of Hong Kong, Hong Kong, Hong Kong.

Background: Steatohepatitic hepatocellular carcinoma (SH-HCC) is a variant of HCC associated with underlying steatosis, steatohepatitis and metabolic risk factors. Only a small portion (18.8%) of patients in previous studies had chronic hepatitis B (HBV). To better determine the incidence, clinicopathological features and prognostic significance of SH-HCC in background of chronic HBV, we studied a retrospective cohort of patients with HBV-related primary HCC undergoing curative surgery.

Design: A retrospective cohort of 389 patients with HBV-related primary HCC undergoing curative surgery was recruited clinicopathological study. A subset (n=302) of the recruited cohort were used to construct tissue microarrays for immunohistochemical studies of stemness markers (CD56, CK19, EpCAM) and Glypican-3.

Results: SH-HCC was identified in 41 patients (10.5%). SH-HCC had higher frequency of diabetes mellitus (*P*<0.001), hypertension (*P*=0.047), underlying fatty liver disease (*P*=0.001) and steatohepatitis (*P*=0.002), and tended to present at early stage disease (80.5% vs. 55.2% as AJCC stage I, *P*=0.006). SH-HCCs were smaller in size (*P*=0.006) with lower frequency of tumour multiplicity (*P*=0.034), major vessel (*P*=0.035) and microvascular invasions (*P*=0.019) than classical HCCs. SH-HCC and classical HCC did not show significant difference in expression in CD56, CK19, EpCAM and Glypican-3.

SH-HCC was one of factors predicting late tumour relapse (relapse beyond 2 year after surgery) in both univariate and multivariate analyses. The adjusted hazard ratio of late relapse for SH-HCC was 4.78 (95% CI: 1.42-10.32, $P<0.001$).



Conclusions: SH-HCC in was an uncommon variant of HCC in HBV patients and associated with underlying steatosis or steatohepatitis, metabolic risk factors and higher risk of late tumour relapse.

1661 Arginase -1 Is Positive in Hepatoid Adenocarcinomas

Vishal Chandan, Sejal Shah, Michael Torbenson, Tsung-Teh Wu. Mayo Clinic, Rochester, MN.

Background: Hepatoid adenocarcinoma is a rare extrahepatic tumor which shows morphological and immunohistochemical similarities to hepatocellular carcinoma (HCC). Hence, hepatoid adenocarcinoma can cause diagnostic confusion with HCC. Arginase-1 immunostain has been recently shown to be an excellent marker of normal hepatocytes and is a sensitive and specific marker for HCC. However, the expression of Arginase-1 in hepatoid adenocarcinoma has not yet been evaluated.

Design: 8 cases of hepatoid adenocarcinoma (age range 31-79 years; 5 males and 3 females) originating from stomach (4), lung (2), pancreas (1) and adrenal gland (1) were immunostained with Arginase-1, Hepar-1, Glypican-3, CK7, CK20, CK19, polyclonal CEA (p-CEA), alpha fetoprotein (AFP), CDX2, and TTF-1. Albumin ISH was performed in 4 cases. None of our patients had a history of HCC or a liver mass. Serum AFP was elevated in 5 cases while it was not evaluated in 3 cases. For each marker, any expression in >5% of the tumor was considered positive. For p-CEA, the staining was also evaluated as canalicular, membranous or cytoplasmic.

Results: All 8/8 cases (100%) were positive for Hepar-1. Arginase-1 was positive in 5/8 cases (62.5%); 2 of these cases showed diffuse strong staining, 2 showed patchy strong staining and 1 showed patchy weak staining. Glypican-3, CK7 and AFP were each positive in 4/8 cases (50%). CDX2 and CK19 were each positive in 3/8 cases (37.5%), out of which 2 were arising within the stomach and 1 in lung. p-CEA showed canalicular/membranous staining in 5/8 cases (62.5%) and cytoplasmic staining in 3/8 cases (37.5%). Albumin-ISH was positive in 3/4 cases (75%). CK20 was positive in 1/8 case (12.5%) while TTF-1 was negative in all cases (0%).

Conclusions: Hepatoid adenocarcinoma has a similar immunostaining profile as HCC. Arginase-1 expression is common in hepatoid adenocarcinoma (62.5%) and hence it is not useful in distinguishing HCC from hepatoid adenocarcinoma.

1662 Hepatobiliary (Mucinous) Cystic Neoplasms (MCN) With Ovarian-Type Stroma: Clinicopathologic Analysis of 32 Cases Highlights the Terminologic Confusion and Reveals Rarity of Carcinoma

Hyejeong Choi, Olca Basturk, Kee-Taek Jang, Michelle Reid, Alyssa Krasinskas, Gizem Akkas, David Kooby, Juan Sarmiento, Shishir Maithel, Malcolm Squires, Volkan Adsay, Brian Quigley. Emory University, Atlanta, GA; Memorial Sloan Kettering Cancer Center, New York, NY; Samsung Medical Center, Seoul, Republic of Korea; Ulsan University Hospital, Ulsan, Republic of Korea.

Background: The literature has highly conflicting data on the relative frequency, clinicopathologic characteristics and incidence of carcinoma in hepatobiliary mucinous cystic neoplasms (MCNs); aka "hepatobiliary cystadenoma/cystadenocarcinoma" (HCA/C), largely because ovarian-type stroma (OTS) has not been a requirement until WHO-2010 and is not widely applied even today.

Design: All hepatic cysts identified in the files of one institution from 1994 to 2014 were reviewed for OTS. Additionally, 8 MCNs were identified in consultation material.

Results: The frequency of MCN (with OTS) among hepatic cysts in the institutional database was 24/229 (10.5%). Eight cases originally designated HCA/C did not have OTS and were re-classified as other (5 non-neoplastic, 2 intraductal papillary neoplasm of the bile duct, and 1 cystic cholangiocarcinoma). Seven/32 true MCNs (with OTS) had been diagnosed as MCN, with remaining 25 as HCA. All true MCNs were female. Mean age = 50 (28-73). Mean size = 11 cm (5-23). 96% were intrahepatic and in the left lobe (82%); one exclusively involved an extrahepatic bile duct. In the pre-op imaging, MCN (or HCA) was mentioned in 50% and carcinoma was a differential in 15% (including one minimally invasive case). Most had at least some non-mucinous cuboidal lining, which was predominant in 12%. Minimally invasive carcinoma was seen in 2 (6.3%), both small (7 and 8 mm). Only the 2 invasive cases had high-grade dysplasia/CIS. One invasive case had "residual cyst or hematoma" at 4 months, and the other was without disease at 3 yrs. Of the non-invasive cases, 22 had F/U and were alive with no evidence of disease at median 21 months, with the exception of 1 case with "residual cyst."

Conclusions: Many examples (26%) of what had been previously reported as HCA/C actually prove not to be MCN. Conversely, true MCNs, defined by OTS, are often diagnosed as "HCA/C." True MCNs are uncommon among hepatic cysts (10.5%), occur exclusively in females, are detected as large (11 cm) tumors, mostly intrahepatic (96%) and in the left lobe (82%). They often contain non-mucinous epithelium which may be predominant (12%). Invasive carcinomas are small and uncommon (6%) compared to their pancreatic counterpart (29/178, 17% in the authors' database).

1663 Utility of an Immunohistochemical Panel Consisting of Glypican-3, Heat-Shock Protein-70, and Glutamine Synthetase In the Evaluation of Hepatoblastoma

Amy Coffey, Stephen Lagana, Helen Remotti. Columbia University Medical Center, New York, NY.

Background: A panel of immunohistochemical markers including glypican-3 (GPC-3), heat-shock protein-70 (HSP-70), and glutamine synthetase (GS) has been shown to have utility in differentiating hepatocellular carcinoma (HCC) from benign liver lesions when at least 2 of the 3 stains are positive. In infants, hepatoblastomas (HB) represent the most common liver malignancy. The aim of this study is to apply the triple stain to a series of HBs to assess its potential utility in the histologic differential diagnosis of HB.

Design: Tissue microarrays (TMAs) with tumor-normal pairs were prepared from a total of 34 HB resections over a 25-year period. At least two areas were sampled per tumor when possible. Mesenchymal components were excluded. Each tumor sample was subtyped based on morphology. Marker analysis with GPC-3, HSP-70, GS and ß-catenin were performed on all TMAs. Positive results were defined as such: HSP-70 ^{3}10%, GPC-3 ^{3}10%, GS ≥90% (diffuse strong cytoplasmic pattern), ß-catenin with any nuclear positivity.

Results: Ages ranged from 10 weeks to 7 years. Cases included primary resections (30/34), metastases (3/34) and one recurrence. Adjacent benign liver was assessed in 31 cases. All but one patient received neoadjuvant chemotherapy. At least 2 of the 3 stains (HSP-70, GPC-3, GS) were positive in 71% of HB compared to positive ß-catenin staining in 68% of HB. Slightly greater sensitivity was seen for the embryonal, crowded fetal, pleomorphic, and mixed epithelial subtypes as compared to the well-differentiated fetal subtypes

Summary of TMA results

	Percent positivity (%)				
	ß-catenin	HSP-70	GPC-3	GS	At least 2 of 3*
Overall (n=34)	68	26	71	91	71
Embryonal (n=20)	75	20	75	85	65
Fetal (n=13)	46	31	46	69	54
Crowded fetal (n=6)	50	0	67	100	67
Pleomorphic (n=2)	0	50	100	100	100
Mixed epithelial** (n=4)	75	50	100	100	100
Macrotrabecular (n=1)	0	0	100	0	0
Teratoid (n=1)	0	0	0	100	0
Benign liver controls (n=31)	0	0	0	0	0

*From HSP-70, GPC-3, GS

**Includes mixed embryonal/fetal and crowded fetal/fetal

Conclusions: An immunohistochemical panel consisting of HSP-70, GPC-3, and GS has utility comparable to ß-catenin in the diagnosis of hepatoblastoma. Sensitivities are comparable to those reported in HCC.

1664 A Clinico-Pathological Audit of Medical Liver Biopsies

Richard Colling, Eve Fryer, Jeremy Cobbold, Jane Collier, Elena Collantes, Lai Mun Wang, Stefan Hubscher, Judy Wyatt, Kenneth Fleming. University of Oxford, Oxford, Oxfordshire, United Kingdom; Oxford University Hospitals NHS Trust, Oxford, Oxfordshire, United Kingdom; University of Birmingham, Birmingham, West Midlands, United Kingdom; St. James's Hospital, Leeds, Yorkshire, United Kingdom.

Background: The number of liver biopsies being performed is declining and there is debate over the need of this investigation within the context of modern imaging techniques. There is now a need to evaluate the usefulness of medical liver biopsies but there has been surprisingly little drive to audit this in the UK.

Design: We are piloting the UK medical liver biopsies audit for Royal College of Pathologists. This is a prospective questionnaire-based audit of all new adult medical liver biopsies carried out within our institution. The audit began in August 2014 and so far 31 cases have been reviewed. Completion (100 cases) will be in early 2015.

Results: Hepatologists felt that 94% of reports were clinically useful and 68% resulted in a significant change in management. A breakdown of the results is shown in the table below. The two cases not clinically useful were due to an inadequate biopsy.

Conclusions: Where an adequate biopsy is provided for assessment, liver pathologists provide reports which clinicians feel are helpful and change management. Furthermore, almost a third of biopsies gave a diagnosis which was not clinically suspected. The data so far provides good evidence for the relevance and positive patient impact that the medical liver biopsy still can offer.

Indicator	Responses
Reports addressing indication	30/31 (97%)
Reports felt to be clinically useful	29/31 (94%)
- which confirmed a diagnosis	16/29 (55%)
- which helped differentiate between differential diagnoses	14/29 (48%)
- which gave an unexpected diagnosis	9/29 (31%)
- which excluded a diagnosis	15/29 (52%)
- which provided required grading/staging information	17/29 (59%)
Reports which resulted in management change	21/31 (68%)
- due to a diagnosis change	8/21 (38%)
- resulting treatment change	10/21 (48%)
- resulting follow up change	17/21 (81%)
Management decisions which could have been made without biopsy	4/31 (13%)

1665 Compensated Versus Decompensated Advanced HCV-Related Chronic Liver Disease: A Morphologic and Morphometric Autopsy Study

Juliano Dettoni, Bruno Cogliati, Isaac de Castro, Venancio Alves. University of São Paulo School of Medicine, São Paulo, Brazil; University of São Paulo School of Veterinary Medicine and Animal Science, São Paulo, Brazil.

Background: Advanced chronic liver diseases are dynamic processes, and, as such, the unified concept of cirrhosis has been questioned. The patterns of fibrosis, vascular changes, necro-inflammation, regeneration and even regression must now be reassessed according to each cause, paving the way for specific staging systems.

Design: From 271 necropsies due to HCV-related advanced chronic liver diseases, we could well characterize 3 cases who died from other casuses, without present or past evidence of decompensation. In order to select candidate histopathological variables that might better reflect a compensated or decompensated status, we compared herein those 3 cases versus 19 necropsies from cases who died due to hepatic decompensation. Major histological variables related to architecture, blood vessels, portal/septal and parenchymal necro-inflammation were semiquantitated. Fibrosis and immunoreactivity for CD34 and K19 were quantitated.

Results: This carefully studied albeit rather small autopsy series depicted a direct statistical relationship of CD34-positive liver area (p=0.018) and decompensated liver disease. Interestingly, the amount of CD34 did not reduce with the evidences of regression of fibrosis (p=0.943). The amount of fibrosis and necro-inflammatory activity did not reach statistically significant relationship with decompensation.

Histological variables	Decompensated (Mean)	Compensated (Mean)	Significance (p)
Regression	69.17	57.14	0.235
Fibrosis score	76.32	79.17	0.753
Vascular score	61.84	43.75	0.027
Necro-inflammation score	85.96	77.78	0.520
Regeneration score	56.58	63.33	0.371
CD34 quantification	2.33	1.04	0.018

Conclusions: These preliminary necroscopic data show the vascular remodeling as the most important variable in staging HCV-related cirrhosis. This study also allows the selection of a list of histological variables to be assessed in liver biopsy samples and/or in explants. Our data suggest that such vascular remodeling persists even with fibrosis regression, indicating a stage of irreversible architectural damage. Further studies with biopsies of cirrhotic patients is expected to assess which of these variables might be clinically prognostically valid to compose a checklist for the assessment of HCV-related advanced chronic liver disease.

1666 Strong CK7-Positive Ductular Reactions Are Valuable in Discriminating Benign Cirrhotic Nudules From Well Differentiated Hepatocellular Carcinoma in Core Liver Biopsies

Xianzhong Ding, Jinping Lai, Yi Zhou, Mohammed Atieh, Stefan Pambuccian. Loyola University Medical Center, Maywood, IL; Saint Louis University School of Medicine, St. Louis, MO.

Background: The diagnosis of well differentiated hepatocellular carcinoma (WD-HCC) by liver core biopsy can be very challenging. Reticulin and CD34 stains are helpful in the differential diagnosis between WD-HCC and benign regenerative nodules. Decreased reticulin stain or widened trabeculae are considered to be reliable for the diagnosis of WD-HCC. However, abnormal reticulin pattern can be patchy and may not be apparent in small biopsies. The endothelial marker CD34 is negative in normal hepatic sinusoids and often positive in WD-HCC. However, sinusoids at the periphery of benign cirrhotic nodules are often CD34-positive, which might lead to difficult interpretation. It has been shown that CK7 immunostain is helpful in the diagnosis of early HCC in resected specimens. Benign cirrhotic nodules are often surrounded by strong CK7-positive reactive ductules while there is no ductular proliferation in WD-HCC. The aim of the current study was to test the value of CK7 immunostaining in the diagnosis of WD-HCC in liver core biopsies.

Design: 16 WD-HCC originally diagnosed on liver cores stained with H&E supplemented by reticulin, CD34, glypican 3 and glutamine synthetase were evaluated by 2 pathologists. Additional immunostains for CK7 were performed in all cases. Strong CK7-positive ductular reactions at the interface between hepatocytes and stroma, excluding weakly CK7-positive intermediate hepatocytes were compared between nodules of WD-HCC and benign cirrhotic nodules present in the nonneoplastic regions of the core biopsies.

Results: All cirrhotic nodules showed marked ductular reactions at their edges. In contrast, ductular reaction was absent in the majority of WD-HCC (15/16, 94%). Although all WD-HCC were CD34 positive, all benign cirrhotic nodules also demonstrates either focal or diffuse CD34 sinusoidal positivity. Glypican-3 is specific for HCC, but only 30% of WD-HCCs were positive for glypican-3. The above findings suggest that CK7-positive reactive ductules are more sensitive than glypical-3 and more specific than CD34 to identify WD-HCC in liver core biopsy specimens.

Conclusions: This study demonstrates that the absence of reactive CK7+ ductules in WD-HCC can be used in combination with reticulin, CD34, glypican-3 and other markers to discriminate between benign cirrhotic nodules and WD-HCC, particularly in core biopsies in which only small fragments of tumor are present.

1667 Liver Biopsy Findings in Patients With Hematopoietic Cell Transplantation

Farzan Eskandari, Parameswaran Hari, Kapke Jonathan, Robert Schneidewend, Catharine Hagen, Kiyoko Oshima. Medical College of Wisconsin, Milwaukee, WI.

Background: Hematopoietic-cell transplantation (HCT) has been increasingly used for the treatment of patients with high risk hematologic malignancies and other life-threatening hematological disease. Liver dysfunction is a frequent complication after HCT. Liver biopsy has an important role for confirming the diagnosis of graft versus host disease (GVHD) or other liver diseases. However, the histological features of GVHD are not specific, and vary by the duration and activity of GVHD. GVHD and other coexisting diseases may be present in the same biopsy, which makes the histologic interpretation of the liver biopsy more complex and challenging. This study was undertaken to analyze liver biopsy to improve the present diagnostic criteria.

Design: We retrospectively analyzed liver biopsies performed after HCT from 2000 to 2014 at our institution. Clinical information, quality of the liver biopsy, and histologic features were analyzed. Assessment of GVHD was performed using the National Institute of Health (NIH) criteria of no GVHD, possible GVHD, probable GVHD and unequivocal GVHD. Possible or diagnostic coexisting diseases were also recorded.

Results: Total 50 liver biopsies were analyzed (mean age 49.9 yrs: M:F, 28:22). Mean numbers of days post HCT was 839.4 days. Most biopsies (46, 92%) showed some features of GVHD. 4 (7.8%) had no GVHD, 19 (37.3%) possible GVHD, 23 (47.1%) probable GVHD and 4 (7.8%) unequivocal GVHD. The majority of the cases (36; 70.6%) had a concurrent disease process. 23 (46%) had steatosis, 11 (22%) sever siderosis (4+), 8 (16%) drug-induced liver injury. Severe iron accumulation in bile ducts made assessment for GVHD difficult. Histologic features including bile ductular proliferation, marked cholestasis, chronic hepatitis and hepatocyte necrosis raised the possibility of concurrent drug-induced liver injury. 6 (12%) had hepatic vein obstruction/sinusoidal obstruction syndrome, 2 (4%) extramedullary hematopoiesis, 1 (2%) chronic hepatitis C, 1 (2.0%) steatohepatitis, 1 (2.0%) cholangitis lenta suggestive of sepsis. No CMV or HSV infections were identified. One clinically typical GVHD showed acute hepatitis with hepatocytes necrosis (hepatic variant of GVHD). 6 (12%) had perisinusoidal fibrosis and 3 (6%) had periportal fibrosis.

Conclusions: HCT patients being evaluated for GVHD often have coexisting disease making the interpretation of liver biopsies in this heterogeneous group complex and challenging. More detailed diagnostic criteria, including specific histologic features, are necessary.

1668 Intermediate Familial Intrahepatic Cholestasis: Phenotypic Spectrum Within the BRIC-PFIC Spectrum

Paola Francalanci, Isabella Giovannoni, Emanuele Bellacchio, Giuliano Torre, Renata Boldrini, Francesco Callea. Bambino Gesù Children's Hospital IRCCS, Rome, Italy; Bambino Gesù Children's Hospital, Rome, Italy.

Background: Benign recurrent intrahepatic cholestasis (BRIC) and progressive familial intrahepatic cholestasis (PFIC) belong to a *spectrum* of autosomal liver disorders: familial intrahepatic cholestases (FIC). Their differentiation is based on genetic and phenotypic presentation. Clinical transition between BRIC and PFIC is rarely reported. We hypothesize that patients with a compound heterozygosity for BRIC and PFIC mutations belong to an intermediate form of familial intrahepatic cholestasis (IFIC).

Design: Two cases, a male (case 1), 11 year-old, with intermittent jaundice since 1 month-old and a female (case 2), 1 year-old, with intractable pruritus and jaundice, since 5 months old, underwent liver biopsies, which were analyzed by histology and immunohistochemistry (IHC) with an anti-BSEP antibody. *ABCB11* gene was sequenced. To define the mutation pathogenicity, the homology modeling was done.

Results: In case 1, liver biopsy showed preserved architecture and mild signs of intrahepatic cholestasis; IHC with anti-BSEP disclosed a cytoplasmic staining. Genetic analysis showed p.E135K (BRIC mutation) and p.L1099LfsX38 (new mutation). The homology modeling revealed that p.E135K has an effect on the glycosylation and is consistent with a trafficking modification without total loss of protein function. Conversely, the p.L1099LfsX38 abrogates completely the protein function (PFIC mutation). In case 2, three liver biopsies displayed progression of cholestasis and of the liver pathology and IHC revealed persistent preserved BSEP canalicular staining. Genotyping showed p.R1050C (BRIC mutation) and p.R1153H (PFIC mutation).The

p.R1153H is more severe than p.R1050C, implying that BSEP protein is normally localized at the canalicular membrane, but it has a lower activity. Therefore both cases presented a compound heterozygosity (BRIC-PFIC).
Conclusions: Familial intrahepatic cholestasis is distinguished into BRIC and PFIC. A clinical progression from benign to severe form is rarely described. Our cases suggest the existence of a *de novo* form of Intermediate FIC, with an intermediate phenotype between the benign phenotype (BRIC) and the more severe (PFIC), genetically supported by a compound heterozygosity (BRIC-PFIC). Absence of phenotype-genotype correlation, at least in our cases, would suggest the possibility of a IFIC *spectrum,* depending on mutation pathogenicity.

1669 Histologic Features, Tissue Copper Levels and Genotype in Wilson Disease

Rondell Graham, Taofic Mounajjed. Mayo Clinic, Rochester, MN.
Background: Wilson disease (WD) is characterized by abnormal hepatic and central nervous system copper (Cu) accumulation. Histologic features are non-specific but together with hepatic tissue Cu levels or genotyping can establish the diagnosis. The relationship between the histologic pattern in WD to tissue Cu levels and genotype has not been studied.
Design: We performed a detailed characterized of the histologic features from liver biopsies of patients diagnosed with WD from 1994 to 2012 at our institution. The results of hepatic Cu levels from each case were obtained and a hepatic Cu index adjusted for patient age was calculated. Genotyping results were also retrieved. Correlates between histology, hepatic Cu levels and genotype were evaluated.
Results: There were 15 cases of WD including 9 males and 6 females with a median age of 27 years (range 14 to 63). The cases could be placed into 3 histologic groups; steatohepatitis (n=6), severe necrosis with cholestasis (n=4) and cirrhosis or chronic hepatitis (n=5). The hepatic Cu levels ranged from 66 mcg/g to 2367 mcg/g and the hepatic Cu index from 0.2 to 12.0. There was no correlation between hepatic Cu levels and histologic groups but a higher hepatic Cu index was seen in cases with prominent bile ductular proliferation. There was no correlation between hepatic Cu index and steatosis, cholestasis, fibrosis and lobular inflammation. Mutations were identified in 7/14 tested cases and H1069Q was the most frequent mutation (n=4). The presence of identifiable mutations did not correlate with hepatic Cu levels. However, both truncating mutations identified in this study were present in 2 of the 3 youngest patients for whom genotyping data were available. No truncating mutations were identified in patients >19 years of age. The limited number of different mutations precluded assessment of histologic and genotypic correlates.
Conclusions: The histology of WD can be grouped into distinct categories. There appears to be no correlation of hepatic Cu levels with histologic characteristics or identification of mutations. Truncating mutations may be associated with earlier clinical presentation. Accrual of more well characterized cases may allow for better delineation of the possible relationships between genotype and histologic features.

1670 Correlation of ß-Catenin Exon 3 Mutations With Glutamine Synthetase Staining Patterns in Hepatocellular Carcinoma

Gillian Hale, Xinxin Liu, Xin Chen, Sanjay Kakar. University of California, San Francisco, CA.
Background: Diffuse glutamine synthetase (GS) expression, is considered a marker of β-catenin activation in hepatocellular adenoma (HCA) and hepatocellular carcinoma (HCC). The strong correlation of diffuse GS staining and β-catenin activation is based on a limited number of studies. GS has a diverse repertoire of patterns and the detailed relationship between each staining pattern and β-catenin mutations in the CTNNB-1 gene has not been established. The aim of the study is to compare GS staining pattern with β-catenin mutations in HCC.
Design: GS IHC in 55 HCC and 20 HCA was classified as follows: 1) Patchy:<50% of tumor cells ± perivascular 2) diffuse heterogenous: staining in 50-90% of tumor cells 3) diffuse homogenous: staining in >90% of tumor cells. Genomic DNA was purified from formalin-fixed, paraffin embedded tissues, and exon 3 of CTNNB1 was PCR amplified and Sanger sequenced.
Results: In HCC, β-catenin mutations were seen in 8/36 (22%) cases with diffuse GS staining: 14% with diffuse homogeneous and 8% with diffuse heterogeneous staining. Two HCCs with patchy GS also had mutations. Although HCA mutation analysis is ongoing and not formally included in this series, our anecdotal experience reveals similar results and the presence of β-catenin mutaitons in a subset of cases with patchy staining.

Tumor	Patchy	Diffuse Heterogenous	Diffuse Homogenous	Total
HCC	13	17	17	47
ß-catenin mutations	2	3	5	10

Conclusions: Using paraffin embedded tissue, exon 3 β-catenin mutations were found in less than half of the cases with diffuse GS staining in both HCA and HCC. The correlation was even lower for the diffuse heterogeneous GS pattern. The presence of β-catenin mutations in a small number of cases with patchy GS indicates that this pattern cannot be used to exclude β-catenin activation, particularly in biopsy samples, and mutation testing may be necessary in these cases.

1671 Glutamine Synthetase IHC in Hepatocellular Lesions: Spectrum of Staining Patterns and Interpretation Concordance

Gillian Hale, Grace Kim, Linda Ferrell, Sanjay Kakar. University of California, San Francisco, CA.
Background: Glutamine synthetase (GS) staining patterns contribute to the diagnosis of hepatocellular lesions. Focal nodular hyperplasia (FNH) shows distinct map-like staining but staining patterns in hepatocellular adenomas(HCA) and hepatocellular carcinomas (HCC) occur along a spectrum. Tumors with ß-catenin activation (ß-cat+) demonstrate diffuse strong homogeneous or heterogeneous staining in majority of tumor cells. Differentiating ß-cat+ patterns from patchy staining in <50% of tumor cells (ß-cat-) can be difficult but important since GS staining influences diagnosis and patient management.
Design: GS IHC was done in 69 HCA, 58 HCC, and 20 FNH cases, and classified independently by 3 pathologists into 4 staining patterns: 1) Patchy:<50% of lesional cells ± perivascular, 2) diffuse heterogeneous: ≥50% lesional cells, 3) diffuse homogeneous:strong in >90% lesional cells, and 4) map-like.
Results: All 3 pathologists agreed on the staining pattern in 105 (71%) cases. Concordance was 90% in FNH cases but only 57% in HCA. As GS staining approached 50%, the distinction between diffuse heterogeneous (ß-cat+) and patchy (ß-cat-) patterns accounted for the majority of discordant cases (23 HCA,3 HCC). Among these cases, interpretation of GS staining intensity was the source of most disagreement. For 5 HCC cases disagreement between diffuse homogeneous and diffuse heterogeneous staining was not clinically relevant as both are considered ß-cat+. When both diffuse patterns were considered together, the overall concordance was 78%.

	Pattern concordance 3 pathologists n=105	Pattern concordance 2 pathologists n=131	kappa values by pathologists3, 2
Total cases n=147	71%	89%	0.74, 0.83
HCC n=58	83%	91%	0.74, 0.81
HCA n=69	56%	83%	0.47, 0.69
FNH n=20	90%	100%	NA

Conclusions: There is high concordance among experienced liver pathologists in GS pattern interpretation with near perfect agreement on map-like staining in FNH, both in resections and biopsies. But differentiating patchy (ß-cat-) from diffuse heterogeneous staining (ß-cat+) is a source of high interobserver variability in HCA (23%). ß-catenin mutation or other assays may help in cases that show GS staining bordering on 50% with variable intensity, but until such testing becomes established in clinical practice, considering these "borderline" cases as ß-catenin activated may be prudent for appropriate management.

1672 Hepatic Steatosis in Liver Transplant (LT) Recipients Is Associated With Deterioration in Adipose Tissue Insulin Resistance and Pro-Atherogenic Lipoprotein Abnormalities

Michael Idowu, Ravi Chhatrala, Bilal Siddiqui, Carolyn Driscoll, Todd Stravitz, Arun Sanyal, Carol Sargeant, Velimir Luketic, Richard Sterling, Scott Matherly, Puneet Puri, Melissa Contos, Mohammad Siddiqui. Virginia Commonwealth University Health System, Richmond, VA.
Background: Hepatic steatosis (HS) recurs in liver transplant recipients (LTRs) for nonalcoholic fatty liver disease (NAFLD) related cirrhosis and in 25% LTR for other indications. Despite its high prevalence there is a paucity of data regarding HS and its association with various clinical parameters. The aim of this study was to evaluate the relationship between hepatic steatosis (HS), insulin resistance and lipoprotein metabolism in LTRs.
Design: We retrospectively reviewed LTR biopsies and included only subjects with complete lipoprotein profile, markers of insulin resistance/inflammation and histological assessment. HS was quantified based on the NASH-CRN criteria. c^2 was used to compare means across the groups and regression analysis was used to determine the association and the strength of the association between HS and various clinical parameters.
Results: 89 patients met selection criteria. 38% (N=34) had HS on biopsy. Patients with and without HS were similar with respect to gender, indication for LT, prevalence of diabetes (DM), and lipid parameters. LTRs with HS were older (61±5.4 vs. 56±12.6 yrs; p<.01), had a higher BMI (32.6±4.3 vs. 27.6±5.2; p<.01); higher serum free fatty acids (FFA) level (0.73±0.27 vs. 0.52±0.25; p<.01). Small-dense LDL-cholesterol (sdLDL-C) levels, a pro-atherogenic molecule that is the byproduct of incomplete hydrolysis of large VLDL particles, was also significantly higher in those with HS (34±17 vs. 22±11; p<.01). Serum adiponectin, an adipose-specific adipokine, was significantly lower in those with HS (11.3±4.2 vs. 20.2±11.6; p<.01). Although, serum apolipoprotein-B levels were similar, very low-density lipoprotein (VLDL) size was higher in those with HS (51.9±6.4 vs. 48.7±6.3; p<.05). Grade of HS was directly related serum insulin concentrations (R=.45; p<.01), FFA (R=.292, p=.018), VLDL size (R=0.34, p=.015), sdLDL-C (R=0.299, P=0.15) and inversely to serum adiponectin levels (R=-0.46, p<.01). The association between HS grade and serum insulin concentrations, FFA, VLDL size, sdLDL-C and adiponectin was independent of age, BMI and presence of DM.
Conclusions: This study shows the close interplay of adipose tissue resistance/deterioration and hepatic steatosis and its subsequent impact on altered lipid metabolism in LTRs.

1673 Rapid Development of Liver Steatosis in the Early Post-Liver Transplantation Period Is a Risk for Progression To Steatohepatitis

Florencia Jalikis, Martin Montenovo, Matthew Yeh. University of Washington, Seattle, WA.

Background: Hepatic steatosis commonly occurs after liver transplantation. However, there is limited data regarding rapid development of steatosis in the early post-transplant period and its risk factors. We aimed to characterize the patients with early rapid steatosis development in the liver allograft.

Design: We systematically searched our database from 2000-2013 (total of 1277 transplantation cases were performed) to identify patients who developed ≥ 30% steatosis within a 3 month period in the first six months post-transplant. Protocol biopsies were performed irrespective of etiology at 1, 3 and 6 months. Slides were reviewed and amount of steatosis was recorded. Patients with steatosis ≥ 5% in the post-reperfusion biopsy were excluded. Histological changes were reviewed. Clinical data including body-mass index (BMI), diabetes mellitus (DM), hyperlipidemia, hypercholesterolemia, arterial hypertension and etiology for liver transplantation were reviewed.

Results: 20 patients (1.5%) developed ≥ 30% steatosis in a period of 3 months in the first six months post-transplant. 16 patients had moderate (33-66%) and 4 had severe (>66%) steatosis. 18 (90%) were transplanted for HCV, 9 had concomitant hepatocellular carcinoma and 2 alcohol use. Underlying indications in the remanining 2 cases included non-alcoholic steatosis (NASH) and alcohol-induced end-stage liver disease. BMI and arterial blood pressure did not change. >10% increase in triglycerides and cholesterol were seen in 4 patients. Histologic recurrence of HCV was seen in 4 patients. 10 patients (50%) subsequently developed steatohepatitis within the first 3 years.

Conclusions: Rapid development of hepatic steatosis in the early post-transplantation period is associated with increased risk to progression to NASH. While the role of underlying metabolic syndrome remains unclear, HCV cirrhosis as the indication for liver transplantation appears to be associated with rapid development of steatosis (90% vs 60% for all cases transplanted during this period). Further study is necessary to elucidate exact underlying mechanism of this observation.

1674 Abstract Withdrawn

1675 Pattern of Hepatic Iron Overload in Recipients of Allogeneic Hematopoietic Stem Cell Transplantation

Young Kim, Ibrahim Aldoss, Susan Groshen, Huiqing Wu, Stephen Forman, Vinod Pullarkat. City of Hope National Medical Center, Duarte, CA; University of Southern California Keck School of Medicine, Los Angeles, CA.

Background: Iron overload is common in allogeneic hematopoietic stem cell (HSCT) recipients, particularly those undergoing HSCT for acute leukemia and myelodysplastic syndrome. Recent studies have demonstrated increased hepatic iron by magnetic resonance imaging in such patients therby confirming earlier serum ferritin based studies. However, the pattern of iron deposition in the hepatic parenchyma versus the liver macrophages in HSCT patients has not been clearly delineaged and this pattern of iron deposition may have long term implications.

Design: We examined liver biopsy specimens obtained after allogeneic HSCT performed for indications other than hemoglobinopathies, for the degree and pattern of hepatic iron deposition by semiquantitative scoring and graded the degree of fibrosis and inflammation. Histologic grading of iron stores was performed by the semiquantitative grading scale proposed by Scheuer and modified by Turlin and Deugnier.

Results: All 38 patients examined had evidence of iron deposits in at least 1 of the 3 compartments (parenchymal, sinusoidal, and protal). Pattern and grade of iron deposition were compared with hepatic inflammation/fibrosis and Patient/Disease characteristics. There was significantly more portal tract iron deposition in patients who have biopsies after 100 days after transplantation. There was a higher degree of hepatic parenchymal iron loading in patients whose serum ferritin were above 1500 (ug/L) compared to those with lower serum ferritin (P=0.014). Sinusoidal but not hepatic iron was higher in receipients of matched unrelated donor transplants (P=0.023). However, there was no significant association between the diagnosis for which HSCT was performed and the pattern or grade of iron loading in any of the 3 hepatic comartments.

Conclusions: Our study, for the first time, documents the pattern of hepatic iron deposition in patients who have undergone allogeneic HSCT and it shows that iron deposition is predominantly a mixed pattern of hepatocytic and sinusoidla iron loading, with less notable involvement of the protal system. This is surprising since given the fact that transfusional iron loading is the most common cause of iron overload in this population which in turn should lead to iron deposition predominantly in the macrophage compartment at least initially.

1676 Prognostic Significance of Histologic Response in Perihilar Cholangiocarcinoma To Preoperative Neoadjuvant Therapy in Orthotopic Liver Transplant Patients

Heidi D Lehrke, Tsung-Teh Wu, Sarah Jenkins, Julie Heimbach, Gregory Gores, Charles Rosen, Taofic Mounajjed. Mayo Clinic, Rochester, MN.

Background: Perihilar cholangiocarcinoma (P-CC) is the second most common hepatic malignancy. Treatment protocols combining the use of chemotherapy, external beam radiotherapy, brachytherapy, and orthotopic liver transplantation (OLT) have shown significant survival benefits. The purpose of this study is to determine whether the extent of residual tumor (ERT) following protocol treatment for P-CC can predict patient survival and disease recurrence.

Design: We collected 152 cases of unresectable P-CC treated with OLT following neoadjuvant chemoradiation therapy between 1993 and 2013. OLT specimens were reviewed for the following: ERT, histologic grade, TNM stage, perineural and lymphovascular invasion. ERT was quantified as the average of viable carcinoma percentage in tumor bed slides (sum of residual tumor percentages in all slides/number of slides). Tumors were classified into 4 categories based on the ERT: 1 (<1%), 2 (1 to <10%), 3 (10 to <30%), and 4 (³30%). Associations with outcome (recurrence or death) were analyzed with Cox proportional hazards regression and were described with 5-year risk estimates (Kaplan-Meier method).

Results: Of the 152 cases, 86 (57%), 25 (16%), 27 (18%), and 14 (9%) cases were placed in ERT categories 1,2,3, and 4, respectively. The median follow-up was 5.1 years. The overall 5-year survival rate was 69%, and the 5-year disease-free estimate was 74%. ERT showed significant correlation with the overall 5-year survival rate and the 5-year disease-free estimate, both by univariate and multivariate analysis adjusting for TNM stage and age. Patients in ERT categories 1, 2, 3, and 4 had 5-year survival rates of 86%, 60%, 39%, and 30% (univariate: p<0.001, multivariate: p=0.002) and 5-year disease-free estimates of 94%, 52%, 42%, and 27% (univariate: p<0.001, multivariate: p=0.009), respectively. Multivariate analysis, adjusting for ERT and age showed that TNM stage was an independent predictor of recurrence (p=0.003). Univariate analysis showed that the TNM stage, pathologic T-stage, and presence of perineural or lymphovascular invasion had significant correlation with the risk of recurrence and death (p<0.001 for all) but histologic grade and lymph node status did not.

Conclusions: The extent residual tumor independently predicts overall survival and risk of tumor recurrence in patients who have undergone neoadjuvant chemoradiation therapy and OLT for P-CC. Reporting ERT in the pathology report of OLT specimens may aid in predicting the overall prognosis in P-CC.

1677 Immunostains Used To Subtype Hepatocellular Adenomas Are Also Positive in Hepatocellular Carcinomas

Liping Liu, Michael Torbenson, Sejal Shah, Bita Naini, Samuel French, Tsung-Teh Wu, Vishal Chandan. Mayo Clinic, Rochester, MN; University of California, Los Angeles, CA.

Background: Immunostains such as Liver Fatty Acid Binding Protein (LFABP), Serum Amyloid Associated Protein (SAA) and C-Reactive Protein (CRP) are used to sub-classify hepatic adenomas (HA). LFABP loss is characteristic of a subset of HA in which the HNF1alpha gene is inactivated, while the expression of SAA and CRP define the inflammatory type of HA. Beta-catenin activation leads to upregulation of glutamine synthetase (GS) which manifests as diffuse and strong GS cytoplasmic staining. These stains are sometimes used in an attempt to distinguish hepatocellular adenomas from hepatocellular carcinoma. However, the expression of these stains in hepatocellular carcinomas (HCC) has not been well studied.

Design: 50 resected HCCs were studied (19 in cirrhotic liver and 31 in non-cirrhotic liver) (age range, 19-85 years; 34 male, 16 female) with immunostains for LFABP, SAA and GS. CRP immunostain was also performed on 18 cases. The HCCs were well differentiated (WD; 21), moderately differentiated (MD; 27), and poorly differentiated (PD; 2). GS was scored positive if moderate or strong staining was seen in >50% of tumor. The rest of the stains were considered positive if moderate or strong staining was seen in >10% of tumor.

Results: LFABP was completely lost in 21/50 (42%) cases (5-WD; 16-MD) while the background benign liver was strongly and diffusely positive in all cases. SAA was positive in 11/50 (22%) cases (3-WD; 8-MD) and CRP was positive in 16/18 (89%) cases (6-WD; 10-MD). 5/18 (28%) cases (2-WD; 3-MD) were positive for both SAA and CRP. GS was positive in 22/50 (44%) cases. There was no statistical difference between the cirrhotic and non-cirrhotic HCC groups regarding loss of LFABP or expression of SAA and CRP, (p for all >0.05).

Conclusions: The same stains used to subtype HA commonly, show similar staining in HCC, including well-differentiated HCC and do not diagnostically separate these tumors. For this reason, these stains should be used only after a diagnosis of HA has been made based on morphological features and other standard stains.

1678 Amplification of Genes at 13q34 Associated With Progression of Intrahepatic Cholangiocarcinoma

Ting Ting Liu, Huey Ling You, Shao Wen Weng, Yu Ching Wei, Hock Liew Eng, Wan Ting Huang. Koahsiung Chang Gung Memorial Hospital, Kauhsiung, Taiwan; Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan.

Background: Amplification of genes at 13q34 has been reported to be associated with tumor proliferation and progression in diverse types of cancers. However, its role in intrahepatic cholangiocarcinoma (ICC) has yet to be explored.

Design: In this study, we examined 86 cases of ICC to analyze copy number (CN) of four target genes at 13q34 by quantitative polymerase chain reaction. A number of selected cases and three ICC cell lines were used to test the relationship between CN alterations and protein expression by immunohistochemical assays and western blotting, respectively. The mobility potential of the cell lines was examined using cell migration and invasion assays.

Results: Twelve cases (13.9%) demonstrated CNs > 4 for all three genes tested (*CUL4A, IRS2,* and *TFDP1*). The amplification of each of these genes was associated with poor disease-free survival, as was a combination of target genes with CN > 4. CN alterations correlated with protein expression levels. Increased staining of CUL4A, IRS2, and TFDP1 was identified in tumors with amplification of target genes. Both the SNU1079 and SNU1096 cells lines containing deletions of the target genes demonstrated decreased protein expression levels, as opposed to the RBE cell line which does not contain CN alterations. Furthermore, both SNU1079 and SNU1096 cells displayed lower migratory and invasive capacities than RBE cells.

Conclusions: Taken together, our data demonstrates that amplification of genes at 13q34 plays an oncogenic role in ICC featuring adverse disease-free survival. Deletion of target genes may suppress migratory and invasive capacities, which may provide new directions for targeted therapy.

1679 Altered Serum Levels of FoxM1, and Its Negative Regulators p14ARF and p53 in Advanced Chronic Liver Disease and Hepatocellular Carcinoma

Lily Mei, Katherine Choi, Rohini Chennuri, Hui Xie, Michael Walsh, Frederick Behm, Paul Brandt-Rauf, Scott Cotler, Grace Guzman, Pradip Raychaudhuri, Ming Jin. University of Illinois, Chicago, IL; Loyola University, Maywood, IL.

Background: Hepatocellular carcinoma (HCC) develops on a continuum of morphological and molecular alterations in advancing chronic liver disease, from inflammation to cirrhosis to dysplasia and ultimately carcinoma. While early detection is desirable, HCC is frequently diagnosed late and confers a poor prognosis. The Forkhead box protein M1 (FoxM1) transcription factor has been implicated as a marker for oncogenesis in a variety of cancers including HCC, and has been found to be over-expressed in tumors. It stimulates expression of genes involved in cell division, tumorigenicity and drug resistance, and is negatively regulated by tumor suppressor genes such as p53 and ARF. Furthermore there is recent evidence that FoxM1, in the absence of ARF, drives HCC metastasis. We investigated the serum levels of FoxM1, p14ARF and p53 in patients with cirrhosis and HCC, and compared the levels of these proteins against subjects with no liver pathology.

Design: Serum samples were obtained from 29 patients with cirrhosis and/or HCC. Sera from 10 subjects with no known liver pathology served as controls. The expression levels of FoxM1, p14ARF and p53 were measured by enzyme-linked immunosorbent assay (ELISA) (USCN Life Science & Life Sciences Advanced Technologies). Statistical analysis (ANOVA) was performed with SAS.

Results: In patients with cirrhosis and/or HCC, serum levels (mean±SD) of FoxM1 (2454±1400 pg/ml) and p53 (8267±4098 pg/ml) were found to be dramatically and significantly increased compared to control samples (FoxM1: 618±241 pg/ml, p53: 856±313 pg/ml) ($p < 0.0001$). In contrast p14ARF levels (131±14 pg/ml) were significantly decreased in comparison to controls (425±162 pg/ml) ($p < 0.0001$).

Conclusions: FoxM1 is known to be over-expressed in HCC tissue. Here we show that in patients with cirrhosis and HCC, FoxM1 serum levels are also significantly elevated, and FoxM1's negative regulator p14ARF showed decreased serologic expression in comparison to normal subjects. Further, increased levels of p53 in cirrhosis and HCC are consistent with the aberrant accumulation of its mutant form. These results suggest that the serologic level of FoxM1, p14ARF and p53 may have clinical significance in chronic liver disease and HCC, and may serve as potential biomarkers in this patient population.

1680 113 Consecutive Endoscopic Ultrasound Guided Transgastric (TG) Liver Biopsies for Parenchymal Liver Diseases: A Single Institution Pathologic Study

Wadad Mneimneh, Yukihiro Nakanishi, Michael Sey, Mohammad Al-Haddad, John DeWitt, Romil Saxena. Mayo Clinic, Rochester, MN; Tulane University, New Orleans, LA; Western University, London, ON, Canada; Indiana University, Indianapolis, IN.

Background: The TG approach is a novel method for obtaining liver biopsies in patients undergoing upper gastrointestinal endosonography. This study elucidates pathologic characteristics and diagnostic challenges in a large series.

Design: We compared 113 TG liver biopsies obtained by 3 different needles (Quickcore, Procore, Flex) with 100 percutaneous and 100 transjugular liver biopsies. We recorded number of cases with ³10 tissue fragments, sizes of the longest and shortest fragments, numbers of complete and incomplete portal tracts, final diagnosis, qualitative features and adequacy for diagnosis and staging.

Results: TG biopsies were more fragmented (³10 tissue fragments) than percutaneous and transjuguar specimens and contained abundant blood clot which often transceted and fragmented tissue cores. The longest cores were shorter in TG and transjugular compared to percutaneous biopsies. Quickcore, Procore and transjugular but not Flex biopsies contained fewer numbers of complete portal tracts than percutaneous biopsies. Transjugular biopsies contained shorter cores and fewer numbers of complete portal tracts compared to percutaneous biopsies. Specimen adequacy was similar for transjugular and percutaneous but less for TG biopsies (statistically significant, $p<0.05$). Portal tracts appeared at the edges of tissue cores and were often crushed but lobular morphology was well preserved in TG biopsies.

	Quickcore (n=45)	Procore (n=33)	Flex (n=35)	transjugular (n=100)	percutaneous (n=100)
≥10 cores (%)	13	88	97	6	2
longest core length (range, median in mm)	1-14, 4	1-11, 4*	1-20, 7*	3-19, 12 **	7-18, 13.5
number of complete portal tracts (range, median)	0-12, 2	0-36, 9*	0-85, 12	1-28, 11.5 **	3-30, 12
adequate cases (%)	42	76*	86*	98	100

* p

Conclusions: 1) Specimen adequacy of TG biopsies is less compared to percutaneous and transjugular specimens.

2) Marked fragmentation of TG biopsies (multiple small cores) may preclude assessment, especially staging, in some cases.

3) Portal tracts may be marginalised and crushed but lobular morphology is well preserved.

4) TG biopsies are adequate for diagnosis of fatty liver disease in which changes are predominantly lobular and which was the foremost indication for the procedure in this series.

1681 Hepatocellular Neoplasms Arising in Association With Androgen Use

Taofic Mounajjed, Sounak Gupta, Bita Naini, Richard Munoz, Michael Torbenson. Mayo Clinic, Rochester, MN; University of California, Los Angeles, CA; Largo Medical Center, Largo, FL.

Background: The correlation is well established between androgen use and the development of hepatocellular neoplasms. This association can be seen with androgen use for treatment of Fanconi's anemia as well as anabolic steroid use for stimulating muscle growth. However, there are no systematic reviews characterizing the histopathology and immunophenotype of liver neoplasms arising in association with androgen use.

Design: Eight cases of hepatocellular neoplasms arising in association with androgen use were identified. Available clinical information was collected. A detailed histopathologic analysis and reticulin stain were performed on all cases. Immunohistochemical analysis for liver fatty acid binding protein (LFABP), β-catenin, glutamine synthetase (GS), C-reactive protein (CRP), and serum amyloid A (SAA) was utilized to subtype the adenomas. Lesions were also assessed for proliferative index by Ki-67 immunostain.

Results: The neoplasms were predominantly seen in males (6/8, 75%). Males were also older than females (mean age: 43 and 24 years, respectively). Only 1 patient (13%) had multifocal disease (2 lesions) with both neoplasms having similar histology and phenotype. Overall, the majority of the lesions had architectural (7/8) and cytological (4/8) atypia. Bile was present in 5 (of 8) cases and prominent lipofuscin pigment was seen in one case. Reticulin was focally disrupted in 5 (of 8) cases. All cases had a low proliferative index (Ki-67 <1%). Based on histopathology and reticulin findings, 5 (63%) were diagnosed as hepatocellular neoplasms of uncertain malignant potential (HUMP) and 3 (37%) were diagnosed as hepatic adenomas (HA). Based on the immunoprofile, 6 (75%) cases were β-catenin activated (2 HA and 4 HUMP, including 1 HA with concurrent HNF-1α inactivation) and 2 (25%) had an inflammatory phenotype (1 HA and 1 HUMP).

Conclusions: Androgen associated hepatocellular neoplasms most often develop in males in their fifth decade of life and are most frequently solitary. Various combinations of prominent atypia, bile production, and focal reticulin disruption result in a diagnosis of HUMP in the majority of cases. Most cases are phenotypically β-catenin activated and a minority expresses an inflammatory phenotype. While β-catenin activation and inflammatory upregulation likely play a role in pathogenesis, the heterogeneous molecular profile of androgen related HNs suggests there are other (yet to be characterized) primary oncogenic mechanisms in this unique tumor type.

1682 Diagnosing Hepatocellular Carcinoma With Immunohistochemistry: Quantitative Assessment of Performance Characteristics for γ-H2AX, Glypican-3, Clathrin Heavy Chain, and Glutamine Synthetase

Craig Poster, Karen Gustafson, Emma Furth, Shannon McCall, Diana Cardona, Xuefeng Zhang, Anand Lagoo, Michalea Lefaivre, Cynthia Guy. Duke University Medical Center, Durham, NC; Fox Chase Cancer Center, Philadelphia, PA; University of Pennsylvania, Philadelphia, PA.

Background: The histological diagnosis of hepatocellular carcinoma (HCC) can sometimes be difficult as focal nodular hyperplasia (FNH), hepatic adenoma (HA) and even cirrhosis may share similar cytological features. Immunohistochemistry (IHC) for glypican-3 (GPC3), clathrin heavy chain (CHC) and glutamine synthetase (GS) have been advocated as ancillary tests. We have previously shown that IHC for the phosphorylated form of the histone variant H2AX (ϒ-H2AX), a central factor in the DNA repair machinery which is activated following DNA double strand breaks (DSBs), is an excellent test for HCC. The goal of this study was to quantitatively determine and compare the performance characteristics of these four IHC markers.

Design: IHC was performed on FFPE tissue sections from 128 liver lesions: cirrhosis (n=22), FNH (n=19), HA (n=21) and HCC (n=66). Following a consensus agreement on the scoring methods, the lesions were randomly divided and scored independently by 5 pathologists. For GPC3, CHC and GS, the percentage of each lesion with a score of no staining (grade 0, G0), mild staining (G1), moderate staining (G2) and strong staining (G3) was recorded. For ϒ-H2AX, four random 400x high power fields were analyzed and the percentage of cells with strong (3+ of 3) nuclear staining was calculated. For HCC versus each lesion, the ROC curve was generated by calculating the sensitivity and 1- specificity for each cut off, and the area under the curve (AUC) determined where a perfect test has a value of 1 and a non-discriminatory test has a value of 0.5.

Results: The ROC AUC data are shown in Table 1.

IHC marker	HCC vs cirrhosis	HCC vs FNH	HCC vs HA	AUC averages
GPC3	0.75	0.83	0.82	0.80
CHC	0.79	0.84	0.76	0.80
GS	0.79	0.63	0.78	0.73
γ-H2AX	0.97	0.93	0.87	0.92

Conclusions: IHC for ϒ-H2AX had the best overall performance for diagnosing HCC compared to the other three antibodies.

1683 Repeat Liver Biopsy Is Essential To Guide the Treatment of Patients With Autoimmune Hepatitis

Juan Putra, Arifa Toor, Arief Suriawinata. Dartmouth-Hitchcock Medical Center, Lebanon, NH.

Background: Liver biopsy at presentation is recommended to establish the diagnosis and to guide the treatment decision of autoimmune hepatitis (AIH). Repeat biopsy is necessary to determine the treatment endpoints and courses of action (AASLD Practice Guidelines, 2010). The role of liver biopsy to evaluate the inflammation and fibrosis has

been challenged by laboratory analysis (Bjornsson et al. 2013) and noninvasive fibrosis markers. However, the temporal association between these findings should be considered as histology improvement lags behind the clinical and laboratory improvement by 3-8 months. The aim of this study was to assess the role of repeat liver biopsy in AIH patients.
Design: Forty liver biopsies from 20 consecutive patients with AIH who underwent repeat biopsy at our institution from 2009-2013 were reviewed. Demographic information, histological characteristics (diagnosis, inflammation grade, and fibrosis stage using Metavir scoring system), and aminotransferase levels (ALT and AST) at the time of each biopsy were recorded. Other laboratory indices (gamma-globulin and IgG levels) were excluded from this study because they were not performed routinely in the majority of cases. Changes in management were determined by comparing therapeutic plan prior to and after the repeat liver biopsies. The correlation between the changes in aminotransferase levels and histologic characteristics was evaluated using statistical analysis.
Results: Twenty AIH patients in our study were mostly female (F:M = 4:1) with an average age of 58.7 years. The average interval between the initial and repeat biopsies was 6.1 years. Inflammatory and fibrosis progression was seen in 3/20 (15%) and 7/20 (35%) of the patients, respectively. Worsening of aminotransferase levels (5/20, 25% patients) did not correlate with both inflammatory (p = 1.00) and fibrosis (p=0.116) progression. Seven of 20 (35%) repeat biopsies revealed overlap histologic appearance of other chronic liver diseases (3 cases of steatohepatitis, 3 cases of primary biliary cirrhosis, and 1 case of autoimmune cholangitis). Changes in the management were observed in 15/20 (75%) of the patients after the repeat liver biopsy.
Conclusions: Repeat liver biopsy is important in the management of AIH patients as aminotransferase levels are not a reliable marker for inflammatory and fibrosis progression. Liver biopsy is also an effective method to recognize comorbidities, which may alter the management of these patients.

1684 Cystic Lesions of the Liver: Appraisal of the Classification, Terminology and Clinicopathologic Characteristics in an Analysis of 229 Cases

Brian Quigley, Hyejeong Choi, Olca Basturk, Gizem Akkas, Kee-Taek Jang, Alton Farris, Alyssa Krasinskas, Juan Sarmiento, David Kooby, Diego Martin, Bobby Kalb, Shishir Maithel, Volkan Adsay. Emory University, Atlanta, GA; Memorial Sloan Kettering Cancer Center, New York, NY; Samsung Medical Center, Seoul, Republic of Korea; University of Arizona College of Medicine, Tucson, AZ.
Background: Data on the clinicopathologic characteristics and relative frequency of various cyst types that occur in the liver is highly conflicting, the controversies mostly attributable to the vast definitional variations in the literature.
Design: 229 consecutive hepatic cystic lesions resected in the authors' institution were re-evaluated by the refined criteria established recently.
Results: By using current definitions, the original diagnosis was revised in 3.9% of the cases (most pertaining to misinterpretation of a non-neoplastic cyst or an intraductal papillary neoplasm of the bile duct as mucinous cystic neoplasm [MCN]). Final classification was as follows. **I. Malformation of ductal plate.** 160 (70%) were lined by biliary epithelial cells *without* ovarian-type stroma, most (137; 60%) showing characteristics of cystic (giant and complicated) bile duct hamartoma (Am J Rad, PMID: 20373435), some (23; 10%) lacking the specifics of this entity (benign non-neoplastic biliary cyst, NOS), and 1 was Caroli, and 35 polycystic liver disease-related. **II. Neoplastic.** 24 cases (10.5%) had convincing ovarian-type stroma; i.e., MCN per WHO-2010. 50% of these had accurate preoperative diagnosis. Only 1 showed invasive carcinoma. Separately, 3 intraductal papillary neoplasms of the bile ducts, 1 cystic degeneration in cholangiocarcinoma, and 1 cystic metastatic adenocarcinoma presented as cysts. **III. Infectious/inflammatory.** Abscesses presenting as cysts (6; 2.6%), Echinococcal cysts (6;2.6%), inflammatory, NOS (1; 0.4%). **IV. Congenital.** Choledochal cyst (14; 6.1%), foregut cyst (4; 1.7%). **V. Others.** Organizing hematomas, hamartomatous cysts, fibrous cysts (2 each; 0.9%), mesothelial inclusion cyst, cystically dilated duct, and cauterized benign cyst of undetermined type (1 each; 0.4%).
Conclusions: 1. Using the recently refined criteria, the most common hepatic cysts (70%) were non-neoplastic benign biliary cysts (cystic biliary hamartomas and NOS-type benign biliary cysts), believed to be ductal plate malformations. 2. Defined by ovarian-type stroma per WHO 2010, the characteristics of MCNs are significantly different than in the literature (all women and only rare cases showing invasion; <5%). 3. Invasive cancers are an uncommon cause of cystic lesions in the liver.

1685 Mast Cell Density in Normal and Early Chronic Liver Disease

Laurel Rose, Romil Saxena. Indiana University, Indianapolis, IN.
Background: The major criterion for diagnosis of systemic mastocytosis is the presence of aggregates of more than 15 mast cells in bone marrow or other affected organs. Mast cells in mastocytosis, but not reactive states, have been shown to express CD25. Prompted by a case of cutaneous mastocytosis with suspected liver (but not bone marrow) involvement and less than 15 mast cells in portal tracts negative for CD25, we undertook a study to determine the number and staining characteristics of mast cells in normal and diseased liver, with emphasis on CD25 positivity.
Design: We identified liver biopsies from adults and children with no pathology (normal or near normal), acute hepatitis, chronic hepatitis C, autoimmune hepatitis, primary sclerosing cholangitis and primary biliary cirrhosis. We excluded cases with more than minimal fibrosis in order to eliminate the confounding role of mast cells in fibrosis. All cases were reviewed to confirm diagnosis and absence of significant fibrosis. Slides were stained immunohistochemically with tryptase, CD117 and CD25. The numbers of positive cells in portal tracts were counted and the average recorded as <5, 6-10 or >10 cells per portal tract.
Results: Most cases showed less than 5 positive cells per portal tract for each marker.

	number of cases	tryptase		CD117		CD25	
		0-5 cells	6-10, 11-15 cells	0-5 cells	6-10 cells	0-5 cells	6-10 cells
normal adult	8	8		8		8	
normal child	7	7		7		7	
acute hepatitis	8	8		8		5	3
chronic hepatitis C	11	11		11		11	
primary sclerosing cholangitis	9	6	1, 2	6	3	9	
primary biliary cirrhosis	8	8		7	1	7	1
autoimmune hepatitis	4	3	1	4		4	

The positive cells were small with scant agranular cytoplasm. Cells highlighted by tryptase and CD117 often had a dendritic appearance. CD25 additionally highlighted large granular cells in necrotic foci of acute hepatitis and, by a faint blush, necrotic or severely damaged hepatocytes in acute and autoimmune hepatitis.
Conclusions: 1) A small number of tryptase and CD117 cells are present in normal and early non-fibrotic stages of chronic liver diseases. These cells are small, spindled or dendritic and contain scant agranular cytoplasm.
2) CD25 marks a small number of small non-dendritic cells. In addition, it marks large cells with coarse cytoplasmic granules in necrotic areas. The latter may represent macrophages and require further characterisation so that CD25, a purported marker of neoplastic mast cells, is interpreted with caution in chronic liver diseases.

1686 Portal Vein Thrombosis (PVT) in Non-Cirrhotic Liver (NCL): Study of 16 Patients With Emphasis on Hepatic Artery (HA) Changes

Natalia Rush, Hongliu Sun, Yukihiro Nakanishi, Wadad Mneimneh, Paul Kwo, Romil Saxena. Indiana University, Indianapolis, IN; University of Toledo, Toledo, OH; Tulane University, New Orleans, LA; Mayo Clinic, Rochester, MN.
Background: PVT is uncommon outside the context of cirrhosis. However, PVT in NCL clinically mimics cirrhosis due to presence of portal hypertension (PH).This series elucidates microscopic changes of PVT in NCL with emphasis on HA branches.
Design: Patients with PVT and no concomitant liver pathology were identified. Age and gender matched livers with normal or minimal changes served as controls. Sinusoidal and central vein (CV) dilation, hepatic plate thinning and thickening were graded as subtle or obvious and focal or diffuse in a blinded fashion. Portal vein (PV) dilation, PV absence/attenuation and fibrosis were recorded. Outer and luminal diameters and wall thickness of HA, and outer diameter of accompanying bile ducts (BD) were measured. Data including ratio of BD:HA diameters were analysed separately for small (‹100mm) and larger (³100 µm) HA.
Results: There were 16 patients (8 males, 8 females; mean age, 46.5 years) who presented with varices (14), ascites (7) and splenomegaly (13). Cavernous transformation of PV was seen in 14 patients. One wedge, 17 cores and 4 resections were available for review.

			Biopsies		Resections	
			Patients	Controls	Patients	Controls
HA	outer diameter	small	59	59	72	65
		large	156	153	175	140*
	luminal diameter	small	30	30	45	39
		large	89	78	152	92*
	wall thickness	small	16	17	16	22
		large	39	36	27	30
BD outer diameter		small	51	51	56	59
		large	-	-	102	95
BD:HA diameters		small	0.9	0.9	0.8	0.9
		large	0.7	0.6	0.6	0.8

Values are means in µm; *, significant at p

	Patients (n=16)	Controls (n=18)
No change	2	4
PV absence	5	0
PV dilation	8	4
CV dilation	2,0,0,4#	3,1,1,1#
Sinusoidal dilation	9,2,0,6#	8,1,0,3#
Thick plates	3,3,0,2#	3,0,0,0#
Thin plates	9,2,0,6#	8,1,0,3#
portal fibrosis	4	0

*subtle & focal, obvious and focal, subtle and diffuse, obvious and diffuse

Conclusions: 1) Dilation of HA branches in resections but not biopsies suggests a compensatory arterial response to longstanding PVT in NCL.
2) Obvious and/or diffuse CV or sinusoidal dilation and plate thinning in a patient with PH and NCL should raise suspicion of PVT; subtle and/or focal changes are nonspecific.

1687 SOX-9 Expression in Primary Liver Carcinomas – Diagnostic and Biologic Implications

Marianna Ruzinova, Ta-Chiang Liu. Washington University, St. Louis, MO.

Background: Biphenotypic primary liver carcinomas (BPLC), which exhibit both hepatocellular and biliary phenotypes, may occasionally be difficult to be distinguished from classical hepatocellular carcinoma (HCC) or cholangiocarcinoma (CC). We hypothesized that a ductal progenitor cell marker, Sex-determining region Y–box containing gene 9 (SOX-9), may be used to label component of biliary differentiation in these tumors. In this study, we evaluated and compared the expression of SOX-9 in cases of classical HCC, CC, and BPLC. The results were compared to that of EpCAM, a marker previously suggested to be associated with liver stem/progenitor cells.
Design: Immunohistochemistry for SOX-9 and EpCAM was performed in 15 cases of classical HCC (well-moderately differentiated; no equivocal biliary component), 17 cases of classical CC (well-moderately differentiated; no equivocal hepatocellular component), and 20 cases of BPLC. BPLC was defined as either combined HCC-CC (per WHO criteria) or classical HCC/CC with a poorly-differentiated/progenitor-like component. The distribution and intensity of the staining was evaluated. Distribution was categorized as diffuse (≥80% tumor cells), patchy (<80%), or none (0%). Staining intensity was scored as: 0 (negative), 1 (weak), 2 (moderate), and 3 (strong). One-way ANOVA was used for statistical analysis.
Results: SOX-9 and EpCAM were expressed in normal bile ducts. SOX-9 and EpCAM were expressed in 100% of the classical CC cases. Diffuse EpCAM and SOX-9 expression was seen in 100% and 47% of these cases, respectively. In BPLC, EpCAM expression was seen in 19/20 cases (95%; all diffuse staining), and SOX-9 expression was seen in 18/20 cases (90%; 15 of which were diffuse staining). SOX-9-expressing CC or BPLC cells also coexpress EpCAM. In contrast, expression of EpCAM or SOX-9 was uncommon in HCC, with only 5/15 cases (33%) expressing patchy expression of either marker ($P < 0.0001$ for both). However, in 3 of these HCC cases, there was focal EpCAM/SOX-9 co-expression. Staining intensity for both markers was also significantly lower in HCC. The mean staining intensity for EpCAM in CC, BPLC, and HCC was 2.5, 2.3, and 0.5, respectively, and that of SOX-9 was 2.3, 2.2, and 0.5, respectively ($P < 0.0001$ for both).
Conclusions: SOX-9 is a reliable marker of biliary differentiation and can be helpful in the diagnostic workup for potential BPLC. Coexpression of EpCAM and SOX-9 in a subset of morphologically classical HCC suggests the possibility of reprogramming in these tumors.

1688 Hepatic Iron Homeostasis: Immunolocalization of Iron Regulatory Factors in Human Liver

Carolyn Sangokoya, Aras Mattis, Raga Ramachandran, Jody Baron. University of California, San Francisco, CA.

Background: The liver is a central organ for iron homeostasis, yet the molecular regulators of cellular and systemic iron homeostasis are not well characterized within the hepatic parenchyma. Because iron accumulation is seen in chronic liver disease, further understanding of the spatiotemporal regulatory background of liver iron balance is needed. This study aims to localize important regulators of iron homeostasis, including hepcidin (HAMP), ferroportin (FPN), ferritin (FTL), and transferrin receptor (TFR1), in human liver samples from early development to adult liver and chronic liver diseases of various etiologies including Hepatitis C, Hepatitis B, non-alcoholic steatohepatitis (NASH), and alcohol cirrhosis.
Design: Paraffin-embedded formalin-fixed liver tissue samples were examined by immunohistochemistry and special stains, with iron scoring performed independently by at least two pathologists.
Results: Hepcidin highlights sinusoidal reticuloendothelial (SE) cells (Kupffer cells and liver sinusoidal endothelial cells) in all tested samples. In addition, hepcidin strongly highlights bile canaliculi and bile duct epithelium in normal adult and noncirrhotic NASH. Cirrhotic samples all show hepcidin expression in large vessel endothelium and cells associated with fibrosis. Ferroportin strongly highlights the bile duct epithelium in fetal, normal adult, cryptogenic cirrhosis, and HCV cirrhosis; SE cells are highlighted for ferroportin in fetal and normal adult liver, but not in cirrhotic samples.
Conclusions: In this study, we demonstrate hepcidin predominantly in SE cells, with expression in bile duct epithelium in normal adult and noncirrhotic samples. Ferroportin is seen in bile duct epithelium across all samples, consistent with known biliary excretion of iron. Ferroportin is seen in the SE cells of normal adult and fetal liver, yet is absent in this compartment in cirrhotic samples, with cirrhotic samples instead showing hepatocyte cytoplasmic staining. Of interest, the SE compartment is a major site for iron turnover in the liver and previous reports support this as a major site for liver ferroportin and hepcidin expression. We look to further characterize these iron-regulating factors in relation to the expression of iron-regulating microRNA miR-485-3p and liver-abundant microRNA miR-122. The findings of this study are important in identification of appropriate targets for therapeutic regulation of liver iron in chronic liver disease and cirrhosis.

1689 MicroRNA In Situ Hybridization Analysis of MiR-485-3p and MiR-122 Expression in Human Liver Development and Disease

Carolyn Sangokoya, Aras Mattis, Raga Ramachandran, Jody Baron. University of California, San Francisco, CA.

Background: Hepatic iron accumulation is associated with pathogenesis in chronic liver disease and cirrhosis of nonalcoholic steatohepatitis (NASH) or hepatitis C (HCV) etiology, yet the molecular mechanisms of dysregulated hepatic iron remain unknown. Recent findings reveal that the microRNA miR-485-3p directly targets the iron export protein ferroportin, suggesting a role for this microRNA in cellular iron homeostasis. Further study of tissue samples has shown increased expression of miR-485-3p in HCV cirrhosis. This present study aims to characterize endogenous spatial localization of the microRNAs miR-485-3p and miR-122 in human liver from development to cirrhosis.
Design: From 50 paraffin-embedded formalin-fixed liver tissue samples, a subset of 10 representative samples of fetal, neonate, adult normal, cirrhosis of cryptogenic, HCV, and NASH etiology without evidence of histologic iron were analyzed by LNA-based in situ hybridization to specifically detect microRNAs miR-485-3p, 122, 126, and appropriate controls. Iron scoring was performed independently by at least two liver pathologists.
Results: MiR-485-3p localizes to the hepatocyte perinuclear region in adult normal liver and cryptogenic cirrhosis, yet highlights the sinusoidal reticuloendothelial (SE) cells (Kupffer cells and liver sinusoidal endothelium) in neonate liver, HCV cirrhosis, and NASH cirrhosis. MiR-485-3p additionally localizes to bile ducts and ductular reaction in HCV and NASH cirrhosis. MiR-122 expression is seen in the hepatocytes of all samples, and in bile ducts and ductular reaction of all cirrhotic samples. MiR-126 expression is strong within the endothelium of all samples.
Conclusions: In this study, we identify expression of miR-485-3p, miR-122, and miR-126 in human liver by in situ hybridization. These findings further characterize expression of these microRNAs by identifying spatial localization to specific cell-types and compartments in liver health and disease. MiR-485-3p localization within the SE compartment in NASH and HCV cirrhosis is physiologically significant, as this is the major site of iron turnover. Due to the intricate network of cell types and systems within liver, the combination of microRNA localization by in situ hybridization in addition to analysis by other molecular methods together allow for better understanding of the etiologic relevance and potential mechanisms of microRNA regulation within the liver.

1690 5% of Hepatocellular Carcinomas Are Positive for CDX2: An Important Diagnostic Pitfall

Sejal Shah, Vishal Chandan, Tsung-Teh Wu, Michael Torbenson. Mayo Clinic, Rochester, MN.

Background: CDX2 is a homeobox gene which encodes a nuclear transcription factor expressed by intestinal epithelium. Immunostain for CDX2 is widely used in tumor surgical pathology as evidence for gastrointestinal origin. However, we have anecdotally encountered occasional hepatocellular carcinomas (HCC) that are positive for CDX2, including cases submitted for consultation with a preliminary diagnosis of possible metastatic carcinoma from the gastrointestinal tract. The aim of this study is to assess the prevalence and significance of CDX2 expression in HCC.
Design: Sections from 172 resected HCC and 6 resected fibrolamellar carcinomas (FLC) were reviewed. Only resected specimens were included, in order to ensure the diagnosis of HCC. Only typical HCC and FLC were chosen for the study. Cases of combined HCC-cholangiocarcinoma were excluded. CDX2 immunostain was performed on all cases and positive nuclear staining was graded in the neoplastic cells as 1+ (1-10%), 2+ (11-25%), 3+ (26-50%) or 4+ (51-100%).
Results: As expected, individuals with HCC were predominately male (114 males, 58 females), with an average age at diagnosis of 63 years. FLC occurred in 3 males and 3 females, with an average age of 32 years. For HCC, 51 cases (29.7%) were well differentiated, 105 cases (61%) were moderately differentiated, and 16 cases (9.3%) were poorly differentiated. None of the FLC cases were CDX2 positive, but 9 HCC cases (5%) were CDX2 positive. The CDX2 staining ranged from 1+ (N=5), to 2+ (N=2) to 3+ (N=2). The 9 positive cases were otherwise typical in morphology for HCC. However, CDX2 positive HCCs were more likely to be poorly differentiated, $p<0.0001$, Chi Square test. Overall, the CDX2 positive tumor grades were well differentiated (N=1); moderately differentiated (N=3), and poorly differentiated (N=5). The demographics for CDX2 positive cases were similar to the CDX2 negative cases, with 6 males and 3 females and average age of 57 years. Likewise, the underlying liver diseases were typical for HCC: hepatitis C (N=3), hepatitis B (N=1), hepatitis C and steatohepatitis (N=1), and no known liver disease (N=4).
Conclusions: CDX2 is considered a highly sensitive and specific marker of intestinal origin in tumor pathology. This study demonstrates an important diagnostic pitfall: CDX2 is positive in approximately 5% of hepatocellular carcinomas, especially in poorly differentiated tumors.

1691 Role of Arginase-1 and Hep Par 1 in Distinguishing Hepatocellular Carcinoma From Intrahepatic Cholangiocarcinoma

Shweta Shinagare, Vikram Deshpande. Tufts Medical Center, Boston, MA; Massachusetts General Hospital, Boston, MA.

Background: The distinction between hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHCC) is generally based on histological criteria. However, with poorly differentiated variants of primary hepatic carcinomas, the distinction is often based on immunohistochemical assays. Common assays for hepatocellular differentiation include Hep Par 1, Arginase-1, Glypican-3 and a canalicular pattern of reactivity with CEA and CD10; the latter two markers are seldom positive in poorly differentiated carcinomas. Albumin, often used as a marker of hepatocellular differentiation, has recently been identified in the majority of IHCC. These assays are also used to identify dual hepatocellular and cholangiocellular differentiation in mixed

neoplasms. Although Hep Par 1 and Arginase-1 are utilized as markers of hepatocellular differentiation, their reactivity profiles have not been rigorously tested on IHCC. In this analysis we assess Arginase-1 and Hep Par 1 reactivity in a large cohort of intrahepatic cholangiocarcinomas and hepatocellular carcinomas.
Design: We analyzed a single institution cohort of HCC and IHCC. Demographic data and the grade of differentiation were recorded. The distinction of IHCC for bile duct and perihilar carcinomas was based on the epicenter of the lesion, as identified on imaging and gross evaluation. Immunohistochemistry for Arginase-1 and Hep Par 1 was performed on all cases.
Results: The mean age of patients with HCC (n=93) was 64 years (range 44 -81) with 65 males and 28 females. Majority of the HCCs were moderately differentiated (55%) or poorly differentiated (39%).The sensitivity for Hep Par1 and Arginase-1 in moderately differentiated HCCs was 84 % and 83 %, respectively, and in poorly differentiated HCCs was 71% and 64%, respectively. The mean age of the IHCC cohort (n=59) was 64 years (range 37-77); M:F =1:1. 14% of IHCC were well differentiated, 62% moderately differentiated, and 24% poorly differentiated. On immunohistochemistry, only 1 of the 59 (1.7%) IHCCs was positive for Arginase-1, while 31 (52.5%) of the IHCCs were positive for Hep Par 1. The reactivity for Hep Par 1 did not correlate with tumor differentiation.
Conclusions: Arginase -1 represents a robust means of distinguishing IHCC for HCC. Hep Par 1, expressed in 53% of IHCC, cannot assist in discriminating these two neoplasms, and furthermore cannot distinguish the two components of a mixed hepatocellular-cholangiocarcinoma.

1692 Transaldolase Deficiency in Hepatocellular Carcinoma Correlates With Poor Tumor Differentiation and Poor Prognosis

Maryam Shirazi, Abby Siegel, Jay Lefkowitch, Marcela Salomao. Columbia University Medical Center, New York, NY.
Background: Transaldolase (TAL) is a key enzyme in the non-oxidative phase of pentose phosphate pathway (PPP). Inborn TAL deficiency results in liver disease in the neonatal period, ranging from fatty liver disease (FLD) to cirrhosis to early development of hepatocellular carcinoma (HCC). TAL1-/- mice show increased oxidative stress, FLD and spontaneous progression to HCC. Recently, proteomic studies identified TAL as a potential biomarker for HCC. However, characterization of TAL expression in HCC is lacking and a possible role of TAL in FLD-associated HCC has not been investigated. This study aims to evaluate TAL expression in HCC and its possible association with underlying liver disease.
Design: Tissue microarrays containing 82 HCC cases (68 male: 14 female; mean age 59.7±7.4 years) were stained with anti-transaldolase-1 antibody (rabbit polyclonal, 1:100, Abcam, Cambridge, MA) on an autostainer (Ventana, USA). The staining intensity was compared to the corresponding non-neoplastic liver and scored as normal (2+), partial loss (1+) or total loss (0). TAL deficiency (TAL-) was defined as partial or total loss of TAL staining. Clinical information was retrieved from medical records under and IRB-approved protocol.
Results: TAL deficiency was identified in a total of 12 of 82 cases (14.6%), 2 of which showing total TAL loss (2.4 %). The corresponding non-neoplastic liver displayed normal TAL staining. There was no association between FLD and TAL loss (41.67% TAL- vs. 46%TAL+, p=0.4), whereas obesity was significantly more prevalent in this group (58.3% vs. 29%, p=0.02). A larger proportion of TAL- tumors recurred within 1 year compared to TAL+ group (25% vs. 9%, p=0.07). Moreover, TAL- HCC displayed significantly higher cytological grade than TAL+ HCCs (p=0.03).
Conclusions: This is one of the first studies to assess TAL expression in HCC. Our results suggest that TAL deficiency is associated with higher tumor grade and higher recurrence rate within 1 year. Further studies are required to better characterize TAL deficient tumors which may result in identification of potential new molecular targets for diagnosis and treatment of HCC.

1693 Citrate Toxicity in Pediatric Liver Failure Patients on Therapeutic Plasma Exchange

Esther Soundar, Reuben Jacob, Vadim Kostousov, Jun Teruya. Baylor College of Medicine, Houston, TX; Emory University, Atlanta, GA.
Background: Regional anticoagulation with citrate is preferred over heparinization to mitigate bleeding complications during therapeutic plasma exchange (TPE). However, patients with liver failure have impaired citrate metabolism leading to citrate accumulation. Citrate binds ionized calcium (iCa) and decreased iCa levels affects hemostasis.Total to iCa ratio and iCa levels are surrogate measures of citrate toxicity and its early identification would enable physicians to monitor patients for bleeding risk and consider prophylactic treatment options. Here, we evaluate the utility of the total to iCa ratio in pediatric patients with varying degrees of liver dysfunction.
Design: A retrospective chart review was done to extract demographic and laboratory variables including calcium levels, liver function test results and bleeding and mortality status for pediatric liver failure patients who underwent TPE from 2011 to 2014. Pediatric End-Stage Liver Disease (PELD)/Model for End-Stage Liver Disease (MELD) scores and total to iCa ratio were calculated. Non-parametric statistical analyses were performed to elucidate the role of total to iCa ratio in predicting bleeding.
Results: We identified 21 patients whose characteristics are listed in Table1. Patients with bleeding (mucosal bleeding and oozing from catheter insertion sites) had significantly higher total calcium (p=0.004) and total to iCa ratio (p=0.009) and no difference in iCa levels (p=0.79). Patients with higher PELD/MELD scores had significantly higher total to iCa ratio (p=0.02). Logistic regression analysis showed that higher total to iCa ratio was predictive of bleeding. Sensitivity and specificity for bleeding were 64% and 100% at a total to iCa ratio cut-off level of ≥ 2.48. The area under the ROC curve was 0.87 demonstrating the ability to discriminate bleeders from their counterparts.

Clinical parameters, median(IQR)		
Age, years		2.69(0.73-9.05)
Weight, kgs		11(8.51-32.4)
PELD/MELD score		28(26-36)
Days on TPE		4(2-5)
Sex	Male	8(38.1%)
	Female	13(61.9%)
Status	Dead	11(52.4%)
	Alive	10(47.6%)
Total Ca:iCa ratio	≤2	5(23.8%)
	>2	16(76.2%)
Bleeding	Yes	7(33.3%)
	No	14(66.7%)
Procedure	TPE	4(19%)
	TPE & CRRT	17(81%)

Conclusions: Total to iCa ratio is a good predictor of citrate toxicity and a total to iCa ratio of >2.4 could possibly alert clinicians of bleeding risk in pediatric patients with liver failure on TPE.

1694 Clinicopathological Challenges in the Detection of Hepatic Hodgkin Lymphoma

Sahr Syed, Aparna Harbhajanka, Brett Mahon, Shriram Jakate. Rush University Medical Center, Chicago, IL.
Background: Hodgkin lymphoma (HL) is largely a nodal neoplasm with rare extranodal dissemination. During staging workup of initial diagnosis of nodal HL, detecting hepatic HL (stage IV) is quite challenging clinically and histologically. Potential hepatic HL may be clinically suspected by virtue of LFT abnormalities or imaging studies. Occasionally, a liver biopsy performed for an unrelated indication reveals a clinically unsuspected hepatic HL. We reviewed 6 cases of hepatic HL to investigate the clinical setting and challenges linked to hepatic HL diagnosis.
Design: We collected 6 cases of hepatic HL (4M; 2F, mean age 60.5 with 27-81 range) from a total of 135 cases of HL in our databases during last 14 years (2000-2014). We then reviewed the clinical setting (LFT and/or imaging abnormalities, unexpected hepatic HL), type of liver biopsy (random or targeted) and the microscopic findings.
Results: 21/135 HL cases (16%) had abnormal LFTs and no radiographic lesion. Random liver biopsies in these showed focal portal HL infiltrate in only 1 case (<1%), while the remaining cases showed drug-induced changes or NASH. 3/135 cases (2%) showed radiographic hepatic lesions which were targeted for biopsies. All 3 of these showed extensive portal and lobular hepatic HL infiltrate. In 2 patients, random liver biopsies were performed for FUO and pancytopenia which showed focal portal unsuspected HL. Subsequent investigations in both of these patients revealed nodal HL. Microscopically, all 6 patients had classical HL with Reed-Sternberg cells and typical immunoprofile (CD30, CD15 and Pax 5 positivity). In the 3 patients with random liver biopsies and no radiographic lesion, the HL infiltrate was subtle, limited to rare portal areas and posed considerable diagnostic difficulty requiring expert hematopathology consultation. The targeted lesions had microscopically obvious extensive portal and lobular infiltrate.
Conclusions: Hepatic HL involvement is rare and seen in <5% of HL cases. Diagnosis is easier when lesions are seen radiographically and targeted biopsies are performed. LFT abnormalities without radiographic lesions are common in HL but rarely indicate hepatic HL. Occasionally, hepatic HL is seen in incidental random liver biopsy, which leads to subsequent clinical discovery of nodal HL. Random, non-targeted liver biopsies pose considerable diagnostic challenges for HL infiltrate.

1695 Are FGFR1 and FGFR2 Activated By Novel DNAJB1-PRKACA in Fibrolamellar Carcinoma?

Michael Torbenson, Rondell Graham, Patricia Greipp, Emily Barr Fritcher, Benjamin Kipp, Joaquin Garcia. Mayo Clinic, Rochester, MN.
Background: Fibrolamellar carcinoma is characterized by a recurrent *DNAJB1-PRKACA* fusion transcript. The functional properties of the fusion are not well known but are believed to include upregulation of *PRKACA*. The downstream targets of *PRKACA* include fibroblast growth factor pathway activation. Fibroblast growth factor receptors (FGFRs) have not been systematically studied in fibrolamellar carcinoma and recently inhibitors for FGFR proteins have been developed for clinical use.
Design: We retrieved cases of fibrolamellar carcinoma from the institutional files. After histologic review, paraffin embedded sections from each case were used for RT-PCR to confirm the presence of the *DNAJB1-PRKACA*, FGFR1 immunohistochemistry with a monoclonal FGFR1 antibody, *FGFR1* mRNA chromogenic in situ hybridization and *FGFR1* DNA copy number fluorescence in situ hybrization (FISH). *FGFR1* mRNA in situ hybridization was semiquantitatively assessed as according to the number of FGFR1 signals per cell:- 0 – negative, 1+ - 1-2 signals per cell, 2+ - 3-5 signals per cell in ³20% cells, 3+ >5 signals per cell in ³20% of cells . Testing with a commercial break apart FISH probe for *FGFR2* was also performed.
Results: There were 19 cases of fibrolamellar carcinoma affecting 12 women and 7 men with a median age of 26 years (range 16-47). Histologically, the tumors showed the characteristic morphologic features and all harbored the *DNAJB1-PRKACA* fusion

transcript by RT-PCR. Immunohistochemistry for FGFR1 was negative in all 19 cases. RNA in situ hybridization was 2+ in 2 cases, 1+ in 4 cases and negative in 4 cases. *FGFR1* FISH revealed trisomy or tetrasomy for the *FGFR1* locus in 17 of 19 cases. The remaining cases were diploid. Break apart FISH for *FGFR2* showed normal *FGFR2* signals in 12/12 cases.

Conclusions: Fibrolamellar carcinoma reveals polysomy of the *FGFR1* locus at the DNA level and modest mRNA overexpression. FGFR1 overexpression at the protein level and activation of *FGFR2* by rearrangement are absent. These data reduce the likelihood that FGFR inhibitors will be effective in the treatment of fibrolamellar carcinoma.

1696 Astrocyte Elevated Gene-1: Effective Immunohistochemical Marker in Separating Benign Liver and Neoplasms From Hepatocellular Carcinoma

Michael Toussaint, Cynthia Cohen, Wanhong Jiang, Momin Siddiqui. Emory University Hospital, Atlanta, GA.

Background: Distinguishing between a well-differentiated hepatocellular carcinoma (HCC) and benign liver neoplasms, such as a hepatic adenoma, can be difficult in certain cases, particularly in small needle biopsies. In such cases, there is a necessity for a biomarker which can aid in differentiating benign liver and benign neoplasms, from HCC. Astrocyte elevated gene-1 (AEG-1), an oncogene, has been found to play a key role in the development of a number of human cancers, including HCC. We evaluated AEG-1 expression in HCC, benign liver tissue and benign neoplasms.

Design: IHC for AEG-1 (rabbit polyclonal ab76742, 1:100, Abcam, Cambridge, MA) expression was performed on 45 liver neoplasm resection slides, consisting of HCC (32) and hepatic adenoma (13), and 119 in tissue microarray, consisting of benign non-neoplastic liver (35) and HCC (84). Finely-granular cytoplasmic staining in greater than 5% of cells was considered positive.

Results:

Table 1: AEG-1 expression in 45 liver neoplasms.

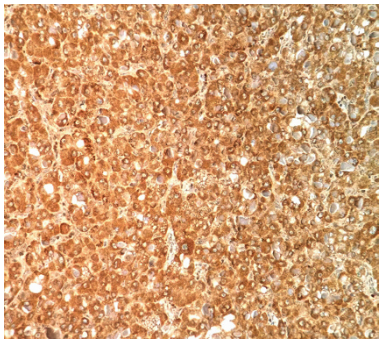
Diagnosis	Positive	Negative
Hepatic Adenoma	2 (15%)	11 (85%)
Hepatocellular Carcinoma	31 (96.8%)	1 (3.2%)

Table 2: AEG-1 expression in 119 cases in TMA.

Diagnosis	Positive	Negative
Benign Non-neoplastic Liver	2 (5.7%)	33 (94.3%)
Hepatcellular Carcinoma	82 (97.6%)	2 (2.4%)

AEG-1 expression is significantly more frequent in HCC (97%) than in hepatic adenoma (15%) or benign non-neoplastic liver (6%).

Figure 1: AEG-1 staining pattern in HCC.



Conclusions: This study demonstrates the utility of AEG-1 IHC stain as an aid to the H&E stain when differentiating between benign non-neoplastic and neoplastic liver lesions, and HCC. AEG-1 was effective in staining the majority of HCC but few benign non-neoplastic liver tissues and hepatic adenomas were immunopositive. This study clearly identifies a strong role for AEG-1 in separating benign liver tissue and lesions, from HCC. This stain may also be very helpful clinically, in small histologic/biopsy specimens in which separating a well differentiated HCC from HA may be diagnostically challenging and difficult.

1697 Telomerase Reverse Transcriptase Promoter Mutations (mTERTp) in Combined Hepatocellular(HCC)-Cholangiocarcinoma(CC; cHCC-CC) Support Clonal and HCC-Like Origin for Both Components

Christos Tsokos, Xinxin Liu, David Solomon, Xin Chen, Gillian Hale, E Scott Seeley, Sanjay Kakar, Gregor Krings. University of California, San Francisco, CA.

Background: cHCC-CC are rare tumors with HCC and CC features, which share risk factors with HCC but outcomes more akin to CC. Distinction of cHCC-CC from CC may be histologically challenging but has prognostic and therapeutic implications. In HCC, mTERTp are frequent and correlate with beta-catenin mutations(mBcat). Conversely, isocitrate dehydrogenase 1 and 2 mutations(mIDH1/2) are recurrent in CC. mTERTp/mBcat and mIDH1/2 remain unevaluated in cHCC-CC. The aim of this study was to determine the mutation status of these genes in cHCC-CC in order to elucidate pathogenesis of these poorly understood tumors and potentially facilitate diagnosis.

Design: Mutation hotspots in TERTp, IDH1(exon4), IDH2(exon4),and Bcat(exon3) were analyzed in 9 cHCC-CC by polymerase chain reaction and Sanger sequencing. HCC and CC areas of cHCC-CC were evaluated separately in 6 cases. Results were compared to 19 HCC and 10 intrahepatic CC.

Results: 78% cHCC-CC had mTERTp, compared to 0% CC (p=.001) and 53% HCC (p=.25). All cHCC-CC with mTERTp and separately evaluable HCC and CC areas showed mTERTp in both areas. Whereas 60% HCC with mTERTp also had mBcat, none(0%) of the cHCC-CC with mTERTp had mBcat (p=.035). All mTERTp in cHCC-CC and 9(90%) mTERTp in HCC were at C228T;1 HCC without mBcat had mTERTp at C250T. Neither mTERTp nor mBcat correlated with grade in cHCC-CC or HCC. No mIDH1 were identfied in cHCC-CC, compared to 40% CC with mIDH1 (all R132C;p=.087). No mIDH2 were found in any tumors.

mTERTp, mIDH1/2 and mBcat in cHCC-CC vs HCC and CC				
	mTERTp	mBcat	mIDH1	mIDH2
cHCC-CC %(n)	78(9)	0(8)	0(9)	0(9)
HCC area %(n)	67(6)	0(6)	0(6)	0(6)
CC area %(n)	67(6)	0(6)	0(6)	0(6)
HCC %(n)	53(19)	42(19)	0(19)	0(18)
CC %(n)	0(10)	0(4)	40(10)	0(10
p (cHCC-CC v HCC)	.25	.06	1.00	1.00
p (cHCC-CC v CC)	.001	1.00	.09	1.00
p (cHCC v CC)	.005	.03	.009	1.00

Conclusions: cHCC-CC but not CC commonly harbor mTERTp, which are present in both HCC and CC components. In contrast to HCC, mTERTp are not associated with exon3 mBcat in cHCC-CC. Conversely, mIDH1 are present in CC but not cHCC-CC. Accordingly, cHCC-CC may be more similar to HCC than CC, and presence of mTERTp in HCC and CC areas of cHCC-CC supports a clonal origin for both components. The findings suggest that identification of mTERTp may facilitate diagnosis of cHCC-CC, especially if only CC areas are sampled. Co-existence of mTERTp and mBcat may support HCC over cHCC-CC in problem cases.

1698 Validation of an RT-PCR Assay for Detection of Recurrent DNAJB1-PRKACA Fusion Transcripts in Fibrolamellar Hepatocellular Carcinoma

Emily Waterhouse, Nancy Joseph, Funda Yilmaz, Deniz Nart, Kimberly Evason, Grace Kim, Sanjay Kakar, Linda Ferrell, Ryan Gill, David Solomon. University of California, San Francisco, CA; Ege Univeristy, Izmir, Turkey.

Background: Fibrolamellar hepatocellular carcinoma (FLHCC) is a distinct histologic variant of HCC that typically arises in young adults without underlying liver disease and is characterized by laminated fibrous layers between neoplastic polygonal hepatocytes with eosinophilic cytoplasm and prominent nucleoli. Immunohistochemical and molecular markers for this aggressive neoplasm have been lacking. A recent study identified recurrent DNAJB1-PRKACA fusion transcripts in FLHCCs generated by an intrachromosomal deletion on chromosome 19 fusing the 5' exons of DNAJB1 with the 3' exons of PRKACA (Honeyman et al. *Science* 2014 Feb 28). The sensitivity and specificity of this novel fusion for diagnosis of hepatocellular neoplasms remains undefined as are the clinicopathologic characteristics of patients with FLHCC harboring these fusions.

Design: 24 cases of FLHCC were retrieved from the archives of two institutions. Total RNA was purified from formalin-fixed, paraffin embedded blocks of both tumor and normal liver. RT-PCR was performed using an antisense primer in exon 1 of DNAJB1 and sense primer in exon 3 of PRKACA that flank the recurrent fusion site, and amplicons were Sanger sequenced. Immunohistochemistry with monoclonal antibodies against four separate epitopes within the C-terminus of the PRKACA protein was performed on paraffin sections of FLHCC and adjacent normal liver.

Results: DNAJB1-PRKACA fusion transcripts were identified in all cases of FLHCC assessed to date. Immunohistochemistry using antibodies raised against the C-terminus of PRKACA revealed increased cytoplasmic expression in FLHCC tumors relative to normal liver but no aberrant cellular localization was seen. The results of RT-PCR testing in the full cohort of 24 FLHCC cases will be presented, as well as testing in additional HCC cases without fibrolamellar features arising in young adults without underlying liver disease, HCC cases with fibrolamellar features arising in older adults with underlying cirrhosis, and cases of conventional HCC, hepatoblastoma, hepatic adenoma, and cholangiocarcinoma.

Conclusions: We have validated a RT-PCR assay for identification of the recurrent DNAJB1-PRKACA fusion in FLHCCs. Herein, we will demonstrate the specificity of this fusion transcript for the diagnosis of hepatocellular neoplasms and will identify patients with tumors harboring this fusion that will benefit from small molecule inhibitors targeting activated PRKACA.

1699 Macrophages in Alcoholic and Nonalcoholic Fatty Liver Diseases

Rao Watson, Elizabeth Brunt. Washington University School of Medicine, St. Louis, MO.

Background: Pathogenesis and progression of nonalcoholic fatty liver disease (NAFLD) are under active study. Kupffer cells, the intraparenchymal macrophages of the liver, play a vital role in complex cytokine and chemokine interactions that lead to inflammatory and fibrogenic processes. The aim of this study is to characterize the macrophages in alcoholic and nonalcoholic fatty liver diseases.

Design: Cases included alcoholic steatohepatitis (ASH), nonalcoholic steatohepatitis (NASH), nonalcoholic steatosis or steatosis with inflammation (S/SI); controls were chronic cholestatic liver disease (CC), including primary sclerosing cholangitis and primary biliary cirrhosis, and donor liver biopsies. Cirrhotics were excluded; stages of fibrosis ranged from none (stage 0) to bridging with nodularity (stage 3) in all groups except donor biopsies. In addition to routine histologic examination, semiquantitative assessment of 5 high-powered fields (400X objective) of dispersed portal and lobular macrophages, and aggregates, were determined by immunohistochemistry for CD68, a pan-macrophage marker, and CD163, an activated macrophage marker.
Results: Ten patients and their biopsies were identified for each group. CD163 macrophages were more numerous than CD68 macrophages for all examined groups. Percent portal versus lobular macrophages were not statistically different between any groups. The same held true for total numbers of CD68 and CD163 macrophages in ASH. Total CD68 and CD163 macrophages were lowest in NASH; this was significant compared to CC (p=0.016, 0.003) and donor biopsies (p=0.007, 0.001). Lobular macrophage aggregates of both CD68 and CD163 were greater in biopsies with steatohepatitis in lobules, and in perivenular areas (p=0.003, <0.001, <0.001, 0.0003). Stratifying by fibrosis stage showed significantly less portal CD68 and CD163 macrophages in higher stages (2-3) compared to fibrosis stages 0-1 (p=0.036, 0.007) in patients with chronic liver disease, and fatty liver disease. No significant differences were seen when patients were stratified by BMI.
Conclusions: This study confirmed that perivenular and lobular macrophage aggregates were more common in steatohepatitis, but total overall CD68 and CD163 macrophage numbers were lowest in NASH compared with ASH, CC and to donor liver. Portal macrophages, not unique to NAFLD, are decreased in both forms of FLD and other chronic liver diseases with advanced fibrosis. These findings support the dynamic roles of hepatic macrophages in differing types and manifestations of liver injury, including fatty liver diseases.

1700 Allograft Liver Biopsies Still Show Histologic Features of Recurrent HCV Following Sustained Virologic Response

Emma Whitcomb, William Gibson, Jamie Koo, Charles Landis, Stephen Rayhill, Joseph Ahn, Ibrahim Hanouneh, Jamak Esfeh, Helen Te, Hanlin Wang, John Hart, Rish Pai, Maria Westerhoff. University of Chicago Medical Center, Chicago, IL; North Shore University Health System, Evanston, IL; UCLA Health, Los Angeles, CA; University of Washington Medical Center, Seattle, WA; Oregon Health & Science University, Portland, OR; Cleveland Clinic, Cleveland, OH.
Background: With recent advances in HCV treatment, more patients, even in the post-transplant setting, are expected to achieve sustained virologic response (SVR) and thus considered clinically 'cured'. The biopsy findings after successful treatment of HCV infection in the post-transplant setting are not well characterized and are the focus of this study.
Design: 127 post-transplant liver biopsies from 26 HCV patients who achieved SVR were assessed. SVR was defined as undetectable serum HCV RNA 24 weeks after treatment cessation. Allograft biopsy findings were rendered masked to the time of SVR, and the following were collected: Batts-Ludwig grading and staging and liver chemistry test (LCT) values at the time of each biopsy (AST, ALT, alk phos, and total bilirubin).
Results: The 26 patients had a total of 52 post-SVR biopsies, an average of 2 biopsies per patient. The indication for biopsy was elevated LCTs in 25% (13/52), protocol in 69% (36/52), and rule out chronic rejection in 6% (3/52) of cases. LCTs were completely normal in 54% (14/26) of patients at the time of post-SVR biopsy. The biopsies in 88% (23/26) of patients continued to exhibit portal interface hepatitis and lobular necroinflammatory activity, consistent with recurrent HCV hepatitis, even after SVR was achieved. In 19% (5/26) of patients, there was progression to periportal or bridging fibrosis despite SVR (all within 1 year of SVR), while in 35% (9/26) there was no change in fibrosis, and 27% (7/26) there was regression of fibrosis (7/26).
Conclusions: The advent of highly effective HCV treatment has now made clinical 'cure' possible for more patients. Current AASLD guidelines state that "hepatitis C-related liver injury stops," in patients "deemed to have achieved an SVR." This study, however, illustrates that in the post-transplant setting: 1) most (88%) patients continue to exhibit histologic features of recurrent HCV hepatitis in biopsies obtained after SVR is attained and 2) a proportion of such patients (19%) demonstrate progression of fibrosis. This suggests that there may be persistent HCV effects in the liver or there may be another process resulting in a chronic hepatitis pattern mimicking HCV, such as idiopathic post-transplantation hepatitis.

1701 Fibrolamellar Carcinoma: Proposal for a New Staging System

Zhen Yan, Michael Torbenson, Carlos Corvera, Dhanpat Jain, Tsung-Teh Wu, Matthew Yeh, Sanjay Kakar. University of California, San Francisco, CA; Yale University, New Haven, CT; Mayo Clinic, Rochester, MN; University of Washington, Seattle, WA.
Background: Local invasion and lymph node(LN) spread are more common in fibrolamellar carcinoma(FLM) than HCC. AJCC T stage for HCC is based on size, multiple tumors and vascular invasion(VI). The relevance of these parameters in FLM staging has not been systematically examined.
Design: An extensive literature search yielded 34 series with at least 10 FLM cases;20 studies(including previous series by us) had studied prognostic features in FLM and were reviewed.
Results: Resectability,LN spread and distant metastasis were the most significant adverse factors.Size and multiple tumors did not affect outcome; microscopic VI and AJCC stage were associated with adverse outcome in half of the studies. Gross VI and direct extrahepatic invasion led to poor outcome in anecdotal cases. A modified staging scheme is proposed based on this data.

Feature	No. of studies showing		Per current AJCC
	Adverse outcome	No adverse outcome	
Size	0	7	> 5 cm is T3
Multiple tumors	2	6	Determines T1 vs. T2
Vascular invasion	4	4	Determines T1 vs. T2
Gross VI	5	0	Defining feature of T3; limited data in FLM
Lymph node met	6	3	Defining feature of stage IVa
Resectable	1	10	Not explicitly stated as part of AJCC staging
AJCC Stage	3	4	Does not predict adverse outcome in > half of studies

T1: Resectable tumor, confined to liver, no vascular invasion	N0: No LN metastasis N1: LN metastasis
T2a: Resectable tumor with microscopic vascular invasion and/or microscopic direct extrahepatic invasion	
T2b: Resectable tumor with gross extrahepatic invasion	M0: No metastasis M1: Metastasis (including non-regional LN)
T3: Resectable tumor with gross vascular invasion	
T4: Unresectable tumor	
T4a: Confined to liver	
T4b: Gross extrahepatic spread or gross vascular invasion	
Stage I:T1N0M0 Stage IIA:T2aN0M0 IIB:T2bN0M0	
Stage IIIA:T3N0M0 IIIB:T1N1M0;T2N1M0	
Stage IVA:T4aN0M0 IVB:T3N1M0;T4bN0M0 IVC:Any T Any N M1	

Conclusions: Size and multiple tumors are used for AJCC HCC staging, but are not relevant in FLM. AJCC stage did not correlate with survival in majority of the series. The proposed staging places emphasis on tumor resectability, the single most important prognostic factor in FLM. In view of the upcoming 8th edition of AJCC Cancer Staging, this is a good opportunity to make clinically relevant changes to staging systems.

1702 Immunohistochemical Study To Differentiate Intrahepatic Cholangiocarcinoma From Metastatic Adenocarcinoma To the Liver

Xuebin Yang, Parvez Lokhandwala, Sarah Voss, Carla Caruso, Faye Smith-Chakmakova, Dipti Karamchandani, Zhaohai Yang. Pennsylvania State Hershey Medical Center, Hershey, PA.
Background: Determination of the origin of adenocarcinoma in the liver is often challenging but critical to optimal patient management and prognostication. There is no specific marker(s) for intrahepatic cholangiocarcinoma (ICC) thus differentiation from metastatic adenocarcinoma is not always possible. We sought to evaluate the value of some of the available markers in this differentiation.
Design: Surgically resected adenocarcinomas, including 26 ICC, 38 triple-negative ductal carcinomas of the breast (TNB), 45 esophageal adenocarcinomas, 30 gastric adenocarcinomas, 18 gallbladder adenocarcinomas, 35 lung adenocarcinomas, and 79 pancreatic ductal carcinomas were retrieved. Tissue microarrays were constructed from representative areas of each tumor and benign control tissue. Immunohistochemistry was performed for GATA3, SLC10A1, SLC10A2, N-Cadherin, bile salt export pump (BSEP), and pancreatic stone protein (regenerating protein 1α/REG1A).
Results: As shown in the table, GATA3 was positive in 73.7% TNB, but rare in other adenocarcinomas. SLC10A1 was variably positive all adenocarcinomas from 23.7% to 65.7%. SLC10A2 was positive in 38.5% ICC, 38.9% gallbladder, 22.9% lung but rare in other carcinomas. N-Cadherin was mainly positive in ICC (50%). BSEP positivity was rare or none in any of the tumors. REG1A was positive in 6.7% esophageal, 16.7% gastric, 11.1% gallbladder and 13.9% pancreatic carcinoma, but negative in ICC, lung and breast TNB.

Tumor type	Total (n)	GATA3 (n/%)	SLC10A1 (n/%)	SLC10A2 (n/%)	N-Cadherin (n/%)	BSEP (n/%)	REG1A (n/%)
ICC	26	0 (0%)	17 (65.4%)	10 (38.5%)	13 (50%)	0 (0%)	0 (0%)
Breast (TNB)	38	28 (73.7%)	9 (23.7%)	1 (2.6%)	3 (7.9%)	0 (0%)	0 (0%)
Esophagus	45	0 (0%)	24 (53.3%)	1 (2.2%)	0 (0%)	0 (0%)	3 (6.7%)
Stomach	30	0 (0%)	11 (36.7%)	2 (6.7%)	0 (0%)	0 (0%)	5 (16.7%)
Gallbladder	18	1 (5.6%)	11 (61.1%)	7 (38.9%)	0 (0%)	0 (0%)	2 (11.1%)
Lung	35	0 (0%)	23 (65.7%)	8 (22.9%)	1 (2.9%)	1 (2.9%)	0 (0%)
Pancreas	79	6 (7.6%)	34 (43%)	7 (8.9%)	2 (2.5%)	0 (0%)	11 (13.9%)

Conclusions: Our data confirmed the predominant expression of N-Cadherin in ICC and GATA3 expression in breast carcinoma including TNB. REG1A and SLC10A2 may have some value in differentiating ICC from pancreatic adenocarcinoma in a subset of cases. SLC10A1 or BSEP is not useful.

1703 Pigmented Hepatocellular Neoplasms Have a High Risk for Atypia and Malignancy

Saba Yasir, Taofic Mounajjed, Michael Torbenson. Mayo Clinic, Rochester, MN.

Background: Pigment deposition is occasionally seen in hepatocellular neoplasms (HN), some of which are densely pigmented and called pigmented hepatic adenoma (HA). Several case reports suggest that pigmented HA has an increased risk for malignancy, but pigmented HNs remain poorly studied.

Design: 108 well-differentiated HNs diagnosed or submitted for consultation as HA or atypical HA, were retrospectively reviewed for pigment deposition; 26 (24%) had pigment identified within hepatocytes at 10x magnification. Pigmented HNs were stained for iron and reticulin, and immunostains for liver fatty acid binding protein (LFABP), β-catenin, gluthamine synthesase (GS), C-reactive protein (CRP), serum amyloid A (SAA), glypican3 (GPC3), and ki67. A subset was evaluated by electron microscopy (EM).

Results: All cases were negative for iron and EM confirmed the pigment was lipofuschin. Lipofuschin showed intense granular staining with GPC3 in 23 (88%) cases, but no diffuse cytoplasmic staining was seen. 11 cases were classified as HA (42%), 6 as HN of uncertain malignant potential (HUMP) (23%), and 9 as hepatocellular carcinoma (HCC) (35%). Of the 9 HCCs, 4 arose in a pigmented HA (overall rate of malignant transformation in pigmented HA: 27%). Most patients (21, 81%) were female, but males (5, 19%) only had HCC (4) or HUMP (1). The average age at diagnosis was 38 years. Tumors averaged 8.1 cm in size. 10 patients (38%) had multiple HNs (2 to >50). Other HNs were not pigmented in 9/10 (90%) of patients with multiple HNs, but only the pigmented HNs had atypia or malignancy, leading to a diagnosis of HUMP or HCC in 4 of the 9 patients. By immunophenotype, HNs were HNF1α inactivated in 13 (50%) cases (8 HA, 4 HUMP, and 1 HCC), β-catenin activated in 7 (27%) cases (6 HCC and 1 HUMP), inflammatory in 3 (12%) cases (2 HA and 1 HUMP), concurrently β-catenin activated and inflammatory in 1 HA, concurrently HNF-1α inactivated and β-catenin activated in 1 HA, and unclassified in 1 HCC. Ki67 was <1% in 24 (92%) cases, and increased in 2 cases (1 HUMP and 1 HCC).

Conclusions: Phenotypically, pigmented HNs represent a heterogenous group, with HNF-1α inactivation being the commonest phenotype. However, pigmented HNs have an increased risk of atypia and malignancy, with most classified as HUMP or HCC. In fact, even cases classified as HA had a high risk (27%) of malignant transformation. The increased risk of malignancy is further indicated by the fact that only pigmented HNs had atypia or malignancy in patients with multiple pigmented and non-pigmented HNs. Male gender is especially associated with malignancy.

1704 Alterations in Degree of Steatosis of Liver Allografts

Yang Zhang, William Twaddell. University of Maryland, Baltimore, MD.

Background: Liver transplantation for patients with acute liver failure and end-stage liver disease has increased in recent years. The demand for donor livers is increasing and organ shortage has become a significant problem. In response, institutions across the United States have started adopting less stringent guidelines regarding which donor livers they will accept. Steatosis in the donor liver has been extensively studied as a potential prognostic factor for success and outcomes of liver transplantation, with macrovesicular steatosis > 30% associated with worse outcomes. However, steatosis remains a relative contraindication rather than an absolute contraindication, and increasingly steatotic livers are being used in transplantation.

Steatosis is likewise a common finding in assessment of liver allografts for dysfunction. In the current study, we aim to investigate how the degree of steatosis in the liver allograft changes in the immediate post-operative period. By looking at how long it takes a liver allograft to lose its fat in its new host environment, we hope to understand when the histologic finding of steatosis indicates pathology in the host rather than the donor.

Design: We selected cases of orthotopic liver transplantation with multiple biopsies of the liver allograft, which included remarks by the pathologist on the degree of steatosis, and evaluated the degree of steatosis at different time points. Data were analyzed using 1-tailed t-tests.

Results: In patients showing an eventual decrease in liver fat content, such changes happened rapidly. Specimens from this group taken within one week of transplantation had a mean of 52% steatosis, while specimens taken two weeks or more following transplantation showed a mean of 7% steatosis ($p = 0.0005$). In patients showing an eventual increase in steatosis a similar change was seen: within one week of transplantation, biopsy showed a mean of 7% steatosis, while after two weeks the mean was 45%. In this case, the value was not statistically significant, probably due to the small number of cases analyzed.

Conclusions: These results indicate that fat content in a donor liver changes precipitously within the first two weeks following transplant. This occurred in patients with an eventual decrease as well as those with an eventual increase in the level of liver allograft steatosis. The findings suggest that beyond the initial two weeks following orthotopic liver transplantation, steatosis seen in the allograft liver most likely represents pathology in the host rather than pathology in the donor.

1705 Histopathologic Features Related To Progression of Fibrosis in Sequential Biopsies in Non-Alcoholic Steatohepatitis (NASH)

Lei Zhao, Rish Pai, Won-Tak Choi, Qin Shao, Maria Westerhoff, Zu-Hua Gao, John Hart. University of Chicago, Chicago, IL; University of Washington, Seattle, WA; Cleveland Clinic, Cleveland, OH; McGill University, Montreal, QC, Canada.

Background: The goal of this study is to identify histologic features in NASH biopsies useful in predicting progression of fibrosis.

Design: 51 NASH patients who underwent 2 biopsies ³1 year apart were studied. Histologic features (ballooning, Mallory bodies, lobular & portal inflammation, lobular neutrophils, steatosis & fibrosis stage) were scored in initial biopsies. Centrilobular zone (CLZ) CK7+ elements were quantitated by form (scattered single cells, string of cells, or ductules) and degree (mild or florid) in initial biopsies (CK7 & glutamine synthetase immunostains performed). Portal ductular reaction (PDR) was scored as mild or florid. Fibrosis stage (NIDDK system) was scored for follow-up biopsies.

Results: The mean interval between biopsies was 2.5 years (range 1.0-7.5). Fibrosis stage progressed in 51%, was stable in 33%, & regressed in 16%. Histologic features of hepatocellular injury in NASH all correlated with current fibrosis stage, however, none predicted fibrosis progression.

Histologic Features in Initial Biopsy	Fibrosis Stage in Initial Biopsy		Progression of Fibrosis	
	Rs	P Value	Rs	P Value
Steatosis	0.26	0.03	-0.14	0.16
Lobular Inflammation	0.36	0.004	0.11	0.23
Neutrophils	0.31	0.01	0.01	0.46
Ballooning	0.44	0.0006	0.004	0.49
Mallory Bodies	0.44	0.0007	-0.05	0.36
Portal Inflammation	0.31	0.01	0.03	0.42

CLZ CK7+ elements also demonstrated high correlation with current fibrosis stage. Furthermore, florid CLZ CK7+ elements showed positive correlation with fibrosis progression(p=0.06).

CK7+ Elements/DR in Initial Biopsy	Fibrosis Stage in Initial Biopsy		Progression of Fibrosis	
	Rs	P Value	Rs	P Value
CLZ Single Cells	0.13	0.19	-0.11	0.22
CLZ Strings	0.54	0.00002	0.01	0.46
CLZ Ductules	0.54	0.00003	0.17	0.11
CLZ mild CK7	0.28	0.02	-0.14	0.16
CLZ florid CK7	0.52	0.00004	0.21	0.06
PDR mild	-0.06	0.32	-0.18	0.1
PDR florid	0.31	0.01	-0.08	0.28

Conclusions: This study confirms that histologic features of hepatocellular damage in NASH are associated with fibrosis, but these features are not predictive of fibrosis progression. In contrast, florid CLZ CK7+ elements appear to be a histologic feature useful to predict fibrosis progression.

Neuropathology and Ophthalmic Pathology

1706 Genomic Alterations in Skull Base Meningiomas

Malak Abedalthagafi, Wenya Linda Bi, Yu Mei, Brian Alexander, Rameen Beroukhim, Ossama Al-Mefty, Ian Dunn, Azra Ligon, Sandro Santagata. Brigham & Women's Hospital, Boston, MA; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA.

Background: The genomic underpinnings of meningiomas remains incompletely understood, despite their prevalence in adults. We prospectively analyzed the genomic profiles of a large cohort of skull base meningiomas and assessed relevant pathological and clinical variables.

Design: Copy-number-alterations (CNAs) were analyzed using high-resolution array-based comparative genomic hybridization. Factors associated with outcome were assessed.

Results: 140 skull base meningiomas from 139 patients (78F/61M, mean age 55 yrs, range 22-90 yrs) were profiled. The majority of tumors were de novo, 37 were recurrent, and 7 patients harbored multiple intracranial meningiomas. 59 tumors had prior radiation exposure, 28 being radiation-induced,and 31 patients having received post-operative adjuvant radiation. The most common tumor locations were petroclival/petrosal (25), sphenoid wing (13), parasagittal/falcine (28), planum sphenoidale/olfactory groove (10), and tuberculum/clinoid (9), followed by intraventricular, middle fossa, tentorial, torcular, cavernous sinus, and foramen magnum locations. 82 were WHO grade I (38 meningothelial, 13 fibroblastic, 17 transitional, 4 secretory, 4 angiomatous, 2 psammomatous); 51 were grade II (42 atypical, 7 chordoid, 2 clear cell); and 7 were grade III (6 anaplastic, 1 rhabdoid). 18 tumors exhibited brain invasion and 37 had intratumoral necrosis. Monosomy 22 was the most frequent copy-number alteration, occurring in 56%. Frequently observed alterations included: loss of chromosome 1p (all:41%, grI:10%, gr II:78%, grIII:83%); 6q (all:22%, grI:5%, grII:50%, grIII:100%); 7p (all:15%, grI:0%, grII:33%, gr III:83%); 10q (all:10%, grI:2%, grII:22%, grIII:33%); and 18q (all:16%, grI:3%, grII:33%, grIII:83%). The incidence of chromosomal loss varied significantly by location. Meningiomas involving the sagittal sinus, torcula, and cavernous sinus harbored the highest rate of CNAs (1p-:65%; 6q-:29%; 18q-:29%; monosomy 22:76%). Petrosal/petroclival and sphenoid meningiomas also expressed higher CNAs than planum sphenoidale/olfactory and tuberculum/clinoid meningiomas. Polysomy involving multiple chromosomes characterized angiomatous meningiomas.

Conclusions: Traditional histopathologic classifications fail to fully account for the natural history and growth patterns of intracranial meningiomas. Systematic genomic characterization of a large series of skull base meningiomas reveal distinct subsets of tumors, which may be further correlated with clinical outcomes.