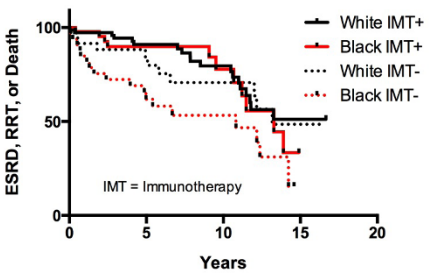
prior to 1998 were excluded. Survival was defined as the time from initial biopsy to eGFR < 15mL/min, renal replacement therapy, or death. Immunotherapy (IMT) was defined as any treatment with cyclophosphamide, azathioprine, mycophenolate mofetil, or rituximab.

Results: 211 patients had follow-up data (AA=80, W=106, Asian=7, NS=18). African Americans (AA) had a larger proportion of class V LN at presentation (27% vs. 16%, p=0.04). Age, BP, BMI, Diabetes, SCr, 24h protein, C3, C4, ANA, and anti-dsDNA Ab positivity were similar between AA and white patients. Results are mean (SD). Baseline characteristics of other groups were not different (not shown). Overall, AA had shorter survival compared to white patients [HR 1.7, 95% CI: 1.0 to 2.8, p=0.042]. Similarly, AA without IMT had shorter survival compared to white patients without IMT [HR 2.2, 95% CI: 1.0 to 4.8, p=0.046]. However, AA with IMT did not have different survival compared to white patients with IMT [HR 1.1, 95% CI: 0.5 to 1.1 , p=0.71].

Conclusions: Immunotherapy reduces the risk for progression to ESRD and closes the gap in racial disparities between African American and white patients.

*=Baseline #=Follow-up	Black	White
*No. Patients (%Female)	94 (84)	132 (80)
*Age	35.6 (14)	32.9 (14)
*SCr	1.4 (1.2)	1.3 (0.9)
*24h Protein	3.9 (2.5)	2.9 (2.4)
*ISN/RPS Class II	15	20
III/IV	49	82
III/IV+V	3	8
V	26	22
VI	1	0
#No. Patients with Follow-up	80	106
#Median Follow-up (y)	5.2	7.0
#Median Survival (y)	12.1	16.5
#ESRD or RRT	14	22
#Death	15	9
#Immunotherapy	58%	66%



Liver

1629 Clinical and Pathologic Features of Nutritional and Herbal Supplements Induced Liver Injury

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Background: Certain nutritional and herbal supplements may have potential hepatotoxic effects. With increasing use of these supplements in the general population, supplements-induced liver injury (SILI) has become a common problem clinically. However, there is not much data about the clinical and pathologic features of SILI, and pathological characteristics of SILI have not been defined.

Design: All liver biopsy cases with diagnoses of hepatitis or liver injury were reviewed from our pathology database from 2014-2015. The cases of SILI were confirmed by pathological and clinical correlation. Pre-biopsy liver function tests (LFTs) were collected from the electronic medical record system. The H&E and Trichrome stain slides were re-assessed for pathologic changes. The morphologic patterns of liver injury, including bile duct injury, portal inflammation, interface hepatitis, lobular inflammation, fibrosis, presence of granulomas, and plasma cell and eosinophil infiltrates were recorded and analyzed.

Results: Total 17 cases of SILI were identified from 323 liver biopsy cases of hepatitis and liver injury. Two of 17 patients with SILI developed acute fulminant hepatic failure and succumbed to the illness. The hepatotoxic nutritional/herbal supplements identified included boswellic acid, carnosyn beta-alanine, whey protein, maca extract, rhodiola, holy basil, creatine, and some unspecified tea and anti-itching supplements. Histologically, the major pattern of liver injury was combined bile duct damage and hepatitis, and the majority of cases showed significant cholestasis. Fibrosis ranged from mild portal fibrosis to cirrhosis. No granulomas were identified. Plasma cells were rare to minimal in all cases, while eosinophils ranged from none up to 12 per high power field. Serologically, the mean values of alanine transaminase, aspartate transaminase, alkaline phosphatase, and total bilirubin were 625 U/L, 447 U/L, 241 U/L, and 12 mg/d, respectively.

Conclusions: Nutritional and herbal supplements have become a common cause of drug induced liver injury that may be under recognized. Histologically, the pattern of SILI in this study is the combination of bile duct and hepatocytic damage, ranging from mild disease to fulminant hepatitis. Significant elevation of LFTs, in combination with mixed pattern of liver injury should trigger the consideration of SILI.

1630 Distinctive Morphologic Pattern and In Situ Hybridization for Albumin Distinguishes Intrahepatic Cholangiocarcinoma from Metastatic Adenocarcinoma

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Background: The distinction of intrahepatic cholangiocarcinoma (IHCC) from metastatic adenocarcinoma is challenging and entails an extensive evaluation to exclude metastatic carcinoma. Albumin, detected on an in situ hybridization platform, is a robust means of distinguishing IHCC from metastatic adenocarcinoma. More recently, IDH1/2 mutations, in the context of biliary tract cancers , have been shown to be highly specific for IHCC. We evaluated the morphologic spectrum of IHCC, in conjunction with albumin expression and IDH mutation status, with the goal of distinguishing IHCC from metastatic adenocarcinoma.

Design: We evaluated 101 cases of IHCC. Histologic patterns evaluated included: anastomosing, tubular, pancreatic, undifferentiated, large duct and cribriform. Targeted sequencing for IDH1/2 mutations and in situ hybridization for albumin was performed in selected cases.

Results: The dominant histologic pattern was anastomosing (41% of cases and as a minor pattern in an additional 24 cases (24%), characterized by angulated anastomosing glands lined by low cuboidal epithelium. Other, albeit less characteristic dominant patterns included tubular (37%); nested (16%), mimicking a neuroendocrine tumor; undifferentiated (10%); pancreatic (6%), mimicking pancreatic ductal adenocarcinoma; large duct (2%); and cribriform (1%). All tumors tested for albumin (60 cases) were positive. There was no correlation between the histologic pattern and strength of the albumin signal with the exception of undifferentiated tumors, 50% of which showed reactivity only seen at 40x objective. 6 of 18 (33%) cases revealed IDH1/2 mutations. A survey of 655 adenocarcinomas, including primary tumors from the gastrointestinal tract, pancreas, lung, breast and ovary, identified only 2 tumors with an anastomosing pattern, both lesions arose in the pancreas.

Conclusions: The presence of an anastomosing growth pattern is highly suggestive of IHCC, noted in 64% of cases. Intratumoral albumin supports a diagnosis of IHCC, and when seen in isolation could also differentiate IHCC from metastatic adenocarcinoma. The combination of an anastomosing histological pattern and albumin reactivity, with or without detection of IDH1/2 mutations, should allow for a definitive diagnosis of IHCC in the vast majority of cases.

1631 Diagnostic Accuracy of the Liver Imaging Reporting and Data System (LI-RADS) for Hepatic Nodules in Cirrhotic Patients: A 2 year Retrospective Analysis

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Background: LI-RADS was created in 2008 by the American College of Radiology to standardize terminology and reporting of CT and MRI for hepatocellular carcinoma (HCC). Imaging plays a critical role in detection, diagnosis, and staging of HCC. The purpuse of our study is to evaluate the diagnostic accuracy of LI-RADS for hepatic nodules in explanted livers.

Design: Between 8/3/2013-8/3/2015, all liver explants with a diagnosis of HCC were retrieved from the pathology electronic record system (CoPath). The histologic diagnosis for each nodule was correlated with the LI-RADS interpretation. For the benign lesions, the histologic diagnosis was documented if the nodule was sampled and the location correlated with that reported radiographically. For the HCCs, the tumor histologic grade, size, multiplicity, and treatment effect were studied.

Results: Final diagnoses of 143 nodules in 67 patients were correlated with the LI-RADS category.

	Histologic Diagnosis in Explant Specimen	
LI-RADS Category	Regenerative Nodule	Hepatocellular carcinoma
0		34 (24%)
1		
2		
3	4 (27%)	11 (73%)
4	1 (9%)	10 (91%)
5	6 (7%)	77 (93%)

11 regenerative nodules and 98 HCCs were documented. An additional 34 nodules of HCC (24% of total nodules) were identified by histology only and not seen on pre-transplant imaging. These nodules ranged in size from <0.1 cm to 4.0 cm. 64% of these nodules measured ≤1.0 cm. Larger nodules (3-4cm) were comprised of many small tumor nodules growing in a military-type pattern. Treatment effect of 73 nodules was correlated with the LI-RADS suspicion (low, moderate, or high) for residual HCC.

Suspicion of residual HCC by imaging	0% viable	1-49% viable	50-99% viable	100% viable
Low	12 (22%)	17 (32%)	18 (34%)	6 (11%)
Intermediate	1 (25%)		2 (50%)	1 (25%)
High	0	3 (19%)	4 (25%)	9 (56%)

Conclusions: LI-RADS category 4 and 5 lesions have high sensitivity (89%) but low specificity (36%) for HCC. Also, a large number of LI-RADS category 3 lesions were HCCs. Many HCCs were detected only histologically when imaging studies reported no suspicious masses. The vast majority of treated tumors, regardless of the radiographic suspicion for residual HCC, did contain viable tumor.

1632 Pathologic Features of Synchronous Hepatocellular and Renal Cell Carcinomas in Non-Cirrhotic Patients

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Background: The development of hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC) in a single patient is rare, and the simultaneous occurrence of these tumors is even more unusual, with only 6 such cases reported in the literature. While RCCs have been subclassified based on morphologic, immunohistochemical, and molecular features, attempts at subclassifying HCCs have been less successful. The presence of HCC in a non-cirrhotic patient who also has RCC raises the possibility of a common genetic defect leading to the development of both tumors, which could indicate that these liver tumors constitute a unique subtype of HCCs. To explore this possibility, we examined the pathologic features of a series of synchronous HCCs and RCCs occurring in non-cirrhotic patients.

Design: Eight cases of simultaneous HCC and RCC were identified from the surgical pathology files of four institutions. H&E slides from the cases were reviewed and morphologic and immunohistochemical features of the tumors were analyzed. Clinical data was also collected.

Results: The median age at presentation was 67.5 years, and 7 of the 8 patients were male. Most of the HCCs were well-differentiated (6/8). Six of the HCCs exhibited areas of intratumoral fibrosis, with 2 cases demonstrating focal fibrolamellar-like morphology. Four of the HCCs showed areas of clear cell change and 4 cases had an associated inflammatory cell infiltrate. The background liver in all cases was free of significant fibrosis, and no patients had underlying chronic liver disease. Of the RCCs, 4 were clear cell RCCs, 2 were papillary RCCs, and 2 were unclassified RCCs. The clear cell RCCs all had Fuhrman grade 2 or 3 nuclei, and 2 of the clear cell RCCs exhibited prominent pseudopapillary areas. Six of the seven RCCs with pathologic staging data available had stage T1a disease. None of the patients had significant underlying kidney disease.

Conclusions: While a handful of case reports on simultaneous HCC and RCC have been published, this study is the first to analyze the pathologic features of a series of synchronous HCCs and RCCs in non-cirrhotic patients. The HCCs in this series were notable for a high frequency of intratumoral fibrosis, clear cell change, and infiltration by inflammatory cells. Molecular analysis is in progress and may provide further insight into the distinctive characteristics of these rare tumors.

1633 Morphoproteomics Provides Tumorigenic Correlates in Hepatitis C-Associated Hepatocellular Carcinoma with and without TACE Treatment

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Background: Hepatitis C virus (HCV) is well known to produce hepatitis and cirrhosis, and in some cases progression to HCV-associated hepatocellular carcinoma (HCC). EZH2 (enhancer of Zeste homolog 2), and the COX (cyclooxygenase)-2 and mammalian target of rapamycin (mTOR) pathways have been implicated in HCV-associated tumorigenesis. The efficacy of TACE (transarterial chemoembolization) treatment on such pathways has not been assessed.

Design: Ten (10) cases of HCV-associated hepatitis and cirrhosis with liver resection were included in the study. Eight (8) cases had HCC. Of these five (5) cases had been treated with TACE. Morphoproteomic analysis for expressions of EZH2, COX-2 and phosphorylated (p)-mTOR (Ser 2448) in the tumor and non-neoplastic liver parenchyma were carried out. This included visual quantification of the signal intensity of the analytes, their subcellular compartmentalization and relative percentage. Percentage of positive cells were graded from 1 to 100% and chromogenic signal intensity graded from 1 to 3.

Results: The nuclear expression of EZH2 was increased in HCC vis-a'-vis the non-neoplastic liver but with a relatively reduced expression in 5/8 cases that had received TACE with doxorubicin chemotherapy. Similarly, the cytoplasmic expression of COX-2 was increased in the HCC cells and p-mTOR (Ser 2448) expression was associated with more nuclear translocation in the tumor, most consistent with increased mTORC2. COX-2 and p-mTOR (Ser 2448) expressions were not appreciably reduced in those treated with TACE.

Conclusions: Morphoproteomics has confirmed the relative overexpression of tumorigenic EZH2, COX-2 and mTOR pathway in HCV-associated HCC vis-à-vis the non-neoplastic hepatic parenchyma with an impact of TACE with doxorubicin therapy on the relative downregulation of EZH2 expression in the residual tumor. Literature review revealed that doxorubicin activates p53 and activated p53 suppresses the *EZH2* gene. Moreover, miR-101 downregulates EZH2 and works synergistically with doxorubicin to induce apoptosis in human hepatocellular carcinoma. The persistent expression of COX-2 and increased expression of nuclear p-mTOR (Ser 2448) regardless of TACE treatment raises the possibility of adjunctive therapies to work with TACE to inhibit these prosuvival pathways. Metformin, which upregulates miR-101 while downregulating EZH2, and inhibits both the COX-2 and mTORC1 and mTORC2 pathways along with celecoxib may be considerations in this context.

1634 Combined Use of Copper Stain and CK7 Immunohistochemistry for Diagnosis of Cholestatic Liver Disease

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Background: Periportal copper deposition is seen in 50-94% of chronic cholestastic diseases like primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). Hepatocytes in normal liver are negative for CK7, while periportal hepatocytes acquire a CK7 positive biliary phenotype in at least 70% of biopsies with chronic cholestatic disease. CK7 is expressed to a variable degree in non-cholestatic diseases such as AIH (10%) and chronic venous outflow obstruction (90%). The use of copper and CK7 can be help distinguish chronic biliary disease from hepatitic disease, but the utility of combined use of copper stain and CK7 in liver disease has not been examined in detail.

Design: Copper and CK7 stains were evaluated in liver biopsies in 42 AIH, 23 PBC, 13 PSC and 18 VOO cases. Copper stain was scored as 0 (negative), 1 (up to 2 hepatocytes) and 2 (>2 hepatocytes). CK7 stain was scored as 0 (negative), 1 (focally positive in at least 3 hepatocytes) and 2 (multifocally positive in >3 hepatocytes). Each case was divided into low stage (no bridging fibrosis) and high stage (bridging fibrosis/cirrhosis).

Results: The sensitivity of copper stain was 52% and 62% for PBC and PSC respectively(all 2+), while that of CK7 was 78% and 61% respectively(71% and 55% 2+). Specificity of copper is 93% vs. 74% of CK7. Combined use of copper and CK7 increased the sensitivity to 77% in PSC (all cases) and 57% in low stage disease. In AIH, copper and CK7 stain were positive in 7% and 26% cases (5% and 20% 2+); all low stage cases were negative. Both copper and CK7 were positive in nearly half of biliary diseases compared to 5% of high stage AIH. Cholestatic features in VOO were more readily demonstrated by CK7 compared to copper stain.

	Copper +	CK7+	Copper and/or CK7+
PBC All cases (n=23) Low stage (n=19)	 12 (52%) 10 (53%)	 18 (78%) 14 (74%)	 18 (78%) 14 (74%)
PSC All cases (n=13) Low stage (n=7)	 8 (62%) 2 (29%)	 8 (62%) 3 (43%)	 10 (77%) 4 (57%)
AIH All cases (n=41) Low stage (n=12)	 2 (5%) 0 (0%)	 10 (24%) 0 (0%)	 10 (24%) 0 (0%)
VOO (n=18)	3 (17%)	13 (72%)	13 (72%)

Conclusions: Periportal CK7 has higher sensitivity than copper stain in demonstrating chronic cholestasis, while copper stain is more specific. Combined use of both stains increases the sensitivity for diagnosis for PSC, and increases specificity for PBC/PSC vs. AIH diagnosis. Positive result with both stains strongly points to biliary disease even in high stage setting. Combined use of copper and CK7 stains is recommended in liver biopsies for all cases of suspected chronic biliary disease.

1635 Aldoketoreductase Family 1B10 (AKR1B10) Is a Sensitive Biomarker to Identify Well-Differentiated Hepatocellular Carcinoma

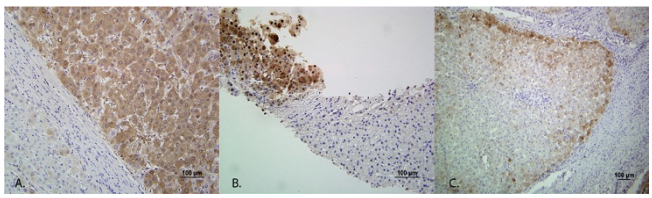
Andrew Bandy, Xiaoming You, Haonan Li, Jie Liao, Sambasiva Rao, Xiaoqi Lin, Guang-Yu Yang. Northwestern University, Chicago, IL.

Background: Well-differentiated hepatocellular carcinoma (WD-HCC) is the most common primary malignant hepatic neoplasm which is extremely challenging for a pathologic diagnosis, particularly for needle core biopsy specimens. Although there are many immunohistochemical and special stains currently employed to aid in distinguishing this malignant disease from metastatic diseases and benign lesions in the liver, each has varying usefulness depending on the differential diagnosis. One recently described protein, AKR1B10, may aid in distinguishing HCC from its benign mimickers, as AKR1B10 has been shown to be upregulated in many HCCs.

Design: A total of 63 cases of HCC were retrieved from our institution, including 23 core needle biopsies and 40 liver explants. Immunohistochemistry for AKR1B10 was performed for all cases with proper positive and negative controls. AKR1B10 staining was evaluated based on intensity of cytoplasmic staining of tumor cells (negative, weak, moderate and strong) and the proportion of overall tumor that stained (<10%, 10-50% and >50%).

Results: In this cohort, 49/63 (78%) of the WD-HCCs showed moderate or higher staining intensity with AKR1B10 in >50% of tumor cells, including 37/63 cases (59%) which displayed strong staining (Fig. 1a). When considering the utility of AKR1B10 in needle core biopsies, 23/23 cases exhibited strong staining, and 20/23 (87%) exhibited strong staining in >50% of tumor cells (Fig. 1b). The morphologically normal liver parenchyma remote from HCC showed negative AKR1B10 staining. Focal and weak positive staining was observed in benign hepatocytes adjacent to HCC (Fig. 1c).

Conclusions: Our study demonstrated that AKR1B10 is upregulated in WD-HCCs. AKR1B10 is a sensitive marker for distinguishing benign hepatocytes from WD-HCC, and this is particularly true in limited sample specimens such as needle core biopsies where architecture cannot fully be assessed.



1636 Unique Morphologic and Clinical Features of Liver Nodular Regenerative Hyperplasia - Single Institution, Large Cohort Study

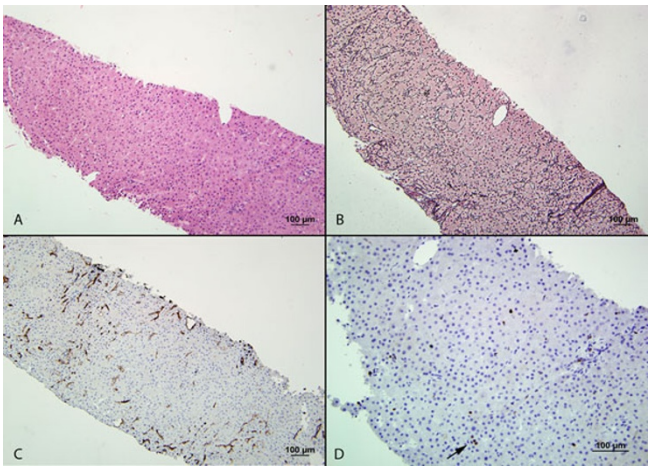
Adam Beattie, Haonan Li, Xiaoming You, Jie Liao, Sambasiva Rao, Guang-Yu Yang. Northwestern University, Chicago, IL.

Background: Nodular regenerative hyperplasia (NRH) is a challenging pathologic diagnosis. Generally, histologic diagnosis is key, with morphologic features of 1) nodular architecture without portal fibrosis as demonstrated by reticulin and 2) two distinct cell populations within the nodule (central hypertrophied hepatocytes and peripheral small/compressed hepatocytes); but inter-observer agreement is poor. Thus, a single institution large cohort of patients was analyzed for clinical, morphologic and immunophenotypic features, and a potential unique set of biomarkers for the diagnosis.

Design: A cohort of 14 NRH were retrieved from our institution from 2010-2015. All cases were confirmed to be NRH based on H&E and reticulin (Fig. 1a and 1b). The age ranged from 29 to 69 years, with the average age being 54. CD34, Ki-67, and glutamine synthetase expression was determined by immunohistochemistry on paraffin embedded sections. 5 cases of cirrhosis and 5 cases of focal nodular hyperplasia (FNH) were evaluated for comparison.

Results: The common clinical and radiographic findings were ascites/portal hypertension (9/14), viral hepatitis/drug toxicity (10/14) and a cirrhotic appearance (7/12). The biomarker profile (CD34, Ki-67, and glutamine synthetase) demonstrated that in NRH, CD34 showed greater staining within the sinusoidal endothelial cells of the small/compressed hepatocyte zone, which corresponded to zone 1 of the hepatic lobule (Fig.1c). In cirrhosis, CD34 labeled the sinusoidal endothelial cells located at the periphery of nodule, while zones 1 and 2 sinusoidal endothelial cells were positive in FNH. Ki-67 showed a similar staining pattern as CD34 in NRH with Ki-67-labeled proliferative hepatocytes being higher in the small/compressed hepatocyte zone (Fig.1d). Lastly, glutamine synthetase showed positive staining in the hypertrophied/perivenular hepatocyte zone in NRH, while FNH demonstrated the characteristic "map-like" distribution in zone 3 of hepatic lobule.

Conclusions: Our results show distinct clinical and immunostaining features for NRH. We demonstrated that the peripheral small/compressed hepatocyte zone in NRH is primarily within zone 1 of the hepatic lobule. These markers together with reticulin stain can serve as surrogates to identify NRH.



1637 Is Von-Meyerberg Complex Preneoplastic for Intrahepatic Cholangiocarcinoma?

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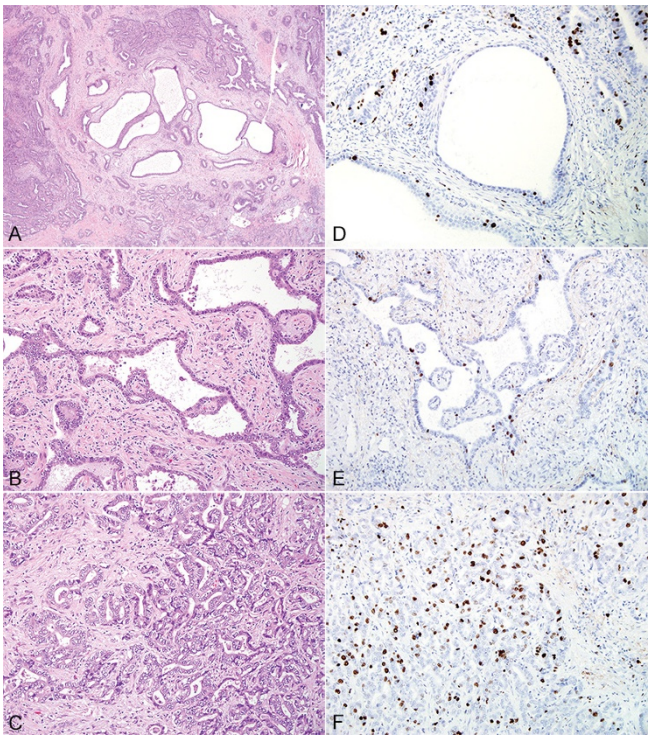
Background: Von-Meyerberg complex (VMC) is generally thought to be indolent. Rare cases of intrahepatic cholangiocarcinoma (iCC) have been reported in association with VMC. In this study, we aimed to evaluate any association between VMC and iCC.

Design: A database search was carried out for cholangiocarcinoma resected during 2007–15. The presence of VMC, dysplasia, tumor differentiation, mitoses were evaluated. Representative sections consisting of both iCC and associated VMC (20 cases) were immunostained with Ki67.

Results: Archived pathology material from 52 patients (mean age 47 years;33–82 years;30 female) with iCC were included. Among them, 21 (40.4%) had associated VMC adjacent to iCC and 2 (3.8%) had dissociated VMC away from tumor. The 21 iCCs present in association with VMC showed a gradual epithelial progression from benign to low- and high-grade biliary dysplasia, and finally iCC [figure1](1a,b,c). Although three cases (5.8%) did not display a benign component of VMC, iCC per se showed architecture resembling VMC where the ductal lining was replaced by dysplastic cells with low or high grade dysplasia and was in proximity to conventional iCC. Among 21 cases with associated VMC, 9 (42%) showed wide spectrum of tumor differentiation,with well differentiated neoplasm in proximity to VMC and poor differentiation at the periphery. One of the well-differentiated iCCs displayed morphologic similarity to VMC in nodal metastasis. Additionally, Ki67 proliferative index demonstrated a gradual increase from benign VMC (range:0–3%) to low-grade biliary dysplasia (3–8%), high-grade biliary dysplasia (4–12%), and iCC (8–55%) (figure 1)(1d,e,f). In one case, VMC and adjacent iCC showed the highest Ki67 indices, 3% and 55%, respectively.



Conclusions: Morphologically, an association between VMC and iCC is appreciated in 40% of cases in this study that illustrates a gradual epithelial neoplastic progression from VMC to dysplasia and finally iCC. In addition, Ki67 proliferative index supports the continuing dysplastic evolution. Taken together, VMC could be preneoplastic, renovating the conventional concept as being innocuous. What molecular events drive the dysplastic progression? What is the incidence rate? There are more questions that await further investigation.

1638 Different Types Of Glutamine Synthetase Immunostaining in Hepatocellular Adenoma

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Background: Diffuse homogeneous glutamine synthetase (GS) staining is used as a surrogate marker to identify b catenin mutated hepatocellular adenoma (b-HCA) without or with associated inflammatory features [b-catenin mutated inflammatory HCA (b-IHCA) expressing CRP]. Both groups are at a higher risk of malignant transformation compared to other HCA subtypes. In non b-catenin mutated HCA (HNF1a mutated HCA, IHCA and unclassified HCA), GS staining is absent to the exception of minor staining around some hepatic veins (HV). In between the 2 extremes: no GS expression and diffuse / homogeneous GS positivity, abnormal GS staining has been observed. The aim of this study was to review all our surgical HCA cases with abnormal GS expression.

Design: GS staining was classified in 3 groups.1- Diffuse and homogeneous GS; 2- diffuse and heterogeneous GS (from strong to mild and from few to many positive cells); 3- GS spill over HV (from more than 3 rows up to bridges between HV); in the remaining areas of this group, GS was either absent or formed patches of irregular size. B-catenin nuclear staining was semi-quantified according to the number of stained nuclei (none, rare, some to many). CD 34 staining was noticed as well as HCA with borderline lesions (cytological and structural abnormalities) or hepatocellular carcinoma foci.

Results: Sixty HCA cases with abnormal GS were found, classified as 26 b-HCA and 34 b-IHCA. Among b-HCA 12, 10 and 4 belong to GS groups 1, 2, and 3 respectively. Among b-IHCA 14, 5 and 15 belong to the GS groups 1, 2 and 3 respectively. In GS group 2 and 3 a GS positive border was always observed. CD 34 positivity was extended and often diffuse in GS group 2 and 3 except at the GS positive border. B-catenin nuclear staining was obviously positive in 23/26 HCA of GS group 1, positive in rare nuclei in 7/15 HCA of GS group 2 and negative in GS group 3 (19/19). Borderline lesions or HCC foci were present in 14/26 cases in group 1, 7/15 in group 2 but none in group 3.

Conclusions: GS classification can be easily applied on surgical specimens. Diffuse and homogeneous GS remains the best marker to identify HCA at risk of malignant transformation, HCA with diffuse and heterogeneous GS are at a lower risk. GS data, that need to be correlated to b-catenin gene alterations, are of clinical relevance to manage patients.

1639 Molecular and Cytogenomic Profiling of Hepatic Adenocarcinoma Expressing Inhibin, a Mimicker of Neuroendocrine Tumors: Proposal to Reclassify as "Cholangioblastic Variant of Intrahepatic Cholangiocarcinoma"

David R Braxton, Debra F Saxe, Kristen Stashek, Stuti G Shroff, Naveena Damjanov, Jennifer JD Morrissette, Rashmi Tondon, Emma E Furth. University of Pennsylvania, Philadelphia, PA; Emory University, Atlanta, GA.

Background: A single case report exists in the literature of hepatic adenocarcinoma expressing InhibinA (InhA) in a young woman in which the authors proposed it to be a rare variant of intrahepatic cholangiocarcinoma (iCCA). We present novel molecular, genetic and outcome data in three cases occurring in young women, preoperatively diagnosed as well differentiated neuroendocrine tumors (NET) on core needle biopsy, with a lineage differentiation model leading us to propose a new tumor classification.

Design: Clinical, pathological, and outcome data were collected. Immunohistochemical (IHC) profiling was performed along with next generation sequencing (NGS) using the Truseq 47 gene solid tumor panel (Illumina), and cytogenomic profiling via the OncoScan FFPE SNP microarray (Affymetrix). IHC for InhA, chromograninA (ChrA), and synaptophysin (Syn) was studied in iCCA, hepatocellular carcinoma [HCC], hepatoblastoma, NET, and fetal liver.

Results: Chronic liver disease and risk factors for iCCA were absent from the resection specimens and clinical histories of all three patients. Two patients recurred with metastatic disease at 6 months and 38 months status post partial hepatectomy, with one confirmed death at 44 months. Histological patterns present in the tumors included solid, organoid, microcystic, and blastemal-like. IHC was positive for cytokeratin 7 in 2/2, cytokeratin 19 in 3/3, inhibinA in 3/3, ChrA in 3/3, Syn in 2/2, Sox9 in 1/1 and HepPar1 in 0/3. NGS was negative for pathogenic mutations. Recurrent cytogenomic abnormalities included gains of 8q and 17q, and losses of 1p, 4q, 6q, 16p, which include genes involved in WNT signaling, TGFbeta signaling, DNA damage repair, RNA processing, and chromatin remodeling. InhA was expressed in 1/10 (10%) iCCA, 2/14 (14%) HCC, in the biliary component of 1/4 (25%) combined HCC-iCCA, 0/4 hepatoblastomas, 0/1 fibrolamellar HCC, and 1/8 (13%) metastatic NET. One of eight (1/8) fetal liver tissues expressed inhA in the developing bile ducts.

Conclusions: Based on our unique clinical, morphological, and molecular data, we propose a molecular pathogenetic model and classification name of "cholangioblastic variant of intrahepatic cholangiocarcinoma" for this rare malignancy. Accurate identification on core biopsy is crucial for clinical management as it may mimic neuroendocrine neoplasms. The true prevalence of this tumor is unknown as it has undoubtedly been previously misclassified.

1640 Histologic Comparison of Donation after Cardiac Death (DCD) Liver Transplant Recipients with Non-Hepatitis C (HCV) Related Cirrhosis

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Background: Liver transplantation (OLT) using DCD donors is becoming increasingly necessary, but histologic features of DCD OLT are not well defined.

Design: Histologic findings in liver biopsies (n=90) from age matched DCD (n=32) and non-DCD (n=58) recipients negative for HCV were reviewed in a blinded fashion. Biopsies were subgrouped into time 0, 0-6 months (m), and >6 m.

Results: The most common DCD and non-DCD pre-OLT diagnoses were cryptogenic cirrhosis (30% vs 48%), alcoholic steatohepatitis (17% vs 22%), and non-alcoholic steatohepatitis (13% vs 9%). At time 0, zone 3 hepatocyte dropout (p=0.01) and confluent (p=0.04) necrosis were more common in DCD. DCD patients had less portal inflammation (PI, p=0.04). Reperfusion injury was diagnosed more in the DCD group (p=0.01).

At 0-6 m, more zone 3 dropout (p=0.02) and confluent (p=0.02) necrosis were still present in the DCD group. Ductular reaction (DR) with neutrophils (PMN, 42% vs 30%) was seen more in DCD, though not statistically significant. Pericholangitis was similar in both cohorts, while cholangitis was noted more in non-DCD (table 1). PI was less severe in the DCD group.

At >6 m, pericholangitis (37% vs 11%), cholangitis (25% vs 11%), and DR with PMN (37% vs 28%) were noted more in DCD. Features of obstruction were noted in all DCD cases. Mild acute rejection (25% vs 0%) was seen more in DCD, whereas non-DCD had more indefinite for rejection and chronic rejection (0% vs 6%). Clinically, DCD donors were younger (26 vs 60, p<0.01). The warm and cold ischemia times and 1 year graft survival were similar between the two groups.

	Time 0		Follow-Up 0-6 m		Follow-up >6 m	
	DCD/Non-DCD	p-value	DCD/Non-DCD	p-value	DCD/Non-DCD	p-value
Total Biopsies	18/17		24/40		8/18	
Portal Inflammation (%)	66/94	0.04	75/98	0.05	100/89	0.3
Pericholangitis (%)	17/18	0.9	25/25	1	37/11	0.1
Cholangitis (%)	0/6	0.3	4/15	0.2	25/11	0.4
DR with PMN (%)	33/47	0.4	42/30	0.3	37/28	0.6
Zone 3 Dropout (%)	95/60	0.01	80/50	0.02	0/11	0.5

Conclusions: Although not evident in the early OLT period, biliary alterations were more common in the DCD group 6 m after OLT raising concern for vulnerability to biliary injury. There were more features of parenchymal ischemia in the early OLT period in DCD patients indicating poor graft perfusion. However, 1 year graft survival between the two groups was similar suggesting graft recovery.

1641 Prognosis of HER2 Expression in Cholangiocarcinoma

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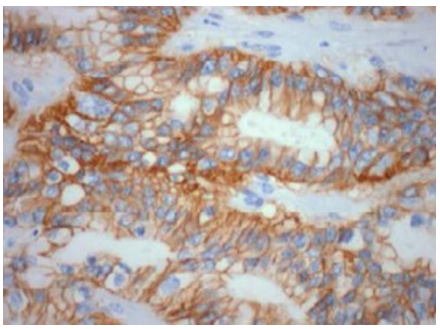
Background: The tumors of the biliary tract can arise anywhere in the biliary tree or less frequent from transdifferentiation of hepatocytes. This tumor is lethal with heterogeneous behavior and complex molecular biology representing 0.6-1% of tumors among adults. Several studies highlight the role of HER2 in cholangiocarcinoma pathogenesis and its expression seems to be present from the onset of carcinogenesis. The prognostic value of HER2 in this population is a matter of debate and the pattern of expression of HER2 is heterogeneous as in gastric cancer. The aim of this study was to evaluate the prognostic role of HER2 by immunohistochemistry using the methodology validated for gastric cancer in a western population with cholangiocarcinoma.

Design: We have done a retrospective review of clinical and pathological features on electronic medical charts of patients with cholangiocarcinoma and HER2 immunohistochemistry testing using gastric cancer methodology. Statistical associations between individual variables and OS were analyzed using the log-rank test. Individual variables with a *P* value less than 0.2 in univariate analysis were tested in a multivariate analysis, using the Cox proportional hazards model.

Results: Among the 46 patients selected, 38 were evaluated for the expression of HER2. The expression of HER2 (2 or 3+) was found in 30% of the cases. In multivariate analysis, the expression of HER2 (2 or 3 +) was a independent prognostic factor of overall survival with a HR for mortality of 3.08 (1.23 to 7.28) with *P*=0.01. This prognostic factor was observed in both localized and metastatic disease.



Conclusions: HER2 immunohistochemistry using gastric cancer methodology was positive (2 or 3+) in 30% of our western population of cholangiocarcinoma and was an independent prognostic factor. Prospective studies are needed to validate the best method for assessing HER2 expression and if there is a predictive value for using anti-HER therapy in this selected population.

1642 Combination of Astrocyte Elevated Gene 1 and Glypican 3 Immunochemistry Improves Diagnostic Accuracy of Hepatocellular Carcinoma

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Background: Expression of Glypican 3 (GPC-3) is often negative or patchy/focal positive in well to moderately differentiated hepatocellular carcinomas (HCC), although GPC-3 is considered as a specific marker in differentiating poorly differentiated HCC from benign hepatocellular proliferation or metastatic carcinoma. Additional markers are needed to assist diagnosing early hepatocellular neoplasms. Recently, astrocyte elevated gene 1 (AEG-1) was identified as a new diagnostic marker for HCC. We studied the diagnostic values of AEG1, GPC-3 and combination of both markers in HCC.

Design: AEG-1 and GPC-3 were studied by immunohistochemistry in a total of 46 resected tumors from 37 HCC patients. They included 37 HCCs (9 well, 20 moderately and 8 poorly differentiated) with adjacent nonneoplastic liver tissues (NON), and 9 dysplastic nodules (DN). The staining of AEG-1 and GPC-3 were evaluated and assigned to one of the following categories: negative, weak staining or ≤5% of tumor cells with moderate to strong staining; positive, moderate or strong staining seen in >5% but ≤50% (focal), or diffuse, in >50% (diffuse) of the tumor cells. Fisher exact analysis was applied to compare the proportions between the groups.

Results: Positive AEG-1 and GPC-3 staining was seen in 91.9% (34/37) and 56.8% (21/37) of HCCs respectively. Diffuse AEG-1 staining was seen in 89% of HCCs, 5% of DNs and 11% of NONs. Diffuse positive GPC-3 was found in 41% of HCCs, 5% of DNs and 0% NONs. 14 (4 well, 6 moderately, and 4 poorly differentiated) GPC-3 negative and 5 (1 well and 4 moderately differentiated) GPC-3 focal positive HCCs showed diffuse positive staining of AEG-1. Two AEG-1 negative HCCs showed focal positive GPC-3 staining. One moderately differentiated HCC was negative for both AEG-1 and GPC-3. The sensitivity and specificity for diffuse AEG-1 staining was 89% and 95% respectively. The sensitivity and specificity for diffuse GPC-3 staining was 41% and 100% respectively. The sensitivity and specificity was 94% and 95% for the combination of diffuse AEG-1 and GPC-3 staining.

Conclusions: AEG-1 shows better sensitivity than GPC-3, whereas GPC-3 appears more specific for HCC. AEG-1 combined with GPC-3 may be a promising approach to discriminate HCC from benign hepatocellular proliferation.

1643 10% of Well Differentiated Hepatocellular Carcinomas Are Negative for Arginase-1 on Needle Biopsies: An Important Diagnostic Pitfall

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Background: The arginase-1 immunostain is an excellent marker of hepatocellular differentiation and is a sensitive and specific marker for hepatocellular carcinoma (HCC). However, we have anecdotally encountered occasional well-differentiated HCC (WDHCC) that were negative for arginase-1, including cases submitted for surgical consultation. The aim of this study was to assess the prevalence of arginase-1 positivity in WDHCC on needle biopsy material.

Design: 68 consecutive cases of WDHCCs diagnosed on needle biopsies (age range 34-93 years; 52 males and 16 females) were retrieved from our pathology files (including consult cases) between 2012-2015. The diagnosis of WDHCC was based on typical morphological findings on hematoxylin and eosin stain with loss of normal reticulin staining pattern on the reticulin stain. Arginase-1 stain was performed on all cases. Additional stains including hepar-1, glypican-3, albumin ISH were also performed as needed. For each stain, any expression within the tumor was considered positive.

Results: 7 of 68 (10%) WDHCCs were completely negative for arginase-1 (age range 55-84 years; 7 males). 6 of these 7 cases included the background non-neoplastic liver parenchyma within the biopsy and this non-neoplastic liver parenchyma was positive for arginase-1 in all 6 cases (100%). All these 7 cases (100%) were positive for hepar-1. Glypican-3 was positive in 4/7 (57%) cases. Albumin ISH was also performed on 2/7 cases and both (100%) were positive.

Conclusions: Our study demonstrates that approximately 10% of WDHCC are negative for arginase-1 on needle biopsy. Awareness of this phenomenon is important, as a negative arginase-1 stain on a needle biopsy should not exclude a diagnosis of WDHCC, when the histological findings and results from other ancillary stains are supportive of WDHCC.

1644 Aberrant Keratin Expression Is Common in Primary Hepatic Malignant Vascular Tumors: A Potential Diagnostic Pitfall

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Background: Epithelioid hemangioendothelioma and angiosarcoma are malignant vascular neoplasms which can occur within the liver. Keratin expression in extra-hepatic angiosarcoma has been reported, however, this has not been well studied in primary hepatic malignant vascular tumors. The aim of this study was to study the expression of keratins such as CK7, AE1/AE3 and OSCAR in primary hepatic epithelioid hemangioendothelioma and angiosarcoma.

Design: 10 cases of epithelioid hemangioendotheliomas (all resection cases; age range, 17-76 years; 5 male, 5 female) and 13 cases of angiosarcomas (8 resections & 5 needle biopsies; age range, 20-86 years; 8 male & 5 female; 8 epithelioid & 5 spindle morphology) were retrieved from our pathology files between 1995-2015. All cases were stained for ERG, CK7, keratin AE1/AE3 and keratin OSCAR. For each marker, any expression with moderate to strong intensity was considered positive and graded on the extent of tumor positivity as 1+ (1-25% of tumor cells positive), 2+ (26-50%), 3+ (51-75%) or 4+ (>75%).

Results: ERG was positive in all 10 (100%) epithelioid hemangioendotheliomas (2, 2+; 1, 3+; 7, 4+) and all 13 (100%) angiosarcomas (1, 1+; 2, 3+; 10, 4+). CK7 was positive in 6/10 (60%) epithelioid hemangioendotheliomas (3, 1+; 1, 2+; 1, 3+; 1, 4+) and 1/13 (8%) angiosarcoma (epithelioid type, 2+). Keratin OSCAR was positive in 6/10 (60%) epithelioid hemangioendotheliomas (5, 1+; 1, 2+) and 4/13 (31%) angiosarcomas (3 epithelioid and 1 spindle type, 2, 1+; 1, 2+; 1, 4+). Keratin AE1/AE3 was positive in 6/10 (60%) epithelioid hemangioendotheliomas (3, 1+; 3; 2+) and 4/13 (31%) angiosarcomas (3 epithelioid and 1 spindle type, 2, 1+; 1, 2+; 1, 4+). Overall, 7 of 10 (70%) epithelioid hemangioendotheliomas were positive for at least one keratin marker and out of these 5 (50%) were positive for all 3 keratins (AE1/AE3, OSCAR and CK7) while 1 (10%) was positive for 2 keratins (OSCAR and AE1/AE3) and another 1 (10%) was positive for only CK7. 4 of 13 (31%) of angiosarcomas were positive for both keratins OSCAR and AE1/AE3, while 1 of these 4 cases was also positive for CK7.

Conclusions: Aberrant keratin expression is common in primary hepatic epithelioid hemangioendotheliomas (7 of 10 cases, 70%) and angiosarcomas (4 of 13 cases, 31%). Awareness of this potential diagnostic pitfall is important for correct diagnosis of these primary hepatic malignant vascular tumors and for avoidance of misdiagnosis as carcinomas.

1645 Copper Deposition in Focal Nodular Hyperplasia and Inflammatory Hepatic Adenoma

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Background: The distinction between focal nodular hyperplasia (FNH) and inflammatory hepatic adenoma (IHA) can be difficult as both show overlapping morphological features. The value of immunostains such as glutamine synthetase (GS), serum amyloid A (SAA) & C-reactive protein (CRP) has been explored to help make this distinction. Copper deposition can be seen in FNH but it has not been studied in IHA. Aims of our study were to examine copper deposition in FNH & IHA and to determine if it can play a role in their differentiation.

Design: 28 FNHs & 19 IHAs from surgical resections showing typical morphological features on H&E were stained with rhodanine to evaluate for copper deposition. All 28 FNHs showed map-like staining for GS. All 19 IHAs were positive for SAA and CRP, with retained expression of liver fatty acid binding protein (LFABP) & none showed diffuse or map like staining on GS. Copper deposition was evaluated as negative (no copper), focal (F=1 or 2 foci of copper in the lesion), patchy (P=more than 2 foci but less than half of the lesion) and diffuse (D=more than half of the lesion). When copper was detected, the intensity of deposition was scored as 1+ (isolated cells containing small sparse granules, not seen at low power), 2+ (moderate to numerous copper granules, seen at low power, mainly around the areas of fibrosis/pseudo portal tracts), 3+ (widespread and heavy deposition of granules throughout the lesion). Histological features like nodularity, fibrous bands, ductular proliferation, steatosis & lymphocytic inflammation were also scored as negative (absent), 1+ (only 1 focus in lesion), 2+ (at least 2 foci but less than half of lesion), 3+ (majority of lesion) and a score of 2+ or 3+ was regarded as positive.

Results: Copper deposition was detected in 96% (27/28) of FNHs (19 P2+, 3 D2+, 3 F2+, 1 F1+, 1 P1+) and 37% (7/19) of IHAs (5 P2+, 1 F1+, 1F2+), $p<0.001$. In all cases copper was seen in the hepatocytes only around the pseudo portal tracts or areas of fibrosis. Copper deposition in IHA was significantly associated with presence of lymphocytic inflammation (all 7 cases positive for copper showed 2+ or 3+ lymphocytic inflammation, $p=0.04$) but not associated with features like nodularity, fibrous bands, ductular proliferation and steatosis ($p>0.05$, for all). In FNH, the presence and degree of copper deposition was not significantly associated with any of the above histological features ($p>0.05$, for all).

Conclusions: Copper deposition occurs more frequently in FNH (96%) than IHA (37%), $p<0.001$. However, the presence of copper alone cannot be used as a feature to differentiate between FNH and IHA.

1646 Alpha 1-Antitrypsin (A1AT) Globules Are Highly Encountered in Liver Explants for Non-Alcoholic Steatohepatitis (NASH) and in Patients with Body Mass Index>30 kg/m2

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Background: A1AT globules can unexpectedly be encountered in liver explants. Prior studies estimate that PAS positive, diastase-resistant (PASD+) globules occur in ~10% of liver transplants. This is clinically significant, since most patients with globules do have an undetected A1AT abnormality. It is still unclear in some, however, if the globules are a nonspecific effect of cirrhosis, or due to specific etiologies of liver disease such as NASH, to A1AT levels, or to other clinical parameters.

Design: All cirrhotic explanted livers from 2 institutions performed from 2013-2015, and all explants performed for NASH from 2006-2015, were retrospectively reviewed. Liver pathology, serum A1AT levels, and general clinical parameters were assessed.

Results: Of 196 (M:F 133:63) explants, 21 (10.7%) had PASD+ globules. The 3 most common etiologies of end-stage liver disease were HCV (n=90; 46%), ETOH (n=43; 22%), and NASH (n=16; 8%), with 61 (31%) other diagnoses including primary sclerosing cholangitis or autoimmune hepatitis. Across diseases (2013-2015), PASD+ globules occurred significantly more often in NASH than in other causes ($p=0.003$). Globules occurred in 50% of NASH, 14% of ETOH, 6.7 % of HCV, and 6.6% of other etiologies. Among all NASH cases (n=34; 2006-2015), the overall rate of PASD+ globules was 44% (15/34). Average BMI at time of transplant was 27.4 kg/m^2. Cases without globules had an average BMI of 26.9 kg/m^2, while those with globules had an average BMI of 31.5 kg/m^2 ($p=0.003$). The higher BMI with globules was true for both NASH (ave BMI 33.3, $p=0.0028$) and non-NASH (BMI 30.7, $p=0.007$). There was no significant difference in other clinical parameters, including ethnicity or gender. Serum A1AT levels were available in <5% of cases.

Conclusions: PASD+ globules occurred significantly more often in explants for NASH than in other diseases. Also, the BMI in pts with PASD+ globules was statistically increased in both NASH and non-NASH. Interestingly, a BMI of 30 kg/m^2, the clinical definition of obesity, significantly predicted the presence of PASD+ globules ($p=0.0002$). This suggests that A1AT globules in explants are not simply a nonspecific effect of cirrhosis, but may be related to obesity. It may further indicate that NASH and A1AT deficiency have a synergistic effect on cirrhosis, or that obesity affects A1AT secretion. The lack of clinical follow-up to correlate with explant findings emphasizes the need to evaluate for A1AT in all liver transplant candidates.

1647 Extramedullary Hematopoiesis Presenting as Focal Lesions in Liver: A Pathological and Radiological Study

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Background: Extramedullary hematopoiesis (EMH) is the presence of hematopoietic stem cells outside of the bone marrow. EMH is a common incidental finding in the organs of the reticuloendothelial system, including the liver and spleen, in patients with myelodysplastic disorders. Diffuse EMH of the liver and spleen may present as hepatosplenomegaly. Far more rare is EMH presenting as a focal intrahepatic lesion, with only 14 case reports within the literature. The purpose of this study is to characterize the pathologic, radiographic, and clinical features of intrahepatic EMH presenting as focal hepatic lesions.

Design: All liver biopsy and explant as well as autopsy cases containing the term "Extramedullary hematopoiesis" dating back 15 years at our institutewere reviewed. The cases were cross-referenced for any cross sectional imaging performed within 1 year of pathology results. Of the 825 cases meeting the initial search parameters, 12 cases had focal hepatic lesion on pre-procedural imaging. This was furthered narrowed to 9 as 2 had other pathology and one was unclear if the biopsy was truly from the focal lesion.

Results: 9 cases (4:5 M:F, 54.7 ($\pm$15) years old) (7 biopsies and 2 explants) had EMH present in focal liver lesions identified on CT or MRI (2 MR and 7 CT, all with at least single phase enhancement). Of the 9 cases, 7 had multiple lesions and 2 had a single focus. The 2 cases identified on liver MR imaging had both arterial enhancement and washout on delayed imaging with multiple lesions all less than a centimeter. The 7 cases identified on CT had 5 with low attenuation and 2 with hyperattenuation on venous phase imaging, and all with arterial phase enhancement when performed. About half

the patients had hematological disorders, with the remaining cases from patients from screening cirrhosis protocols and metastatic disease work up. Most cases of prospectively identified hepatic EMH were classified as indeterminate, an equivalent grade of Li-Rads 3, and several were suggestive of a hemangioma.
Conclusions: This is the largest report of hepatic EMH presenting as focal lesions. Focal EMH generally presents as multiple ill-defined arterially enhancing subcentimeter lesions on MRI and CT with most lesions having hypoattenuation on venous phase imaging. Focal hepatic EMH identified in CT and MRI, although rare, should be a consideration in indeterminate liver lesions. In addition, given the high frequency of patients with hematological disorders, these need to be considered clinically when EMH presents as focal lesions on imaging.

1648 Distinct Patterns of Reticulin Framework Alterations in Telangiectatic/Inflammatory Adenoma: Diagnostic Clues and Pitfalls

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Background: Reticulin loss is a diagnostic criterion in differentiating hepatocellular carcinoma (HCC) from several benign hepatocellular lesions. Reticulin loss can be observed in fat-containing areas of benign hepatocellular lesions, however. Anecdotally, we noted several cases of telangiectatic/inflammatory hepatocellular adenoma (TA) with focal reticulin loss in areas that did not contain fat, including a case that had been diagnosed as HCC.
Design: A case-finding search from 2011 to 2015 yielded 21 specimens from 15 patients (1 male, 14 females from 30-51 years old; mean: 39.8) of TA for which adequate tissue remained in the paraffin block. These were comprised of 5 biopsies and 16 resections and included 2 biopsies with subsequent resection specimens. The cases were re-reviewed to confirm the diagnosis of TA and representative blocks were chosen to assess reticulin pattern. The amount of fat was noted, but reticulin pattern was only assessed in the areas devoid of fat.
Results: Three patterns of reticulin alterations were identified. Twenty (95%) specimens showed regenerative hyperplasia (RH)-like staining in the periportal areas whereby the hepatocellular plate thickness was increased to 3-4 cells, but there was no HCC-type reticulin loss. Twenty (95%) of specimens showed a sinusoidal-obstruction syndrome (SOS)-like pattern in the telangiectatic areas in which the sinusoidal spaces were filled with fine reticulin fibers. Finally, a third subset (24%; 2 biopsies; 3 resections) showed reticulin loss similar to that found in HCC.
Conclusions: Reticulin loss in fat-containing benign hepatocellular lesions is a well-recognized pitfall for misdiagnosis of HCC. HCC-type reticulin loss also occurs in a minority of TAs and should not be the sole determinant of malignancy in an otherwise typical TA, especially on needle core biopsies. Further, we found that RH-type reticulin staining adjacent to portal-like structures and SOS-type staining in areas of telangiectasia are quite common in TA, and these features may aid in the diagnosis of TA.

1649 Comparison of C4d Immunostaining Patterns on Posttransplant Liver Biopsies Using Two Different Antibodies

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Background: The histopathologic diagnoses of antibody-mediated rejection (AMR) in posttransplant liver biopsies are challenging. Studies suggest that patterns of immunohistochemical staining for C4d correlate with the presence of donor-specific antibodies and may aid in the histopathologic diagnosis of AMR. However, C4d staining patterns vary widely in different studies. One potential explanation may be due to different antibody preparations used by different researchers.
Design: Posttransplant liver biopsies with diagnoses of acute cellular rejection (ACR) and chronic ductopenic rejection (CDR) were retrieved and re-reviewed to confirm the diagnoses. Immunohistochemicalstaining was performed using a polyclonal anti-human C4d antibody from Alpco Diagnostics (Salem, NH, Catalog no. 04-BI-RC4D) and a polyclonal anti-human C4d antibody from Cell Marque (Rocklin, CA, Catalog no. 404A-16). The immunostained slides were evaluated and the staining patterns were analyzed independently by three observers. Results were statistically analyzed with Fisher exact test.
Results: A total of 30 cases were evaluated. Interobserver variability among three pathologists in portal and central vein endothelial staining patterns was statistically insignificant. However, interobserver variability of portal stroma pattern was statistically significant (p=0.005). There were statistically significant differences in staining patterns of portal and central vein endothelium between the two antibodies (p=<0.05). No sinusoidal staining was observed with either antibody.

	Alpco anti-C4d			Cell Marque anti-C4d		
Diagnostic Category	Portal endothelium	Portal Stroma	Central Vein Endothelium	Portal endothelium	Portal Stroma	Central Vein Endothelium
Pathologist 1	63%	67%	30%	13%	53%	3%
Pathologist 2	63%	67%	36%	13%	43%	3%
Pathologist 3	57%	30%	20%	17%	43%	0%

Conclusions: Interobserver variability among three pathologists was insignificant in portal and central venin endothelial staining patterns. Alpco and Cell Marque antibodies have statistically significant discrepancies in portal and central vein endothelial staining patterns. Alpco antibody shows variable background positivity compared to Cell Marque, which shows no background staining. This finding correlates with low positive staining patterns in portal and central vein endothelium of Cell Marque antibody compared to Alpco. Our data demonstrate that different antibodies may contribute to different patterns for C4d immunostaining.

1650 Leptin Signaling-Related Proteins in Nonalcoholic Fatty Liver Disease

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Background: Nonalcoholic fatty liver disease (NAFLD) is a clinicopathological condition characterized by build-up of excessive fats within the liver cells, and non-alcoholic steatohepatitis (NASH) is more serious form of NAFLD, in which the liver becomes inflamed. NASH can cause scarring of liver tissue, and eventually can progress to cirrhosis. Leptin is a hormone produced by adipose tissue and its role was initially known to be in controlling food intake and energy balance. Recently, the close association of leptin with visceral adiposity suggests its crucial role in the pathogenesis of NAFLD including NASH. In the present study, we aim to investigate the relationship among the histopathological features [NAFLD activity score (NAS), the steatosis, activity and fibrosis (SAF) score], clinical factors [body mass index (BMI), serum aminotransferase levels, age, sex, etc.], and expression of leptin signaling-related proteins, furthermore, to interpret the implication of those relationships.
Design: We evaluated the NAS, SAF score, clinical factors and immunohistochemical expression level of leptin, leptin-receptor, mammalian target of rapamycin (mTOR), extracellular signal-related kinase (ERK), phospho-signal transducer and activator of transcription 3 (pSTAT3), estrogen receptor (ER) in needle-biopsied liver tissue of NAFLD and other chronic liver diseases showing > 5% macrovesicular steatosis.
Results: Total 35 cases of liver biopsy specimen were classified into; NAFLD [n=18; with NASH (n = 9), without NASH (n = 9)], alcoholic hepatitis (n=11), viral hepatitis (n = 3), and others (drug-induced hepatitis or incidental finding in the work-up of other diseases). Immunoexpressions of leptin and leptin-receptor were observed in 94% and 78% of NAFLD cases, respectively. The expressions of ERK, pSTAT3 and ER were more frequent in NAFLD than in other subgroups ($p < 0.05$, respectively). Interestingly, ER expression was correlated with lower grades of lobular inflammation, ballooning change and fibrosis ($p < 0.05$, respectively), while pSTAT3 expression was associated with higher grades of lobular inflammation, ballooning change, and fibrosis ($p < 0.05$, norespectively).
Conclusions: Leptin signaling-related proteins may be involved in the pathogenesis of NAFLD. ER and pSTAT3 may be used as biomarkers predicting hepatic fibrosis in liver diseases showing steatosis.

1651 Histologic and Clinical Outcomes after Transplantation of Donor Livers with Small Versus Large Droplet Macrovesicular Steatosis

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Background: Donor liver steatosis is considered a risk factor for allograft problems. Although it is generally accepted that donor livers with < 30% large droplet macrovesicular steatosis, and/or small droplet macrovesicular steatosis (irrespective of percentage) are safe to use (with > 60% "steatosis" reported as unsafe), this consensus is based on variable definitions of macrovesicular steatosis subtypes, sometimes including "microvesicular steatosis" in the same category as "small droplet macrovesicular steatosis," and/or without a reproducible scoring system or consistent clinical variables.
Design: 75 deceased donor liver biopsies from allografts transplanted at UCSF Medical Center between 2009 and 2015 were analyzed to determine if large and/or small droplet macrovesicular steatosis is a risk factor for poor outcome. Frozen and/or permanent section specimens were reviewed to determine the degree and type of steatosis. Large droplet macrovesicular steatosis was defined as a fat droplet occupying greater than one-half of an individual hepatocyte, with nuclear displacement, and scored as the percentage of parenchyma replaced by large droplets on 4x magnification. Small droplet macrovesicular steatosis was defined as one to several fat droplets, each occupying less than one-half of an individual hepatocyte, and scored as the percentage of hepatocytes containing small droplets on 10x magnification. Electronic medical records were reviewed to determine histologic and clinical outcomes.
Results: There is a significant increased risk for biliary obstruction (hazard ratio (HR) = 6.0, $p = 0.0398$) in the donor livers with ≥ 30% small droplet macrovesicular steatosis. However, there was no significant difference in the rates of acute/chronic rejection (HR = 1.2, $p = 0.6376$), vascular obstruction (HR = 2.3, $p = 0.2834$), recurrent disease (HR = 1.5, $p = 0.3886$), or patient survival (HR = 2.3, $p = 0.2834$) between the two groups. Similarly, 30-60% large droplet macrovesicular steatosis was not a risk factor for poor outcomes ($p = 0.1362$-0.9947, n = 7).
Conclusions: Distinct assessment of small and large droplet macrovesicular steatosis is important in donor liver biopsy evaluation as ≥ 30% small droplet macrovesicular steatosis was associated with increased risk for post-transplant biliary obstruction.

1652 MUC6 Is a Unique Biomarker for Bile Duct Type of Intrahepatic Cholangiocarcinoma

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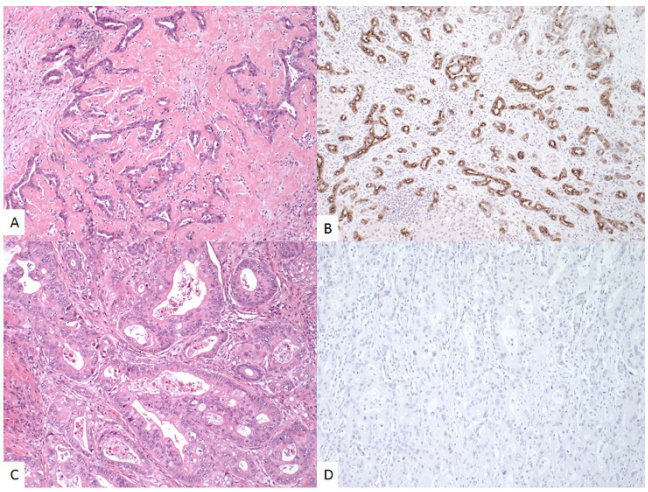
Background: Recent publications have asserted that subclassification of intrahepatic cholangiocarcinoma is possible based on morphologic, clinical and molecular findings. The two main types of intrahepatic cholangiocarcinoma are cholangiolar and bile duct types. Morphologically, the bile duct type (Fig. 1a) shows infiltrating, small ducts with low cuboidal epithelium, while the cholangiolar type (Fig. 1c) shows a large glandular pattern with columnar epithelium. Whether there are different histogenesis and molecular phenotypes in these two types of tumors is not known. Generally, the bile duct type of cholangiocarcinoma shows morphologic findings similar to those seen

in a bile duct adenoma. Since bile duct adenoma displays foregut histogenic origin and MUC6 serves as a foregut biomarker, in this study, MUC6 expression is evaluated immunohistochemically on intrahepatic cholangiocarcinomas and bile duct adenomas.
Design: A total of 25 intrahepatic cholangiocarcinomas and 14 bile duct adenomas were assessed. Formalin-fixed paraffin-embedded sections were labeled with a monoclonal antibody to MUC6 with appropriate positive and negative controls. Tumors were scored as positive if dense cytoplasmic staining was seen.
Results: 14 of 14 (100%) of the bile duct adenomas and 11 of 25 (44%) of the intrahepatic cholangiocarcinomas showed strong positive staining for MUC6. All 11 of the MUC6-positive cholangiocarcinomas showed a bile duct type of cholangiocarcinoma morphology (Fig. 1b), while the cholangiolar type showed no positive staining (Fig. 1d). Positive staining with MUC6 was seen in the reactive ductules surrounding the tumor but not in the bile ducts away from the tumor.



Conclusions: Our results indicate that MUC6 is a unique biomarker for bile duct adenomas and bile duct type of intrahepatic cholangiocarcinoma that distinguishes it from the cholangiolar type of cholangiocarcinoma. Given the morphologic overlap of the bile duct type of cholangiocarcinoma with bile duct adenoma, further investigation into the subclassifying of intrahepatic cholangiocarcinomas is warranted with regards to bile duct adenoma-carcinoma sequence, prognostic information and clinical behavior.

1653 The Incidence of Steatosis and Steatohepatitis in Intrahepatic Cholangiocarcinoma and Extrahepatic Cholangiocarcinoma

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Background: With the epidemic of obesity in the United States, there is increased incidence of nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD). Interestingly, incidence of intrahepatic cholangiocarcinoma (ICC) has also increased, raising the intriguing possibility of an association between the two. There have been variable reports of the concomitant prevalence of NASH with ICC. We propose using the incidence of a separate, yet anatomically similar malignant neoplasm, extrahepatic cholangiocarcinoma (ECC), to potentially compare the relative incidence of NASH with ICC.
Design: We investigated 73 ICCs and 30 ECCs with associated histologically assessable liver tissue. Each cases was graded for steatosis, on a four tier scale: absent, mild, moderate and severe. Furthermore the presence of steatohepatitis and the grade of fibrosis was also determined. Standard Chi Squared analysis was used to compare the relative incidence of steatosis, steatohepatitis and fibrosis between the groups, ICC and ECC.
Results: Steatosis between ICC and ECC was similar, with the presence of any steatosis being 36% (26/73) in the ICC group, and 30% (9/30) in the ECC group. The breakdown of steatosis severity for the ICC group was: absent 64% (47/73), mild 25% (18/73), moderate 11% (8/73) and severe 0% (0/73). The ECC group had a similar distribution of steatosis: absent 70% (20/30), mild 23% (7/30), moderate 7% (2/30) and severe 0% (0/30). Chi Squared analysis demonstrated no significant difference between the presence of steatosis in the ICC group or the ECC group, with a p value = 0.29. The prevalence of steatohepatitis was also similar between the two groups, with no steatohepatitis found in 93% (68/73) in ICC and 93% (28/30) in ECC cases. The Chi squared analysis had a p value = 0.95. Furthermore, the fibrosis was very similar between ICC and ECC, with 89% of ICC cases having none, similar to 92% of ECC cases. There was a slightly increased amount of cirrhosis identified in the ICC group compared to the ECC group, 8% (5/63) vs 0% (0/23), however there was a non-NASH etiology for all but one of the ICC associated cirrhosis cases: hemochromatosis, hepatitis B infection, hepatitis C infection, and alcohol abuse.
Conclusions: These results show overall similar incidence of NASH occurring with ICC in our hospital's history of resectable ICC's when compared to recent studies. However, this incidence is very similar to the incidence of NASH in an anatomically similar, though potentially etiologically different malignancy, ECC.

1654 Frequency and Pathological Characteristics of Drug-Induced Liver Injury in a Tertiary Medical Center

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Background: Drug-induced liver injury (DILI) accounts for approximately 10 % of all cases of acute hepatitis. DILI can arise as either idiosyncratic or intrinsic injury from hundreds of drugs, herbals, and supplements. It is essential to recognize DILI as one of the differential diagnoses of hepatitis in a liver biopsy. The purpose of this study is to investigate the frequency and pathological characteristics of DILI related to the variety of hepatotoxic agents, to aid in accurate diagnosis.
Design: We searched our pathology database for all patients with hepatitis or liver injury diagnosed by liver biopsy from 2014 and 2015, and selected patients with a diagnosis of DILI. Medical records were reviewed for patient medication list, history of herbal medicine or supplement use, and pre-biopsy liver function test (LFT) results. Clinical and pathologic correlation was used to determine the causative or related agents for DILI. We then assessed histopathologic features of liver injury including bile duct injury, lobular inflammation, portal inflammation and interface hepatitis. Histopathologic findings were categorized as primarily bile duct injury, lobular/portal hepatitis, or mixed changes.
Results: 323 total cases of liver biopsies for hepatitis or liver injury were identified, of which 84 cases (26.0%) carried the diagnosis of DILI confirmed by clinical correlation. The most common etiologies associated with DILI were nutritional/herbal supplements (17 of 84; 20.2%), antilipidemics (9 of 84, 10.7%), antibiotics (7 of 84, 8.3%), chemotherapeutics (6 of 84, 7.1%), and NSAIDs, antihypertensives and psychiatric drugs (5 of 84, 5.9% each). Pathologically, NSAIDs and antihypertensives showed a predominantly hepatitis pattern, and antilipidemics (statin or statin family drugs) predominantly caused bile duct injury. Nutritional/herbal supplements, antibiotics, and psychiatric medications produced a mixed pattern of DILI. LFT results were positively correlated with histological findings.
Conclusions: Nutritional/herbal supplements have emerged as one of the major hepatotoxicity agents. DILI can manifest as predominantly hepatitis, bile duct injury or combination. Histological pattern recognition in the liver biopsy may help identify specific hepatotoxic agents causing DILI.

1655 Evaluation of the Clinical TNM Staging System, Pathological TNM Staging System, and BCLC Staging System of Hepatocellular Carcinoma: A Study of 1021 Cases of Curative Liver Resection

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Background: Vascular invasion(VI), including macrovascular invasion(MacroVI) and microvascular invasion(MVI), is one of the most critical prognostic factor in hepatocellular carcinoma(HCC) after surgical resection. In the postoperative clinical TNM (cTNM) staging system, only MacroVI was considered, and a new study of 754 patients in HongKong considered MVI in its' staging system (pathological TNM, pTNM staging system). In the well-known BCLC staging system considered imaging MacroVI as its' prognostic factor.
Design: In this single-center retrospective study, the pathology and preoperative imaging data of 1021 HCC patients who underwent subsegmentectomy in Zhongshan Hospital (Fudan University, Shanghai, China) between January 2015 and August 2015 were analyzed, including both MVI & MacroVI data in pathology and preoperative imaging reports.
Results: 1. Of the 1021 HCC patients who underwent surgical resection, MVI was found in 411 cases (40.3%).Pathological reports showed that 389 (38.1%) cases had MVI detected by pathologists but without MacroVI, only 22(2.2%) cases had both MVI and MacroVI determined by pathologists. There were 0.7% (7) patients who had MacroVI but didn't have visible MVI.2. Comparison of the cTNM and pTNM staging system (n=1021).

cTNM staging system			pTNM staging system		
T1	602	59.0%	T1	347	34.0%
T2	76	7.4%	T2	383	37.5%
T3a	336	32.9%	T3	106	10.4%
T3b	6	0.6%	T4	185	18.1%
T4	1	0.1%			

3. Related to MacroVI between imaging &pathology diagnosis, there were 18(1.8%) cases had MacroVI detected by both radiologists and pathologists, 30(2.9%) cases detected MacroVI by radiologists only, 11(1.1%) cases detected MacroVI by pathologistsonly only.
Conclusions: 1.Despite the MVI incidence rate is over 40% in HCC, there were only 2.2% cases who had both MacroVI & MVI;
2. Recent data have shown that the seventh edition of the TNM staging system fails to demonstrate accuracy in predicting longterm survival in patients undergoing hepatic resection, pTNM staging system may give insight into a more perfect staging system in HCC;
3. There was significant difference between MacroVI & MVI occurrence. And the accurate diagnosed MVI should be used for tailoring clinical management.

1656 BSEP and MDR3: Useful Immunohistochemical Markers for the Discrimination of Hepatocellular Carcinomas from Not Only Intrahepatic Cholangiocarcinomas but Also Hepatoid Carcinomas

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Background: In addition to morphological features, immunohistochemistry has been widely used for liver tumor typing. Immunohistochemical markers that are commonly used to prove hepatocellular differentiation include arginase-1, hepatocyte paraffin-1 (HepPar-1), CD10, glypican-3 and carcinoembryonic antigen. However, none of these are entirely specific for hepatocellular carcinomas (HCCs), as they are known to be variably positive in other primary liver cancers and extrahepatic neoplasms (e.g., hepatoid carcinomas).

Design: In this study, we examined immunohistochemical expressions of two hepatocyte-specific transporters (BSEP and MDR3) in HCCs (n=54), intrahepatic cholangiocarcinomas (ICCs, n=34), combined hepatocellular and cholangiocarcinomas (CHCs, n=23), and hepatoid carcinomas (n=27) to compare their diagnostic values with those of arginase-1 and HepPar-1. We also applied BSEP and MDR3 immunohistochemistry to 8 biopsy cases of poorly differentiated primary liver cancer, in which original diagnosis was not conclusive.

Results: BSEP was expressed in 91% of HCCs, and MDR3 was in 83%. Although their sensitivities were slightly lower than those of arginase-1 (96%) and HepPar-1 (93%), the two transporters appeared to be more specific for HCCs. Arginase-1 and HepPar-1 were expressed in ICCs (9% and 6%) and hepatoid carcinomas (22% and 44%, respectively), while BSEP and MDR3 were entirely negative in those neoplasms except for one case of BSEP-positive hepatoid carcinoma of the esophagus. The highly specific expressions of BSEP and MDR3 in hepatocytes were recapitulated in additional examinations on CHCs, where expressions of the transporters were restricted to morphologically hepatocellular areas. In contrast, arginase-1 and HepPar-1 were variably positive in areas of biliary or indeterminate differentiation as well. In the biopsy series, the diagnosis of HCC was retrospectively suggested in two cases, which were found to be positive for both BSEP and MDR3.

Conclusions: Given highly specific expressions of BSEP and MDR3 in HCCs, immunohistochemistry for these transporters will be useful for not only determining hepatocellular differentiation in primary liver cancers but also discriminating HCCs from hepatoid carcinomas.

1657 PRKACA Fluorescent In Situ Hybridization Reveals Novel Findings in Fibrolamellar Carcinoma

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Background: Fibrolamellar carcinoma (FLC) has a distinct morphology and immunophenotype, including CK7 and CD68 positivity, and is also characterized by activation of the protein kinase A pathway through a recurrent somatic 400 bp deletion, leading to a *DNAJB1-PRKACA* fusion gene. This genomic event can be detected by a novel break-apart fluorescence in situ hybridization (FISH) assay for the *PRKACA* locus. We examined the diagnostic performance of this FISH assay in a multicenter study.

Design: Cases of FLC were reviewed for diagnostic confirmation by H&E, CK7 and CD68 immunohistochemistry. Formalin-fixed paraffin embedded whole tissue sections from samples of FLC (n=49) from 46 patients and a tissue microarray of 88 hepatocellular carcinomas, 6 fatty liver and 7 normal liver tissues were evaluated with *PRKACA* break-apart FISH by 2 experienced technologists who each scored 50 consecutive tumor nuclei.

Results: All FLC cases were positive for CK7 and CD68. Seven (14%) of the FLC samples were needle biopsies. By FISH, 48/49 samples (98%) were positive for *PRKACA* rearrangements. The single FISH-negative FLC case had the classic histologic findings and was CK7 and CD68 positive. Interestingly, this tumor arose in the setting of the Carney complex, where the Protein kinase A pathway is activated most often by germline mutation in another gene. Two additional FLCs had unique findings: one case showed 4 or more copies of the rearrangement pattern in 20% of tumor cells; a second case showed FISH signal patterns indicating a variant translocation instead of the classic 400 bp deletion. None of the 88 hepatocellular carcinomas or normal liver tissues from the tissue microarray were positive for *PRKACA* rearrangement.

Conclusions: Detection of *PRKACA* rearrangement by FISH is highly sensitive (98%) for the diagnosis of primary or recurrent FLC, even on small biopsies. The single negative case affirms the importance of histologic assessment in rare FISH negative cases and underscores the importance of the Protein kinase A pathway in FLC biology. Also, unusual FISH patterns may occur rarely and recognition of these will prevent misinterpretation. *PRKACA* rearrangement is highly specific for FLC among primary liver tumors.

1658 Novel Chromogenic RNA In Situ Hybridization Assay Is an Accurate Method for Tissue Diagnosis of Hepatitis E Virus Infection

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Background: Hepatitis E virus (HEV) infection is an increasingly recognized and treatable cause of chronic liver disease in solid organ transplant recipients. The diagnosis of HEV infection currently relies on serologic testing. Serum and tissue-based PCR have also been performed but are not widely available. False positives have been reported with HEV IgM, and so other diagnostic adjuncts are needed.

Design: We optimized a novel pan-genotypic chromogenic *in situ* hybridization (ISH) assay for HEV RNA using RNAscope technology and validated the assay using HEV PCR-confirmed porcine and human controls. Next, we tested 7 liver biopsies from a single patient with unexplained allograft hepatitis over 4 years, clinically suspicious for HEV (positive HEV IgG). Then, we extended testing to 101 formalin fixed paraffin embedded tissue specimens from 85 patients with native livers (n=54) and allograft livers (n=47). The native livers had unexplained massive necrosis (n=23), chronic viral hepatitis B/C (n=9), autoimmune hepatitis (n=7), chronic biliary disease (n=4), presumed drug induced injury (n=6), hepatitis A (n=2), fatty liver disease (n=1) and the allografts had chronic rejection (n=17), chronic viral hepatitis (n=9), vascular disease (n=7), chronic biliary disease (n=4) unexplained allograft dysfunction (n=5), and protocol biopsies (n=4).

Results: The novel ISH assay was positive in each of 7 consecutive biopsies from the patient with unexplained hepatitis. These biopsies showed non-specific mild portal and lobular inflammation without fibrosis. Ribavirin therapy in this patient led to rapid normalization of aminotransferases. Confirmatory HEV PCR on 6 of 6 biopsies for this patient was positive for HEV RNA. HEV ISH testing of the next 101 cases revealed a HEV positive rate of 2% (n=2); both patients had PSC and presented with unexplained allograft failure leading to re-transplantation after 4 and 6 weeks respectively because of graft dysfunction. One of the explants after re-transplantation showed diffuse non-necrotizing granulomata and the other marked cholestasis with mild portal and lobular inflammation.

Conclusions: HEV ISH can be a useful tool for the diagnosis of HEV infection. Histologically confirmed cases of HEV affected patients after liver transplantation, displayed varied non-specific histologic features and contributed to allograft loss.

1659 Histological Features of Autoimmune Hepatitis: A Critical Appraisal

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Background: Lymphoplasmacytic interface hepatitis, emperipolesis and hepatocyte rosettes have been regarded as 'typical' features of autoimmune hepatitis (AIH) and are included in the 2008 International AIH Group Simplified Criteria. Our aim was to critically assess the incidence of these and other histological features in AIH patients.

Design: A retrospective search of the pathology database (2010-2014) identified liver biopsies from patients with clinically confirmed AIH. Biopsies (matched for inflammatory grade) from Hepatitis C (HCV) patients served as controls. Only biopsies containing ≥6 portal tracts were included. Histological features that were recorded while blinded to the diagnosis included: nature of the inflammatory infiltrate, emperipolesis, hepatocyte rosettes, Kupffer cell hyaline globules, plasma cells with Russell bodies, portal and lobular plasma cell clusters (defined as ≥5 plasma cells), cholestasis, bile duct injury and endothelialitis. The inflammatory infiltrate was considered *plasma-lymphocytic* when plasma cells were >50% of the mononuclear cells and *lympho-plasmacytic* when they were ≤50%.

Results: 51 AIH (7 male, 44 female, 6 children, mean age of 43, range 4-71) and 41 HCV patients were included. A plasma-lymphocytic infiltrate (35% AIH, 5% HCV, p=0.00023), Kupffer cell hyaline globules (79% AIH, 24% HCV, p=0.043), portal (48% AIH, 26% HCV, p=0.024) and lobular (26% AIH, 5% HCV, p=0.0046) plasma cell clusters were statistically significant features of AIH. In contrast, there was no significant difference in emperipolesis (36% AIH, 24% HCV, p=0.17), hepatocyte rosettes (32% AIH, 17% HCV, p=0.077), plasma cells with Russell bodies (11% AIH, 5% HCV, p=0.077), cholestasis (16% AIH, 5% HCV, p=0.077), bile duct injury (51% AIH, 41% HCV, p=0.29) or endothelialitis (20% AIH, 7% HCV, p=0.062).

Conclusions: A *plasma-lymphocytic* (rather than *lympho-plasmacytic*) inflammatory infiltrate, Kupffer cell hyaline globules and plasma cell clusters in lobules and portal tracts, but not emperipolesis or hepatocyte rosettes, were the more discriminating histologic features of AIH. Our data suggest that clinical-pathologic scoring systems may overemphasize the significance of emperipolesis and hepatocyte rosettes. These findings also support the emerging concept that while these 'typical' features of AIH should be evaluated on biopsies, their absence may not preclude the diagnosis.

1660 Distinct Clinicopathological and Genetic Features of Two Histologic Subsets of Intrahepatic Cholangiocarcinoma

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Background: Intrahepatic cholangiocarcinoma (ICC) is histologically heterogeneous and has been categorized into at least two subtypes. One subtype frequently affects the perihilar portion of the liver and the other is usually located on the peripheral portion of the liver. Although the two subtypes should be distinguished clearly in terms of their distinct clinicopathologic characteristics, previous classification schemes, such as anatomic location, cellular or architectural features and mucin productivity, are often not applicable and a more practical classification is required.

Design: A clinicopathologic and genetic analysis of intrahepatic ICC was performed to identify distinctions between the two histologic subsets, such as mucin productivity, immunophenotype, major genetic alterations, histologic features and prognostic factors.

Results: Type 1 ICC (42 cases), characterized by mucin production and diffuse immunoreactivity to S-100P arose less frequently from chronic liver diseases (26.2% vs. 48.2%, P = 0.027). Type 1 ICC displayed a higher level of serum CEA and CA 19-9 (P < 0.001) than type 2 ICC, which generally showed little mucin production or immunoreactivity to N-cadherin and/or NCAM. Type 1 ICC was characterized by higher frequencies of periductal spreading on macroscopic appearance, the presence of a poorly differentiated component, intraductal growth, cellular fibrosis, hepatic hilar involvement and perineural invasion (P < 0.001). Type 2 ICC more frequently

displayed multifocal scar-like fibrosis (P < 0.001). Type 1 ICC was associated with a significantly worse recurrence-free and overall survival than type 2 ICC (P < 0.001). Genetically, KRAS mutation was more frequent in type 1 ICC (29.4% vs. 2.0%, P < 0.001), whereas IDH1/2 mutation was restricted to type 2 ICC (0.0% vs. 39.6%, P < 0.001). FGFR2 translocation was noted in only 6 of 95 cases examined, 5 of which were from type 2 ICC. Multivariate analysis revealed that the presence of a poorly differentiated component and intrahepatic metastasis were independent prognostic factors of recurrence-free and overall survival.

Conclusions: The two histologic subsets defined here displayed distinct clinicopathologic and genetic characteristics, supporting the rationale for classification and indicating its importance both clinically and pathologically.

1661 Lymphocyte Infiltration Is a Promising New Prognostic Factor for Hepatocellular Carcinoma

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Background: Hepatocellular carcinoma (HCC) is a major health problem worldwide. Despite recent advances in resection and ablation techniques, prognosis remains worse than for other carcinomas and using chemotherapy to treat recurrence after resection has limited success. The tumor microenvironment and lymphocyte infiltration is now thought to contain the key to treat refractory cancers.

Design: In this study, we defined hepatocellular carcinoma with lymphocyte infiltration (LI-HCC) as "HCC with dense lymphoplasmacytic infiltration, multifocal or diffuse, in multiple foci under low power objective". A large number of continuous solitary HCC series (more than 500 HCC cases) in a single institute were retrieved to evaluate lymphocyte infiltration and other historical factors. Cases were classified into two groups (LI-HCC and non-LI-HCC) and clinicopathological features were compared.

Results: 201 (39.4%) of 511 cases were classified as LI-HCC. LI-HCC were smaller in size, less necrotic and contained more steatosis and fibrosis. A Kaplan–Meier analysis revealed a significantly better prognosis for LI-HCC in both overall and recurrence-free survival (both log-rank P < 0.0001). Both a univariate and multivariate Cox regression analysis indicated that LI-HCC has a significantly better prognosis than non-LI-HCC. Notably, a Cox-hazard ratio indicated that lymphocyte infiltration is a more sensitive prognostic factor for overall survival than common histological prognositc factors, such as liver cirrhosis, maximum tumor size, histological grade, vascular invasion, bile duct invasion and intrahepatic metastasis.

Conclusions: Lymphocyte infiltration is a promising new prognostic factor for HCC that is important both pathologically and clinically. Lymphocyte infiltration is associated with a better prognosis and may have an anti-cancer effect by causing fibrosis , although further research is necessary.

1662 Interobserver Variability in Interpreting Liver Biopsies with a Diagnosis of Alcoholic Hepatitis

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Background: Alcoholic hepatitis (AH) is a clinical syndrome of jaundice and liver failure and the most severe form of alcoholic liver disease. Recently, a histologic scoring system for predicting prognosis in this patient cohort was proposed as Alcoholic Hepatitis Histologic Score (AHHS) (Altamirano J et al. Gastroenterology 2014;146:1231-9). We aimed to assess interobserver variability in recognizing histologic features of AH, and the effect of this variability on the proposed AHHS categories.

Design: Hematoxylin-eosin and trichrome stained slides from 32 patients diagnosed with AH between 2000 and 2015, were reviewed by 5 gastrointestinal pathologists. Histologic features of AH were assessed, an AHHS was calculated and an AHHS category (mild, moderate, severe) was assigned. Interobserver agreement analysis to determine the Fleiss' kappa coefficient (K) was performed.

Results: A poor-to-moderate level of interobserver agreement was reached among 5 reviewers on histopathological features of AH with K value ranging from 0.20 (95% CI: 0.03-0.46, Megamitochondria) to 0.52 (95% CI: 0.40-0.68, PMN infiltration) (Table 1). Consequently, there was only a fair level of agreement in assigning the different AHHS categories to a case (K=0.33, 95% CI: 0.20-0.51).

Histologic feature	K value (95% CI)	Strength of agreement
Fibrosis stage (None/Portal fibrosis/Expansive periportal fibrosis/Bridging fibrosis/Cirrhosis)	0.42 (0.31-0.51)	Moderate
Lobular fibrosis (None/Zonal 3/Zonal 3+2/ Panlobular fibrosis)	0.31(0.19-0.45)	Fair
Pericellular fibrosis (Absent/Present)	0.41 (0.26-0.63)	Moderate
Steatosis (None/<5%/5-33%/33-66%,>66%)	0.43 (0.31-0.57)	Moderate
Bilirubinostasis (None/Hepato-canalicular/ Cholangiolar bilirubinosis/Both)	0.52 (0.36-0.72)	Moderate
Ballooning (None/Occasional/Marked)	0.37 (0.26-0.50)	Fair
Mallory bodies (None/Occasional/Marked)	0.44 (0.30-0.58)	Moderate
Megamitochondria (Absent/Present)	0.20 (0.03-0.46)	Poor
PMN infiltration (None/Mild/Severe)	0.52 (0.40-0.68)	Moderate

Conclusions: Features of AH can only be classified with a poor-to-moderate level of interobserver agreement. Even though AHHS was reported to be useful in predicting short-term outcome in patients with AH, a significant interobserver variability among liver pathologists as revealed by the current study can limit its usefulness in everyday clinical practice.

1663 Reproducibility of Evaluation of Liver Biopsies from Patients with Congestive Heart Failure

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Background: Long standing congestive heart failure can induce a constellation of histopathology changes in the liver that ranges from mild sinusoidal dilation to advanced fibrosis. Liver biopsies might be performed to assess the peri-operative risk of these patients or to determine the need of synchronous liver transplant. We aimed to assess interobserver variability in recognizing these histologic features in patients undergoing evaluation for heart transplantation.

Design: Hematoxylin-eosin and trichrome stained slides from 36 cases were reviewed by 4 gastrointestinal pathologists. Histologic features of congestive hepatopathy (CH) were reviewed, including evaluation of the overall fibrosis (stage) using a recently developed congestive hepatic fibrosis score (CHFS, Dai D-F et al. Mod Pathol. 2014;27:1552-8). Interobserver agreement analysis to determine the Fleiss' kappa coefficient (K) was performed.

Results: Sinusoidal dilation, centrilobular hepatocyte atrophy, fibrosis and hemorrhage were the most common findings in this cohort. A fair-to-good level of interobserver agreement was reached among 4 reviewers on histopathological features (Table 1). The overall agreement on the diagnosis of CH and CHFS was moderate (K=0.55, 95% CI: 0.32-0.73) and fair (K=0.35, 95% CI: 0.24-0.49), respectively.

Histologic feature	K value (95% CI)	Strength of agreement
Sinusoidal dilation (Absent/Present)	0.66 (0.41-0.86)	Good
Centrilobular atrophy (Absent/Present)	0.51 (0.35-0.70)	Moderate
Centrilobular hemorrhage (Absent/Present)	0.35 (0.19-0.53)	Fair
Centrilobular fibrosis (Absent/Present)	0.43 (0.21-0.68)	Moderate
Lobular inflammation (None/Mild/Severe)	0.50 (0.34-0.68)	Moderate
Portal fibrosis (Absent/Present)	0.49 (0.30-0.65)	Moderate
Portal inflammation (None/Mild/Severe)	0.43 (0.24-0.62)	Moderate
Fibrosis stage (CHFS)	0.35 (0.24-0.49)	Fair
Simplified fibrosis stage (CHFS 0-2B/3-4)	0.45 (0.31-0.61)	Moderate

Conclusions: Most common features of CH can be interpreted with fair-to-good level of agreement, with an overall moderate level agreement for the diagnosis of CH and fair agreement for CHFS. This finding raises the need for developing consensus standardized histologic criteria and a better staging system for CH.

1664 Glutamine Synthethase Expression in Liver Biopsies from Patients with Congestive Heart Failure

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Background: Long standing congestive heart failure can induce a constellation of histopathology changes in the liver and can alter the metabolic function. One small study reported loss of perivenular glutamine synthetase (GS) expression in 7 of 7 cases of congestive hepatopathy (Fleming KE and Wanless IR, Liver International 2013; 33:525-34). We aimed to characterize the expression pattern of GS in biopsies with a clinicopathologic diagnosis of congestive hepatopathy (CH).

Design: 24 liver biopsies with a consensus diagnosis of CH and 8 liver biopsies with no significant pathological changes were stained with GS. Normal GS expression was defined as a rim of strongly positive hepatocytes around the hepatic veins (perivenular pattern). Histologic features of CH were assessed and correlated with the staining pattern of GS. Kendall's tau-b correlation tests were performed to determine the correlation coefficients.

Results: All 8 control cases showed strong perivenular GS staining. 12 cases of CH showed retained and 12 cases of CH showed loss of the normal perivenular GS staining. Histologic features of CH (presence of sinusoidal dilation, centrilobular hepatocyte atrophy, hemorrhage, centrilobular or portal fibrosis) and the stage of fibrosis (congestive hepatic fibrosis score, CHFS) did not correlate with the loss of normal GS staining pattern (Table 1).

Histologic feature	Correlation coefficient	p value
Sinusoidal dilation (Absent/Present)	0.209	0.317
Centrilobular atrophy (Absent/Present)	0.092	0.66
Centrilobular hemorrhage (Absent/Present)	0.192	0.356
Centrilobular fibrosis (Absent/Present)	-0.126	0.546
Portal fibrosis (Absent/Present)	0	1
Fibrosis stage (CHFS)	0.107	0.571

Conclusions: Only half of the liver biopsies with CH show loss of the normal perivenular GS staining pattern, therefore this alteration is not a sensitive marker of CH. Furthermore, histologic features of CH and the stage of fibrosis cannot predict the loss of normal perivenular GS staining pattern in the biopsy.

1665 Hepar-1 Loss in Telangiectatic/Inflammatory Hepatic Adenomas – A Novel Observation with Potential Tumor Biology Implications

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Background: Hepatic adenomas (HA) are benign neoplasms generally thought to have normal expression of hepar-1 (an antibody that recognizes carbamoyl phosphate synthetase 1, a rate-limiting enzyme in the urea cycle) and other markers of hepatocellular differentiation. We have noted, however, that a subset of inflammatory/telangiectatic HAs may show aberrant loss of hepar-1 expression. In this study, we document and further characterize the prevalence of aberrant loss of expression of hepatocellular markers in HAs.

Design: Resection cases of hepatic adenomas diagnosed between 1997 and 2014 at our institution were retrieved and the diagnoses were confirmed independently by 3 liver pathologists. HAs were classified by immunohistochemistry using antibodies against liver fatty acid binding protein [LFABP], glutamine synthetase [GS], B-catenin, hepatic serum amyloid [SAA], and C-reactive protein [CRP]). Hepar-1 (predilute, clone OCH1E5, Ventana, AZ) and arginase (predilute, clone SP156, CellMarque, CA) were performed in all cases. Polyclonal CEA and glypican-3 immunostains, reticulin stain, and albumin in situ hybridization were performed in cases showing areas of hepar-1 loss.

Results: A total of 41 HAs (type I [HNF1-alpha mutated], n=10; type 2 [beta-catenin mutated], n=1; type 3 [inflammatory/telangiectatic], n=26; and type 4 [unclassified], n=4) were studied (mean age: 40 years [range: 17-74 years], gender [male=2 , female=39], median tumor size = 6.5 cm [range 1.6-17 cm]). Unequivocal areas of hepar-1 loss were seen in 8/41 cases (19.5%), with a median area of loss of 30% (range 5-95%). These foci of hepar-1 loss also showed at least some arginase loss in 7/8 cases. Albumin in situ hybridization and pCEA (canalicular pattern) were positive and reticulin stain was normal in all cases showing hepar-1 loss (Figure 1).

Conclusions: Aberrant loss of hepar-1 expression by immunohistochemistry is a novel observation in inflammatory/telangiectatic HAs and further investigation of the role of urea cycle enzymes and mitochondrial dysfunction in these lesions would be of interest from a tumor biology perspective.

1666 The Prognostic Value of Mitotic Rate in the Fibrolamellar Variant of Hepatocellular Carcinoma in a Well-Characterized Series of 13 Cases Showing DNAJB1-PRKACA Transcript

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Background: Fibrolamellar carcinoma (FLC) represents a rare variant of hepatocellular carcinoma which generally occurs in young, otherwise healthy individuals. Little is known about the proliferative rate in FLCs and its impact on prognosis.

Design: We have retrieved liver resection cases diagnosed as FLC at our institution from 1994-2014. All cases showed typical histologic features as well as the characteristic DNAJB1-PRKACA transcript by RT-PCR. In each case, a representative paraffin block was selected and tumor mitotic rate was assessed on H&E slides. Nikon digital DS-Fi2 camera and NIS-Elements Br software were utilized for mitosis and cell counts on 3 high-resolution digital images including a total area of 90 mm^2 and at least 500 tumor cells.

Results: A total of 13 cases were included (median age 27 [range, 19-48 years], gender: 5 males and 8 females, median tumor size 11.1 [range 8-17.5] cm). An average of 770 (range 509-1288) cells per case were assessed. The overall number of mitoses in FLCs was remarkably low, with 7/12 cases showing no identifiable mitotic figures in the examined fields. The remaining 5 cases showed an average of 3.3 (range 2-9) mitoses per 1000 tumor cells and an average of 3.4 (range 1-10) mitoses per cm^2 of tumor tissue. Mitotic activity ($\geq$1/1000 tumor cells or cm^2) was predictive of significantly increased mortality (P=0.006) and decreased disease-free survival (P=0.04) on Kaplan-Meier analysis, was associated with stage>II at presentation (P=0.008), and showed a trend towards increased risk of distant metastasis (P=0.06). All long-term (>2 years) disease-free survivors (n=3) had undetectable mitotic activity by the above-described method.

Conclusions: The proliferative rate is an important prognostic indicator in the fibrolamellar variant of hepatocellular carcinoma and identification of even a small proportion of mitotically active tumor cells may be clinically significant.

1667 In-Situ Hybridization for Albumin RNA in Pediatric Liver Cancers Compared to Common Immunohistochemical Markers

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Background: In situ hybridization (ISH) for albumin is known to be a sensitive and specific test of primary liver tumors. Previous use has been limited by lack of a simple commercially available protocol. A recently released albumin ISH platform has been studied in adult primary liver tumors (hepatocellular carcinoma, intrahepatic cholangiocarcinoma) and demonstrated high sensitivity for these tumors, while non-liver primary tumors did not react. Pediatric liver tumors have not been previously tested. Two pediatric liver malignancies which can be challenging for histopathologists include hepatoblastoma (HPB) and fibrolamellar hepatocellular carcinoma (FL-HCC). HPB may be challenging due to varied morphology (fetal and embryonal patterns) while FL-HCC often resembles adenocarcinoma. The aim of this study is to determine if ISH for albumin is a viable option in the pathologic work-up of these childhood malignancies. A secondary aim is to compare albumin ISH to common immunohistochemical markers, HepPar1 (HEPA) and Arginase-1 (ARG).

Design: Tissue microarrays (TMA) including 27 HPB and 10 FL-HCC were constructed. We evaluated a commercially available RNA ISH method using branched DNA technology to detect albumin (Affymetrix, Santa Clara, CA). Immunohistochemistry for HEPA (DAKO, Carpinteria, CA) and ARG(Sigma-Aldrich, St. Louis, MO) was carried out in the usual fashion.

Results: 27 of 27 HPB had appreciable albumin RNA by ISH. These included 15 with fetal pattern, 8 embryonal pattern and 4 mixed (embryonal and fetal) patterns. One mixed pattern showed reactivity only in the fetal component (3/4 stained both components). 23/27 cases showed diffuse positivity whereas 4/27 were focal. All 10 FL-HCC were diffusely positive. Sensitivity was 100% for HPB and FL-HCC. The number of signals in the positive cells was generally very high and easily appreciated. ARG also had 100% sensitivity for HPB (26 of 26 cases) and FL-HCC (9 of 9). HEPA stained only 23 of 27 HPB (85% sensitivity) and 7 of 9 FL-HCC (78% sensitivity).

Conclusions: Albumin RNA ISH is a useful test to determine hepatocytic origin in the relatively rare pediatric liver malignancies HPB and FL-HCC. ARG was equally sensitive and easy to interpret. HEPA was inferior to both in HPB and FL-HCC.

1668 Applying Criteria for Hepatocellular Neoplasm of Uncertain Malignant Potential Reclassifies >50% of Hepatocellular Adenomas

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Background: It can be impossible to differentiate hepatocellular adenoma (HA) from hepatocellular carcinoma (HCC). Hepatocellular neoplasm of uncertain malignant potential (HUMP) is a proposed diagnostic term for these problematic lesions. Criteria include focal reticulin loss, focal atypia, β-catenin (BC) activation, age >50 or <15 years, male sex, and tumors in glycogen storage disease. This study sought to validate the criteria on previously diagnosed HAs.

Design: 41 HAs resected from 1994 to 2013 from 31 patients were retrospectively reviewed. All were previously characterized morphologically and immunohistochemically with BC (Cell Marque, Rocklin, CA) and glutamine synthetase (GS, BioCare, Concord, CA). GS and/or nuclear BC positivity was considered BC activation. Available records were reviewed.

Results: 24 (59%) tumors met ≥1 criterion for HUMP. 10 (24%) met ≥2 criteria. The table lists criteria for each HUMP. 18 (58%) patients had a HUMP. HUMPs were 0.3-17 cm (mean: 5.9 cm) and HAs were 0.2-8.5 cm (mean: 3.9 cm), a difference approaching significance (p=0.509). 4 HUMPs had patchy GS staining without nuclear BC staining. For 2, this was the only HUMP-defining criterion. Of 31 patients, 3 had separate concurrent HCCs, only 1 of whom had a HUMP.

HUMP	Male	Glycogen Storage Disease	>50 or <15 Years Old	Atypia	BC	GS
1			X			
2				X		
3				X		
4			X			
5			X			
6	X					
7	X			X		
8	X			X		X
9				X		
10	X			X	X	X
11				X		X
12	X	X		X		
13	X	X				
14	X	X		X		
15	X	X		X		
16				X		
17				X		
18			X			
19	X					
20				X	X	X
21			X			
22						X
23						X
24	X		X		X	X

Conclusions: Patients with concurrent HCC did not correlate with those with HUMPs. >50% of HAs were reclassified as HUMP using the proposed criteria. Even more may have been called HUMP prospectively if reticulin stains had been applied to multiple sections. In the authors' experience, clinicians will not accept such a high rate of tumors placed in a category of uncertainty. Additional investigation is warranted into whether ≥2 criteria may be a better cutoff to define HUMP and to determine the role of GS in defining BC activation.

1669 Arginase Is Superior to Hepar for Distinguishing Clear Cell Hepatocellular Carcinoma from Clear Cell Tumors Metastatic to the Liver

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Background: Arginase (Arg) and hepatocyte paraffin antigen 1 (Hepar) are specific and sensitive markers of hepatocellular differentiation. Hepar is a granular cytoplasmic immunostain that may be negative in some clear cell variants of hepatocellular

carcinoma (CCHCC). Arg shows smooth cytoplasmic positivity and, in some reports, nuclear positivity. This study was undertaken to determine the staining pattern of Arg in CCHCC and compare its use to Hepar.
Design: 15 CCHCC resections and 31 biopsies of clear cell liver tumors (14 CCHCC and 17 metastases) were retrieved from departmental files. Resections were stained with Arg (Biocare, Concord, CA), and biopsies were stained with Arg (n=31) and Hepar (n=28) (Dako, Carpinteria, CA). Arg staining was characterized as cytoplasmic, nuclear, or combined; intensity graded as 0 (none), 1+ (weak), or 2+ (strong) compared to cirrhotic liver as a control; and distribution was described as negative (0%), focal (1-10%), patchy (11-50%), or diffuse (>50%). Hepar intensity and distribution were described similarly. In cases with areas of conventional hepatocellular carcinoma, only CCHCC areas were examined. Each immunostain was interpreted with the accompanying H&E-stained slide, but blinded to the diagnosis and to the status of the other immunostain.
Results: Resections: 13/15 (87%) CCHCC showed diffuse Arg staining, with 1 showing patchy and 1 showing focal staining. 14/15 (93%) showed nuclear and cytoplasmic staining. 1 showed only nuclear staining. 12/15 (80%) showed 2+ intensity, and 3 showed 1+. Biopsies: 8/14 (57%) CCHCC showed 2+ Arg staining, and 5 showed 1+. 9/14 (64%) CCHCC showed nuclear and cytoplasmic staining, and 4 showed cytoplasmic only. See the table for comparison of Arg and Hepar in biopsies. Arg was 92.9% sensitive and 100% specific for CCHCC on biopsy. Hepar was 91.7% sensitive and 37.5% specific.

	Biopsies	
	CCHCC (n=14)	Metastases (n=17)
Arg positive	13	0
Hepar positive	11	6
p=0.0237 (Fisher's exact test)		

Conclusions: Arg is more sensitive and specific for CCHCC compared to metastatic clear cell tumors than Hepar. Most cases show nuclear and/or cytoplasmic Arg positivity, and nuclear staining is preserved even when the cytoplasm is overtaken by fat or clearing. Overall, Arg appears to be superior to Hepar for distinguishing CCHCC from clear cell tumors metastatic to the liver.

1670 Mechanical Forces Directly Modulate Hepatocellular Expression & Distribution of Nuclear Lamina Proteins Lamin A & B: Congestive Hepatopathy as a Pure Force Injury Model

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Background: The nuclear lamina is predominately composed of intermediate filament proteins lamin A/C & lamin B. Decreased expression of lamins increases nuclear deformability & cell mobility. While there is clear data to show the impact of altered lamin expression on cell-matrix behavior, there are no studies on the effect of the extracellular physical space on lamin expression. Congestive hepatopathy offers a unique model in which mechanical forces are the sole cellular injury variable. We use this system to test our hypothesis that mechanical forces alone may directly alter hepatocellular nuclear structure through modulated expression & nuclear distribution of lamin A/C & B.
Design: IHC for lamins A/C & B was performed on fixed liver sections from normal (9), cirrhotic ("Cir", 11 HCV, 3 NAFLD, 1 Etoh), & congestive hepatopathy ("CH", 38 CHF, 1 Budd-Chiari). The degree of fibrosis in CH was scored from 1-5 (5=central-to-portal). Slides were scanned into images according to standard protocol for the Vectra® slide imaging system. Using InForm® image analysis software, hepatocyte nuclei were differentiated from other cells & expression levels of lamins A/C & B & nuclear measurements were measured.
Results: Lamin B increased in intensity by a factor of 1.75 & 1.3 in CH & Cir, respectively, relative to normal livers but maintained the same nuclear area distribution in normal, CH and Cir. In contrast, lamin A/C did not change in Cir compared to normal but did increase 1.5 fold in CH with a smaller, normalized nuclear area distribution (0.73) compared to normal & Cir. Lamin B was always expressed more than A/C by a factor of 4. The shape of the nuclei with regard to lamin A/C distribution in normal & Cir was slightly elliptical & became more spherical in CH (nuclear axis ratio: 1.45, 1.38 & 1.25, respectively) while that for lamin B remained elliptical (nuclear axis ratio: 1.47, 1.47, & 1.41, respectively). In CH, there was no relationship with the degree of fibrosis & the expression of lamins or their nuclear distribution.
Conclusions: Increased external pressure alone was associated with increased hepatocyte expression of lamins, decreasing nuclear deformability to buttress against this force, & a spherical nuclear shape, the optimal physical form to buttress increased pressure. Interestingly, the minimal changes with cirrhosis may reflect altered fluid dynamics & pressure. We thus show the importance of the physics, independent from the composition, of the microenvironment on nuclear structure.

1671 TFE3 Immunohistochemistry Is Useful to Distinguish Epithelioid Hemangioendotheliomas from Angiosarcomas and Hemangiomas of the Liver

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Background: Epithelioid hemangioendotheliomas (EHEs) of the liver can be difficult to diagnose, with up to 75% misdiagnosed at original presentation. In particular, EHE is difficult to distinguish from angiosarcoma, as both may show similar histologic and immunohistochemical (IHC) features. Genetic testing for CAMTA1-WWTR1 or YAP1-TFE3 translocations can be used to definitively diagnose EHE, but these tests are expensive and not currently readily available for clinical use. Recent work has shown that TFE3 IHC staining is present in up to 75% of EHEs. To date, however, no systematic study has been carried out to determine whether TFE3 IHC can differentiate EHE from other vascular tumors.
Design: We performed TFE3 IHC on 12 EHEs, 21 angiosarcomas and 15 hemangiomas. The proportion of tumor cells stained and the intensity of staining was recorded.
Results: Eight of twelve EHE cases had positive staining for TFE3, whereas only 2 of 21 angiosarcomas (p=0.0012) and 1 of 15 hemangiomas (p=0.0027) were positive. The overall sensitivity of TFE3 staining for EHE was 66.7%, and overall specificity was 91.7% compared to other vascular tumors.
Conclusions: TFE3 IHC is useful in the diagnosis of EHE and, in conjunction with morphologic and clinical features, is helpful in distinguishing EHE from angiosarcoma and hemangioma.

1672 Fatty Liver Binding Protein 4: A New Mediator in Liver Carcinogenesis Related to Metabolic Syndrome

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Background: Metabolic syndrome (MS) is becoming the leading risk factor for hepatocellular carcinoma (HCC) worldwide. In addition to common pathway associated with cirrhosis, liver carcinogenesis may involve more specific molecular pathways related to MS, such as systemic inflammation due to cytokines and adipokines production. Fatty Acid Binding Protein 4 (FABP4) is one of them. We have previously shown FABP4 upregulation in HCC related to SM, mainly through peritumoral endothelial cells, and its oncogenic effects in hepatoma cell lines.
The aim of our study was to investigate (1) the expression of FABP4 during human hepatic carcinogenesis, (2) FABP4 regulation in endothelial cells and (3) the role of microvesicles as messengers conveying FABP4 from endothelial cells to tumoral cells.
Design: FABP4 plasma levels were quantified by ELISA on samples from patients with cirrhosis related to MS (MS, n=14) or Hepatitis C Virus (HCV, n=14), with or without HCC and from controls (n=7). Expression,regulation and secretion of FABP4 were investigated in endothelial cells using HUVEC and Liver Sinusoidal Endothelial Cells (LSEC) by Western Blot upon various mediators (insulin, glucose, TNFα, VEGF) and inhibitors (metformin, sorafenib and everolimus).
Results: FABP4 plasma levels were significantly higher in MS patients than in HCV patients (30.1 *vs* 13.0 ng/mL, p<0.01) and in controls (11.5 ng/mL, p=0.01).FABP4 expression was significantly upregulated in endothelial cells by VEGF (50 ng/mL, 24 hours, p<0.01) and MS factors (glucose 25 mM, insulin 20 nM, and TNFα 10 nM, 24 hours, p<0.01). Significant downregulation was observed when mTOR pathway was inhibited using, either metformin (10mM, 24 hours, p<0.05), sorafenib (1 μM, 24 hours) or everolimus (0.1 μM, 24 hours). Endothelial cells secreted FABP4 partially linked by microvesicles. Free fraction and fraction linked to microvesicles represented each 50% of total FABP4. Finally, confocal microscopy demonstrated the presence of endothelial microvesicles at the surface of hepatoma cell lines confirming the microvesicles potential to transport FABP4 from endothelial to tumoral cells.
Conclusions: This study supports the role of FABP4 in liver carcinogenesis related to SM and highlights the crosstalk between tumoral hepatocytes and endothelial cells.

1673 Early Hepatocellular Carcinoma with High-Grade Atypia in Small Vaguely Nodular Lesions

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Background: Multistep hepatocarcinogenesis progresses from dysplastic nodules to early hepatocellular carcinoma (eHCC) and to advanced HCC. The aim of this study was to investigate the detailed histopathological features of eHCC.
Design: We investigated 66 small vaguely nodular lesions resected from 40 patients. The degree of cellular and structural atypia and stromal invasion were assessed. The immunohistochemical expression of HCC-related markers adenylate cyclase-associated protein 2 (CAP2), heat shock protein 70 (HSP70), Bmi-1, CD34, and h-caldesmon were evaluated.
Results: Of the 66 nodules, 10 were diagnosed as low-grade dysplastic nodules (LGDN), 10 as high-grade dysplastic nodules (HGDN), and 46 as eHCC. Among the 46 eHCCs, 18 nodules (39.1%) showed marked stromal invasion and/or the presence of the scirrhous component and were subclassified as high-grade eHCC (HGeHCC). The remaining 28 eHCCs, which lacked these features, were subclassified as low-grade eHCC (LGeHCC) and were examined further. HGeHCC showed high levels of cellular and structural atypia and large tumor size. The immunohistochemical expression of CAP2 and the area of sinusoidal vascularization showed increases from LGDN to HGeHCC. The density of arterial tumor vessels was high in HGeHCC compared with other nodule types. Cluster analysis of these parameters subclassified 65 nodules into HGeHCC-dominant, LGeHCC and HGDN-dominant, and LGDN-dominant groups.
Conclusions: These results indicate the increased malignant potential of HGeHCC and suggest that it is already a transitional stage to advanced HCC. We consider that our grading classification system may be valuable for considering treatment strategies for eHCCs around 2 cm in diameter.

1674 Are Eosinophilic Glassy Globules in Autoimmune Hepatitis, a Histologic Clue to Diagnosis?

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Background: The diagnosis of autoimmune hepatitis (AIH) is a combination of autoantibodies, IgG level, histology and exclusion of other diseases. However, none of these parameters are pathognomonic for its diagnosis. A recent study on pediatric AIH described the presence of hyaline droplets in Kupffer cells as a useful diagnostic clue for AIH. The aim of the study was to evaluate significance of eosinophilic globules (EG) in diagnosis of AIH and their correlation with clinical and histologic features in adult population.

Design: We reviewed 88 liver biopsies and their clinical data with AIH (n=62) and HCV (n=26) diagnosis. AIH included 6 cases of overlap syndrome. H&E and PAS-D sections were evaluated for the presence of EG in Kupffer cells. Presence or absence of EG was correlated clinically with serum IgG, ANA, SMA and AMA; and with histology including plasma cells (PC), interface hepatitis, emperipolesis and rosettes. The EG, rosettes and emperipolesis were assigned a score of 0-2, with 0: no EG, rosettes or emperipolesis, 1+: 1-2/HPF and 2+: >=3/HPF. PC was scored as 0-3, with 0: no PC, 1:1-2/HPF, 2: at least 1 cluster of 5 PC; 3: > 1 cluster. ANOVA and T-test were utilized for statistical analysis.

Results: Mean age of AIH patients was 52.3 years. Male:Female was 8:54. EG was identified in 46 of 62 cases (74.1%) in AIH group; 24 (38.7%) showed 2+ EG and 22 (35.5%) 1+. 16 (25.8%) showed no EG. Sensitivity was 74.2%. All 6 overlap syndrome cases were positive for EG. Presence or absence of EG showed a significant correlation with histologic parameters except stage.

Eosinophilic Globules	Interface Activity (average score)	Plasma cells (average score)	Rosettes (average score)	Emperipolesis (average score)	Grade (average)	Stage (average)
2 + (N=24)	2.04	1.58	1.04	1.08	2.45	1.70
1 + (N=22)	1.90	1.45	0.77	0.72	2.09	1.68
0 (N=16)	0.50	0.50	0.12	0.00	0.68	1.68
Significance(p)	<0.0001	0.002	0.0002	<0.0001	<0.0001	0.998

Clinical parameters did not show any significant correlation with EG; but average serum IgG (normal: 700-1600 mg/dl) was high in EG positive group (2042 mg/dl with 2+EG and 1831 mg/dl with 1+EG) and normal (1514 mg/dl) in no EG group (p=0.26). Among HCV, only 1 in 26 (3.7%) case was positive for EG and this patient had high IgG of 4314 mg/dl. Specificity was 96.2%.

Conclusions: EG in Kupffer cells is an important morphologic clue to the diagnosis of AIH. In contrast to pediatric AIH, EG significantly correlates with AIH histology in adult population.

1675 Neuroglobin and Cytoglobin, Regulators of Oxidative Stress Are Associated with Poor Prognosis in Hepatocellular Carcinoma

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Background: No reliable immunohistochemical marker is available to clinically predict the prognosis of Hepatocellular carcinoma (HCC). Neuroglobin (Ngb), and Cytoglobin (Cytb), both serve as reactive oxygen species sensor, functions as tumor suppressor proteins in HCC. Previous studies have shown lower levels of Ngb and Cytb mRNA in Hepatic cancer cell line. We, for the first time evaluated Ngb and Cytb expression in human hepatocellular carcinoma, in wedge resections and correlated with patient survival.

Design: With the approval of IRB, a total of 49 wedge resection specimens from 49 patients were selected for the study. 5 µm paraffin sections were immunostained with Anti-Ngb and Anti-Cytb antibodies. The expression of Ngb and Cytb was evaluated with H-score method for both staining intensity (0-3) and percentage of positive cells (0-3). The mean value of the H-score of Ngb and Cytb in hepatocellular carcinoma and adjacent cirrhotic liver tissue were analyzed by two-way analysis variance. Survival curve was calculated using the Kaplan-meier method. All results with a p value <0.05 were considered statistically significant.

Results: Most were males (40, 80%), predominatly Caucasians (28, 57%), with pre-existing cirrhosis with a mean age of 63 years (range, 28-76 years), size ranges [55% had multiple nodules (average 1.5 cm) and 45% had single nodules (average 3.6 cm), vascular invasion (5/46,11%) and distant metastasis (2/49, 4%). Positive Ngb and Cytb displayed cytoplasmic/ perinuclear staining in hepatocytes. Compared to the adjacent cirrhotic areas, HCC's areas showed significant lower expression of Ngb (H score for Ngb, 141±71 in cirrhosis vs 88 ±53 in HCC, p< 0.01) and Cytb independent of age, >5 cm of tumor size, pTNM staging, vascular invasion/metastasis. The median cancer free survival is 4 years and 7/48 (15%) patients died during the 60 months median clinical follow-up. The patients with lower expression of Ngb and Cytb had a shorter survival compared to the ones with higher expression.

Conclusions: Ngb and Cytb expression is decreased in HCC. The decreased expression of Ngb and Cytb may predict poor prognosis independent of tumor size, advanced TNM stage, presence of vascular invasion and metastasis.

1676 Role of the Histone Acetyltransferase hMOF and H4K16 Acetylation in Vascular Invasion and Tumor Progression in Hepatocellular Carcinoma

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Background: Microvascular invasion (mVI) is a major prognostic factor in hepatocellular carcinoma (HCC). We previously showed that a modified form of histone H4 (histone H4 acetylation on lysine 16, H4K16ac), was significantly overexpressed in HCC with mVI (HCC/mVI+) compared to HCC without mVI (HCC/mVI-) (*Poté et al.,* HEPATOLOGY 2013). H4K16 acetylation plays a major role in transcription activation, and it has been shown that hMOF (human Males absent On the First), the H4K16 acetyltransferase, was involved in many cancers. How hMOF and H4K16 acetylation contribute to liver carcinogenesis remains elusive. Since chromatin-modifying enzymes have recently gained paramount importance in cancer therapy, it is worthwhile to investigate the role of hMOF in vascular invasion and tumor progression in HCC.

Design: We first assessed hMOF expression by immunohistochemistry (IHC) and RT-qPCR in 55 HCC surgical specimens (mVI+, n=29; mVI-, n=26). For IHC, a semi-quantitative score (0-300) was calculated (% of stained cells [0-100] x staining intensity [1 weak; 2 intermediate; 3 strong]), blinded to the clinicopathological data. We next assessed hMOF role in cell proliferation, migration and invasion in hepatoma cell line PLC/PRF/5 using siRNA. Finally, a microarray transcriptomic analysis was performed to globally determine genes specifically regulated by hMOF and H4K16 acetylation in PLC/PRF/5 cell line.

Results: hMOF was significantly overexpressed at the protein level in HCC/mVI+ compared to HCC/mVI- (IHC median score 180 *versus* 70; p= 0.002). siRNA-mediated hMOF knockdown led to a significant H4K16ac overall decrease and cell proliferation inhibition. Transcriptomic analysis showed that hMOF downregulation was associated with repression of genes involved in cell proliferation, migration, invasion and angiogenesis, including *AXL, CYR61, LGALS1, FRS2, S1PR3 and CEACAM1*.

Conclusions: In summary, our results underpin a critical role for hMOF and H4K16 acetylation in vascular invasion and tumor progression in HCC, *via* transcriptional activation of genes involved in these processes. Furthermore, these data pave the way for future *in vivo* validation and additional experiments would further confirm the role of these genes in liver carcinogenesis.

1677 A Panel of Three Markers (H4K20me2, H4K16ac and PIVKA-II) for Prediction of Microvascular Invasion in Hepatocellular Carcinoma

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Background: Microvascular invasion (mVI) is a major risk factor for hepatocellular carcinoma (HCC) post-operative recurrence, only assessable on microscopic examination of the surgical specimen. There are currently no validated predictive tissue biomarkers of mVI. We previously showed that PIVKA-II (Prothrombin Induced by Vitamin K Absence-II) and two modified forms of histone H4, namely H4K20me2 (Histone H4 dimethylated on K20) and H4K16ac (histone H4 acetylated on K16), were performant predictive tissue biomarkers of mVI in HCC on surgical specimens (*Poté et al.*, J Hepatol 2015 and Hepatology 2013).

This study aimed to assess (1) the concordance of H4K20me2, H4K16ac and PIVKA-II immunostainings between surgical and biopsy specimens of HCC, and (2) the performance of this panel for prediction of mVI on biopsy samples of HCC.

Design: This retrospective study included sixty four HCC surgical specimens (mVI+, n=33 ; mVI-, n=31) and an independent series of fifty two HCC biopsy samples (mVI+, n=31 ; mVI-, n=21) (« routine biopsies »). Immunostainings for H4K20me2, H4K16ac and PIVKA-II were performed on consecutive slides for each case, and the percentage of immunoreactive tumor cells was semi-quantitatively assessed, blinded to the clinico-pathological data. Optimal cut-off values for prediction of mVI for each marker were first determined in surgical specimens, and then applied in " virtual biopsies " performed on digitalized slides of these specimens, and in the series of routine biopsies samples.

Results: Concordance of immunostainings between the surgical specimens and the virtual biopsies was high (H4K20me2, rs = 0.82 ; H4K16ac, rs = 0.83 ; PIVKA-II, rs = 0.79. p <0,001). H4K16ac had the best performance for prediction of mVI in both virtual and routine biopsies, with a sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) of 45%, 87%, 79% and 60% in virtual biopsies and 58%, 52%, 64% and 46% in routine biopsies, respectively. When combined with PIVKA-II immunostaining, performance of the panel reached a Se, Sp, PPV and NPV of 21%, 97%, 87% et 54% in virtual biopsies and 35%, 81%, 73% and 46% in routine biopsies, respectively.

Conclusions: The panel of three markers is efficient for predicting mVI in biopsy samples of HCC and then could allow the identification of HCC patients with high risk of post-operative recurrence.

1678 Liver Transplantation in the Setting of Hepatocellular Carcinoma: Role of Tumor Differentiation in Predicting the Risk of Recurrence

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Background: The criteria for liver transplant in the setting of hepatocellular carcinoma (HCC) are largely based on tumor size and number, as determined by imaging. Pre-transplant liver biopsy is seldom used for diagnosis or risk stratification of these cases.

This study examines the correlation of pathologic features of the tumor with recurrence, with emphasis on tumor differentiation, a feature that can potentially be evaluated on pre-transplant biopsies.

Design: Of the 1,060 liver transplants performed at our institution between 1997 and 2015, 167 had a pre-operative diagnosis of HCC. 143 (86%) cases fell within Milan criteria, and 17 (10%) within UCSF criteria. The pathologic features of the tumor in the explant were recorded, along with clinical and follow-up data, and correlated with HCC recurrence risk.

Results: The risk of recurrence was significantly higher in poorly differentiated HCC (23%), compared to moderately differentiated (12%) and well differentiated histology (4%) (p=0.02). Three or more masses on pre-transplant radiologic evaluation was also a significant risk factor for recurrence (31% recurrence rate, p=0.04). In explants with one or two masses on pre-operative imaging (12% and 5% recurrence rate, respectively), those with poor differentiation showed a significantly higher recurrence rate of 31% (p=0.003, see table).

HCC Recurrence from Explants with 1 or 2 Masses on Pre-operative Imaging			
Histologic Grade	**Total cases**	**Recurrent cases**	**Percentage**
Well differentiated	55	0	0.00%
Moderately differentiated	65	12	18.46%
Poorly differentiated	13	4	30.77%

Conclusions: Poor differentiation and presence of multiple tumors (>3) are significant risk factors associated with recurrence of HCC. Even in HCC forming one or two nodules, poor differentiation was associated with a significantly higher recurrence. Pre-transplant liver biopsy can provide valuable prognostic information about the risk of HCC recurrence and should become a standard procedure in the work-up for patients who have a radiologic diagnosis of HCC and are being considered for transplantation.

1679 Caught in Action! Hepatic Arteriolar Thrombi Are a Likely Cause of Ischemic Cholangiopathy (IC) in Donation after Cardiac Death (DCD) Allografts

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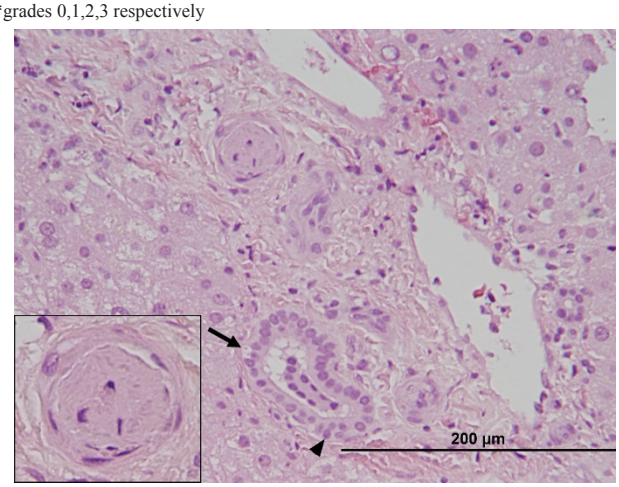
Background: Allografts from DCD donors are associated with a 15-50% incidence of IC. A possible cause is thrombi formation in peribiliary arteriolar plexi due to flow stasis. Surgeons at our institute have initiated a protocol to flush the hepatic artery with tissue plasminogen activator (tPA) during procurement to prevent thrombi formation, eliminate IC and reduce risk of bleeding in DCD recipients. We compared liver biopsies taken during the first week post-transplantation from DCD allografts that received a tPA flush with those from DCD allografts that did not receive a tPA flush during procurement.

Design: DCD allograft recipients with and without tPA flush at procurement were identified and clinical data obtained from the transplant surgery database. H&E stained slides of biopsies performed during the first week of transplantation were retrieved from the pathology archives. Hepatocellular necrosis, biliary epithelial injury, peribiliary neutrophilic infiltrate and bile ductular proliferation were each graded from 0 to 3. Acute rejection was graded as indeterminate, mild, moderate or severe. Presence of arteriolar thrombi was recorded.

Results:

	DCD with tPA (n=18)	DCD without tPA (n=21)
acute rejection: %; indeterminate, mild, moderate, severe	17%; 1,2,0,0	38%; 1,4,3,0
arteriolar thrombi	0	2
hepatic necrosis*	8,6,3,1	12,9,0,0
biliary epithelial damage*	0,5,12,1	0,10,10,1
peribiliary neutrophils*	1,12,5,0	0,9,10,2
bile ductular proliferation*	4,11,3,0	5,5,11,0
IC	0	10
follow-up: range; median	9 mths- 4 yrs; 2.5 yrs	6 mths-11 yrs; 8 yrs

*grades 0,1,2,3 respectively



Occlusive thrombus in hepatic arteriole (inset). Bile duct shows apoptosis (arrow) and overlapping nuclei (arrow head)

Conclusions: 1) Hepatic arteriolar thrombi are a likely cause of IC in DCD allografts. A liver biopsy samples smaller peripheral portal tracts, thus limiting the finding of thrombi which are thought to form mainly in peribiliary plexi of large perihilar ducts. This may explain why thrombi were seen only in 2 biopsies that had not received a tPA flush.
2) Hepatic arterial tPA flush virtually eliminates IC.
3) Incidence of rejection is lower in allografts that receive tPA flush.

1680 Primary and Secondary Hepatic Presentation of Hodgkin Lymphoma: A Multi-Institutional Study

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Background: Hodgkin lymphoma (HL) is usually a nodal-based malignancy that spreads contiguously. Hepatic involvement occurs late as advanced disease or during relapse. Primary hepatic HL is rare with only limited reports in the literature. We studied the pathologic manifestations of HL in the liver, primary or secondary, to identify diagnostic clues to facilitate recognition.

Design: From 4 medical institutions, 22 patients (mean age 50 years;range 14–77 years;7 females) with HL in the liver were identified. Demographics, clinicopathological features, and IHC were evaluated.

Results: Eight patients (36.4%) had primary hepatic HL and 14 had secondary HL. Four (50%) with primary hepatic HL were immunocompromised (3 on immune-modulators for Crohn disease, lung transplant and liver transplant and 1 with HIV/AIDS); none in the secondary involvement group. Pathologically, there were 2 patterns, patchy portal involvement by HL in association with granulomas (54.5%) and sclerosing nodules diffusely involving the liver. The lesional cells included Reed-Sternberg (RS) cells (36.4%), variant Hodgkin cells (63.6%), eosinophils (100%), lymphocytes and plasma cells in both hepatic presentations. The patchy involvement was observed in 75% and 42.9% of primary and secondary groups, respectively. The frequencies of granulomas were 50% and 28.5% in primary and secondary groups, respectively. RS cells were appreciated in 50% and 28.5% and variant Hodgkin cells were present in 50% and 71.5 % of primary and secondary groups, respectively. EBER reactivity rates were 83.3% and 55.6% in primary and secondary hepatic groups, respectively.

Conclusions: Primary hepatic HL occurs frequently in the setting of immunodeficiency, which appears to be related to EBV infection. Hepatic HL manifests as 2 distinct histologic patterns – patchy portal involvement by HL in association with granulomas and diffuse sclerosing nodules. The morphological clue leading to the diagnosis is the presence of enlarged atypical cells resembling RS or lacunar/mummified cells, which can be confirmed by immunohistochemistry. Relying on typical RS cells for diagnosis yields low sensitivity as they are often absent whereas variant Hodgkin cells are more common. Abundant eosinophils in the infiltrate are also a morphological hint. Acquaintance of histologic features of hepatic HL is the key to avoid diagnostic errors, especially when clinical indication is ambiguous.

1681 Sinusoid Endotheliitis as an Early Histological Parameter for Diagnosing Liver Allograft Rejection

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Background: Histological diagnosis of acute cellular rejection in liver allografts is based on Banff schema that includes portal inflammation; bile duct damage; and venous endotheliitis. Each component of Banff schema is scored on a scale of 0 - 3 and the added scores are reported as the final rejection activity index (RAI). One of the limitations of this traditional pathological evaluation is the variation in portal number in each liver biopsy and the patchiness of portal changes. The relatively low circulation pressure and large surface area make sinusoidal endothelium a unique interface between the graft and the recipient's immune system.

Design: In this study, we investigated the feasibility of using sinusoid endotheliitis (SE) as an early diagnostic marker for liver allograft rejection by comparing the histological features of 45 liver transplant (LT) biopsies with acute cell rejection (ACR) and 37 cases with no evidence of ACR.

Results: SE was scored as 1, focal linear lifting up the endothelial cells by inflammatory cells with no obvious damage to adjacent hepatocytes; 2, focal disruption of endothelial lining with subendothelial cluster of inflammatory cells; 3, severe confluent endotheliitis with hepatocyte loss and fibrosis. The sensitivity and specificity of diagnosing ACR using SE were 84% and 57%, respectively. The Positive predictive value (PPV) was 0.70, whereas the negative predictive value (NPV) was 0.75. Among 16 patients without ACR at the time of diagnosing SE, 6 cases (37.5%) had subsequent ACR in repeat biopsy.

Conclusions: Our data suggest that SE scoring was a sensitive and specific parameter for diagnosing early ACR as well as predicting the occurrence of ACR in appropriate clinical setting.

1682 The Effect of Post-Liver Transplantation Therapy with Ledipsavir/Sofosbuvir on the Risk of Acute Graft Rejection

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Background: Infection with hepatitis C virus (HCV) is the leading indication for liver transplantation in the US. Recurrent infection is universal in patients with detectable serum HCV RNA at time of transplantation and is a major cause of graft loss and death, creating a need for effective treatment for HCV recurrence after transplantation. Recently treatment of recurrent HCV has significantly improved with the development of direct-acting antivirals with high rates of sustained virologic response (SVR). Ledipasvir/sofosbuvir (LS) is the first once-daily oral combination therapy that does not

require the coadministration of interferon (IFN) and/or ribavirin. This is significant as IFN-based therapy has been associated with increased rates of acute rejection (ACR). Although studies have shown LS to have superior SVR rates compared to historical controls in the non-transplant population, its outcome on liver transplant recipients has not been studied. In this study, we examine the incidence of ACR of liver transplant recipients treated with LS.

Design: We performed retrospective chart reviews of liver transplant recipients from 1/2012 to 8/2015. They were classified into 4 groups by the post-transplant protease inhibitor: LS, simeprevir (S), telaprevir (T), none (N). We collected data on recipient variables: sex, age at transplant, date of transplant as well as whether they received IFN therapy. ACR data included incidence, interval until first episode, severity, and number of episodes. Statistical analysis using Fisher's exact test was performed.

Results: Out of 139 transplant recipients, 32 received LS, 13 received S, 5 received T, and 89 N. The T group received significantly more IFN therapy (80%) than other cohorts (N 2.2%, LS 9.3%, S 23%). The incidence of ACR did not differ significantly among the treatment groups: N (24%), S (46%), LS (50%), and T (60%), nor did the severity of ACR episodes by average Banff score (N 5±0.91, S 6±0.82, LS 8±0.82, and T 5±0.91). The N and LS groups both averaged 1 episode of ACR, which differed significantly from the S and T groups (mean = 2 episodes, $p < 0.05$) . The S group had significantly longer time free from ACR from the N and T groups; the LS group did not show a significant difference from other groups.

Conclusions: Treatment of recurrent HCV with LS after liver transplantation has a similar risk and severity of acute rejection as other protease inhibitors, and may result in fewer episodes of ACR. The decreased episodes of acute rejection may be partially due to the agent's allowance of IFN-free therapy.

1683 A Novel Histologic Diagnostic Algorithm for Hepatic Graft Versus Host Disease

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Background: The pathologic diagnosis of hepatic graft versus host disease (GVHD) post bone marrow transplantation (BMT) can be difficult, but timely and unambiguous diagnosis is essential for favorable patient outcome. To address this diagnostic dilemma, we identified histologic features specific for GVHD and developed a diagnostic algorithm.

Design: Two hepatopathologists blindly evaluated 42 liver biopsies from well characterized patients with definite GVHD and 22 matched controls (TPN, DILI, steatohepatitis, normal) for % bile duct [BD] loss, BD damage (0=none, 1=single cell necrosis/apoptosis, 2=confluent dropout, 3=loss), intraepithelial lymphocytes [IELs] (0=none, 1=1, 2=2-3, 3=>3), ductular reaction [DR] (0=none, 1=isolated, 2=beyond two hepatocytes, 3=extensive), hepatocyte apoptoses/10 HPF, cholestasis (0=none, 1=zone 3, 2=zones 2 & 3, 3=panlobular/bile infarct), portal and lobular inflammation, and endotheliitis.

Results:

Table 1. Histologic features.

Feature	GVHD	Controls	p value
% BD loss	24.1±14.1	7.4±14.1	<0.0001
BD damage	2.2±0.8	0.6±0.9	<0.0001
Apoptoses/10 HPF	1.4±1.4	0.2±0.5	0.0006
Cholestasis	1.5±1.2	0.2±0.7	<0.0001
DR	0.3±0.5	1.0±0.8	0.0001
IELs	0.4±0.5	0.2±0.4	NS
Portal inflammation	0.8±1.0	1.0±0.6	NS
Lobular inflammation	0.9±0.7	0.9±0.9	NS
Portal endotheliitis	0.3±0.5	0.3±0.7	NS
Hepatic endotheliitis	0.0±0.2	0.1±0.3	NS

There were no differences in histologic features in acute (<80d post BMT) vs chronic (>80d) GVHD. An algorithm to predict the likelihood of GVHD was developed: [BD loss (0=<10, 1=10-24, 2=25-49, 3=>50%) + BD damage (0-3, as above) + hepatocyte apoptoses (0=<1, 1=≥1 per 10 HPF) + cholestasis (0=absent, 1=present)] ─ [DR (0=absent, 1=present)]. Scores are interpreted: -1-2=not GVHD; 3-4=possible GVHD; 5-8=unequivocal GVHD. This algorithm had a sensitivity of 92% and specificity of 95%.

Conclusions: 1) We identified histologic features with specificity for GVHD and developed a simple algorithm for pathologists to predict the likelihood of GVHD, distinguishing this critical diagnosis promptly from mimickers with vastly different treatments and prognoses. 2) Our findings support the continued value of liver biopsy. 3) No histologic findings are specific for the current acute/chronic definition of GVHD; delineation based on BD loss, as in chronic rejection, may be more meaningful.

1684 Poorly Differentiated Hepatocellular Carcinomas and Hepatocellular Carcinomas with a Brisk Lymphocytic Infiltrate Are Enriched for PD-L1 Expression on Tumor Cells

Michael Torbenson, Taofic Mounajjed, Robert R McWilliams, Rondell Graham. Mayo Clinic, Rochester, MN.

Background: The need for clinical targeted therapies for hepatocellular carcinoma (HCC) is currently unmet and the prognosis for non-resectable HCC is poor. Programmed cell death protein (PD-1) blockade is a novel means of immunotherapy, the efficacy of which may be predicted by programmed death-ligand 1 (PD-L1) expression in tumor cells. HCC has not been evaluated for PD-L1 expression and correlation with histologic characteristics.

Design: We retrieved 80 HCC and assessed them for grade, histologic subtype, underlying liver disease, cirrhosis, tumor size, vascular invasion, tumor infiltrating lymphocytes (TILs) and PD-L1 expression of tumor cells by immunohistochemistry (clone E1L3N, Cell Signaling). PD-L1 was scored as follows: 1+ 1-10%; 2+ 11-50% and 3+ >50%). Statistical analysis was by Fisher's exact 2-tailed t test.

Results: PD-L1 was positive in 8 cases (10%); 1+ (n=3), 2+ (n=4), 3+ (n=1) including 3 conventional, 3 lymphocyte-rich, 2 sarcomatoid HCC. These tumors affected 5 men and 3 women and ranged in size from 0.7 to 12.3 cm. PD-L1 positive tumors were poorly differentiated (n=5) and moderately differentiated (n=3). Five (62.5%) PD-L1 positive cases showed brisk TILs; 3 of which were lymphocyte-rich (>50% of tumor). Underlying liver disease (hepatitis B (n=1), hepatitis C (n=3) and NASH (n=2)) was present in 6 (75%) positive cases. In 2 cases, there was no underlying liver disease. In 4 cases, there was cirrhosis. PD-L1 expression was more likely in cases with brisk TILs (62.5% vs 7%; p=0.0005) and in cases which were poorly differentiated (62.5% vs 14%; p=0.007). No other significant associations were observed.

Conclusions: PD-L1 expression by tumor cells of HCC was significantly associated with high grade and brisk TILs. Studies and clinical trials evaluating PD-1 blockade would benefit from selecting and stratifying patients by these morphologic features. Our data suggest high grade HCC and HCC with brisk TILs are more likely to respond to this targeted therapy.

1685 Programmed Death Ligand-1 Expression on Tumor Cells in Cholangiocarcinoma Is More Frequent in Poorly Differentiated and Intrahepatic Tumors and Tumors with Brisk Tumor Infiltrating Lymphocytes

Michael Torbenson, Taofic Mounajjed, Benjamin R Kipp, Robert R McWilliams, Rondell Graham. Mayo Clinic, Rochester, MN.

Background: Programmed death-ligand 1 (PD-L1) expression by tumor cells may predict response to immune checkpoint inhibition, a novel form of immune-oncology therapy. Non-resectable cholangiocarcinoma (CCA) has a dismal prognosis and targeted therapies are an important approach for improving patient outcomes. CCA has not been assessed for PD-L1 expression and correlation with histologic and mutational characteristics.

Design: We retrieved 82 CCA and characterized them for tumor location, grade, tumor size, density of tumor infiltrating lymphocytes (TILs), PD-L1 expression (clone E1L3N), *FGFR2* rearrangement and *IDH* mutation status. PD-L1 was scored as follows: 1+ 1-10%; 2+ 11-50%; 3+ >50%. Fisher's exact 2-tailed t test was used for statistical analysis.

Results: PD-L1 was positive in 24 cases (29%); 1+ (n=18), 2+ (n=5), 3+ (n=1) affecting 11 women and 13 men ranging from 31-80 years. The tumors ranged from 0.7 to 13.5cm, were moderately (n=8) or poorly differentiated (n=16) and predominantly intrahepatic (n=22). Eleven cases (46%) which were positive for PD-L1 showed brisk TILs. *IDH* mutations were present in 2 of 8 PD-L1 positive cases and *FGFR2*-rearrangements were present in 2 of 12. PD-L1 expression was significantly associated with intrahepatic location (92% vs 71%; p=0.047); brisk TILs (46% vs 15%; p=0.006) and high tumor grade (67% vs 53%; p=0.014). No other significant observations were noted.

Conclusions: CCA with PD-L1 expression by tumor cells are typically intrahepatic, poorly differentiated and show brisk TILs. Studies on PD-L1 directed therapy would benefit from selecting patients based on these pathologic features. Ongoing molecular analysis will evaluate the relationship of PD-L1 expression in CCA to *FGFR2* rearrangements or other molecular biomarkers.

1686 Clinicopathologic Review and Outcome of 31 Cases of Liver Transplant with Both Hepatocellular and Cholangiocarcinoma

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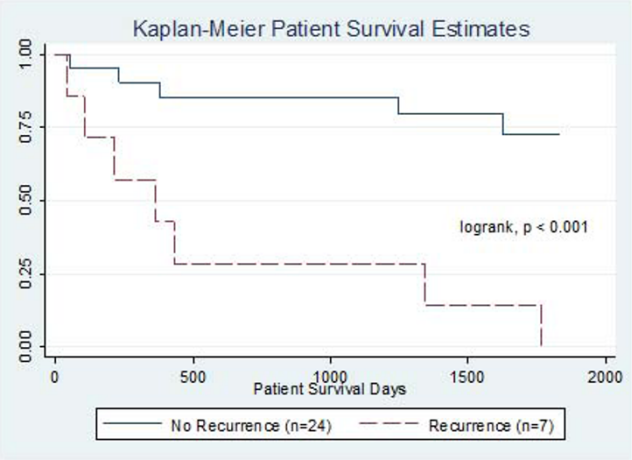
Background: Liver transplant (LT) for intahepatic cholangiocarcinoma (CC) is contraindication due to poor outcome. The study purpose was to assess the clinico-pathologic features and outcomes following LT in patients who were incidentally found to have both hepatocellular (HCC) and cholangiocarcinoma on explant.

Design: Between 2000 and 2015, 31 patients were transplanted and their explanted livers revealed one or more tumors of either combined or separate HCC and CC. The diagnosis of CC was not known prior transplant. Their medical records and pathology were reviewed and retrospectively analyzed.

Results: The patients primary liver disease was HCV (18), cryptogenic (5), ETOH (3), NASH (2), HBV (2), and PSC (1). HCC was suspected in 29 cases. 2 were incidentally found. Radiographically, 27 were within expanded Milan criteria (UCSF). Pathologically, only 16 met the expanded Milan criteria (UCSF). 23 had at least one nodule of mixed HCC/CC morphology. 8 cases had separate nodules of HCC and CC. The tumors with CC were intrahepatic in 29, at the hilum in one and in the gallblader in one. Post-transplant, recurrence occurred in 7(23%) (1-26 mo., median 3 mo.), this group had significantly worse survival than patients without recurrence (Kaplan-Meier ($p<.001$).



Histology of recurrence was examined in 6; CC was seen in 2, HCC in 1 and poorly differentiated carcinoma in 3. Examination of clinicopathologic parameters at the time of transplant including age, sex, MELD score, wait time, DCD donor, original disease type, serum tumor markers, tumor type, stage, grade, tumor number, size, vascular and neural invasion did not show statistically significance differences.
Conclusions: 1) Liver transplant patients whose explant livers contained both HCC and CC have significantly worse survival after recurrence compared to those without recurrence. 2) Reasonable five year survival for patients with CC can be achieved with liver transplant if recurrence can be avoided. 3) Most recurrences were poorly differentiated carcinoma or CC. 4) These patients may represent a heterogeneous population as some present as truly mixed tumors within the same nodules and others present as separate nodules of HCC and CC.

1687 Investigating Predictive Models Based on Circulating Cell-Free INK4A DNA Methylation, Alpha-Fetoprotein, Platelet Count, and Age for Diagnosis and Prognosis of Hepatocellular Carcinoma

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Background: As hepatocellular carcinoma (HCC) rates continue to rise in the U.S., management remains limited with lack of adequate diagnostic markers. Hypermethylation of CpG dinucleotides in the promoter region of inhibitor cyclin-dependent kinase 4A (INK4A) has been shown to be a potential biomarker associated with HCC. Additional laboratory measurements including total gammaglobulin, alpha-fetoprotein (AFP), and platelet count levels have been suggested as potential markers for HCC (Eur J Intern Med 2013;24:846-851). In this study, we examined the laboratory profiles of several markers of both HCC and non-HCC patients. Our objective was to create a predictive model that identifies patients with early HCC.
Design: We examined INK4A promoter methylation using circulating cell-free DNA in serum specimens from 153 patients, including 74 patients with HCC and 79 without HCC. Methylation for seven CpG sites was examined using pyrosequencing. The following additional sets of data were recorded: Patient age, sex, AFP levels, total gammaglobulin levels, platelet count, and presence or absence of viral hepatitis. Statistical analysis was performed using logistic regression procedure in Statistical Analysis System (SAS) 8.0.
Results: In our study, a total of 153 serum specimens were analyzed, all from different subjects (74 HCC patients and 79 Non-HCC patients). 136 (89%) were male and 17 (11%) were female. Average age was 54.5 years (standard deviation- 8.68). Of the 74 subjects with HCC, 24 (32.44%) were stage 1, 18 (24.32%) were stage 2, 16 (21.62%) were stage 3, and 16 (21.62%) were stage 4. Older subjects were more likely to have HCC than the younger subjects group (means in HCC and non-HCC groups were 56 years and 52 years, respectively, p=0.03). High AFP values were associated with HCC (means in HCC and non-HCC groups were 1583 and 318, respectively, p<0.01) as were low platelet values (means in HCC and non-HCC groups were 131 and 151, respectively, p=0.03). INK4A methylation was not statistically significant risk factor of HCC, however, it was significantly associated with stage 3 and 4 (odds ratio>1000, p=0.02). Among INK4A, AFP, platelets, gammaglobulin, and age, only INK4A and AFP were statistically significant when comparing stages 1 and 2 with stages 3 and 4 [probability of stages 1 and 2=1/(1+exp(-(1.44-10.84* INK4A-0.00003*AFP)].
Conclusions: Older age, high AFP, and low platelets are associated HCC. Similarly, INK4A promoter methylation rates and AFP are associated with advanced HCC stage.

1688 Immature B-cells Can Be Detected in a Subset of Adult and Pediatric Liver Biopsies: A Potential Pitfall in the Diagnosis of B Lymphoblastic Leukemia/Lymphoma

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Background: Terminal deoxynucleotidyl transferase (TdT) is a nuclear enzyme restricted to precursor lymphoid cells and their malignant counterparts. TdT is helpful in recognition of lymphoblasts, which can resemble mature lymphocytes. The diagnosis of B lymphoblastic leukemia/lymphoma (B-ALL) is occasionally first established on liver biopsy, which raises questions about a possible normal complement of immature B-cells in liver tissue that could represent a pitfall in work-up to exclude B-ALL.
Design: We collected 41 liver biopsies from the UCSF liver pathology service and selected cases with a significant portal and/or sinusoidal lymphoid infiltrate, which included cases of viral hepatitis, non-alcoholic steatohepatitis (NASH), Epstein-Barr virus hepatitis, Q-fever, chronic vascular outflow obstruction, acute cellular rejection, B-ALL, hairy cell leukemia, NK-cell leukemia, diffuse large B cell lymphoma, inflammatory variant hepatocellular adenoma, neonatal hepatitis, ductopenia, and biliary atresia. Relatively normal liver tissue was also included in our evaluation. Immunohistochemical stains for TdT and PAX-5 (labels B-cells) were performed on paraffin embedded tissue and positive staining was defined as strong nuclear labeling.
Results: A significant number of TdT positive B-cells were present in pediatric biopsies (40%, 4/10) and all biopsies from patients under age 9 weeks had an immature B-cell infiltrate. Specifically, immature B-cells were present in neonatal hepatitis (multifocal/sinusoidal and portal infiltrate in 2/2 cases), biliary atresia (multifocal portal infiltrate in 1/1 case) and a biopsy with mild non-specific changes (focal portal infiltrate in 1/1 case). In adults, immature B-cell infiltrates were less common (10%, 3/31) and were encountered in NASH (focal portal infiltrate in 1/4 cases) and acute cellular rejection (focal sinusoidal infiltrate in 1/3 cases).
Conclusions: Immature B-cells can be detected in liver biopsies in a variety of clinical settings, most commonly in children, and should not be interpreted as evidence for B-ALL unless there is extensive portal and sinusoidal involvement by blasts with diffuse strong TdT labeling. Peripheral blood and/or bone marrow evaluation can then be suggested to provide confirmation of the diagnosis and further classification with molecular/cytogenetic testing.

1689 Clinical Significance of Liver Biopsy Findings "Suggestive of", "Suspicious for" or "Consistent with" Biliary Obstruction

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Background: Biliary obstruction is primarily a clinical and radiographic diagnosis but histologic examination of a liver biopsy may provide useful information especially for cases with no or low clinical suspicion. In this study, we aimed to determine how often clinicians proceed in investigating possible biliary obstruction when a diagnosis on a liver biopsy is "suspicious for", "suggestive of" or "consistent with" biliary obstruction and how frequent the radiographic studies actually show definitive biliary obstruction.
Design: We retrospectively analyzed a cohort of 203 cases with a liver biopsy diagnosis relating to biliary obstruction ("suggestive of", "suspicious for", or "consistent with"). Their clinical and radiographic records were extensively reviewed. Detailed histologic analysis on liver biopsies was also conducted to determine if there were recognizable features that would help separate biopsies with confirmed biliary obstruction from those without.
Results: Of 203 cases, 117 (57.6%) were investigated for biliary obstruction with various radiographic modalities, The studies were performed either on the same day of biopsy or after in 89 cases (76.1%), or prior to biopsy in 28 cases (23.9%). In 54 (46.2%) of these cases, biliary obstruction was confirmed by radiographic studies. Retrospective re-review of the biopsies showed no significant differences between cases with radiographically confirmed biliary obstruction and those without. The histologic features analyzed mainly included portal edema, ductular reaction, neutrophilic infiltrates in portal tracts, cholestasis, bile duct injury and fibrosis.
Conclusions: Our study demonstrated that more than half of cases (57.6%) with liver biopsy findings suggestive of, suspicious for or consistent with biliary obstruction underwent radiographic investigation and almost half (46.2%) of these cases actually confirmed the diagnosis. Recognition of histologic features of biliary obstruction is thus important in guiding the clinical management of patients. It remains unclear why a large number of cases without clinical and radiographical evidence of biliary obstruction show similar histologic features.

1690 Interpretation of Core Biopsy of Liver Mass Lesion: A Comparison Study between Cytopathologist and Gastrointestinal Pathologist

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Background: Needle biopsy is a main diagnostic tool for the evaluation of liver mass lesion. When a core biopsy is performed along with fine needle aspiration (FNA), the core biopsy may be interpreted by the same cytopathologist who reviews the FNA smear or separately by a gastrointestinal pathologist, depending on the practice in each institution. This study was designed to compare the interpretation of liver mass biopsy between cytopathologist and gastrointestinal pathologist in the era of subspecialty practice.
Design: Three hundred and forty-nine cases of liver mass lesion with FNA and core biopsy concurrently performed during the past 5 years were retrieved. All cases were initially interpreted by a cytopathologist and retrospectively reviewed by a gastrointestinal pathologist.
Results: Overall the gastrointestinal pathologist and cytopathologist agreed on the diagnosis in 332 of 349 cases (95.1%). Among the 65 cases that were initially interpreted as non-neoplastic by a cytopathologist, the gastrointestinal pathologist agreed on 57 cases (87.7%). The discordant cases included 4 steatosis (steatohepatitis was missed in 3 cases, 1 case was re-interpreted as focal nodular hyperplasia); 3 inflammation (1 had necrotizing granulomatous inflammation, 1 had massive necrosis instead of fibrosing cholestatic hepatitis with marked fibrosis, and 1 had scant viable hepatocellular carcinoma which was initially missed); and 1 case initially deemed normal and re-interpreted as focal nodular hyperplasia. Among the 284 neoplastic cases, there was an agreement in 275 cases (96.8%). The discordant cases included: 2 cases initially interpreted as hepatocellular carcinoma (now 1 was considered metastatic adrenal cortical carcinoma and another as mixed hepatocellular cholangiocarcinoma); 2 adenocarcinomas (excluding prostatic) (1 re-interpreted as metastatic prostatic carcinoma and another with concurrent well-differentiated neuroendocrine tumor [WDNET]); 3 metastatic carcinomas (1 had tumor-induced fibrosis instead of cirrhosis,

1 large cell neuroendocrine carcinoma [LCNEC] now considered prostatic carcinoma, another LCNEC re-interpreted as WDNET); 1 poorly differentiated carcinoma (now LCNEC); and 1 spindle cell tumor (leiomyosarcoma instead of sarcomatoid carcinoma).
Conclusions: The cytopathologist and gastrointestinal pathologist are highly concordant in the interpretation of liver mass core biopsy, especially for neoplastic cases. Consultation between them will likely improve diagnostic accuracy in certain non-neoplastic biopsies.

1691 GATA4 Expression Is a Prognostic Factor of Recurrence in Hepatocellular Carcinoma

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Background: GATA4 is a transcription factor playing roles in development of varying organs, especially cardiac development. Recently, aberrant GATA4 expression has been studied in tumors of gastrointestinal tract, breast, lung, ovary, pancreas, and brain. However, the role of GATA4 in human cancers is still controversial. For example, down-regulation of GATA4 expression by promoter hypermethylation has been found, and acts as a tumor suppressor in colorectal and gastric cancers. On the other hand, high GATA4 expression has been revealed as a poor prognostic factor in ovarian granulosa cell tumors and breast cancers. We examined the expression of GATA4 protein in hepatocellular carcinoma and correlated with the clinicopathological parameters.
Design: Tissue microarrays were constructed using 213 surgically resected primary hepatocellular carcinomas. Immunohistochemical stain was performed and interpreted by immunoreactive score, which was calculated by multiplying staining intensity score (0-3) and proportion score (0-4). Histology of the tumors and medical records of the patients were reviewed and statistical analyses were performed to investigate the relationship between clinicopathologic factors and GATA4 expression.
Results: The tumors with 4 or more immunoreactive score were regarded as 'positive', accounting for 48.8%. GATA4-positive tumors were significantly associated with higher pathologic stage ($p<0.001$, chi-square test), higher histologic grade ($p<0.001$, chi-square test), more frequent small vessel invasion ($p<0.001$, chi-square test), and tumor recurrence ($p = 0.039$, log-rank test). Furthermore, mean Ki-67 proliferative index of GATA4-positive tumors was significantly higher than GATA4-negative tumors (11.60% vs. 3.56%, $p<0.001$, t-test).
Conclusions: While silence of GATA4 expression due to epigenetic mechanism was suggested to have roles in some human cancers, this result is implying GATA4 has an oncogenic role and may confer aggressive biology and poor prognosis to the hepatocellular carcinoma.

1692 Steatosis and Steatohepatitis in Hepatocellular Carcinoma: What Is the Significance?

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Background: Steatohepatitic hepatocellular carcinoma (SH-HCC) is a recently described variant of hepatocellular carcinoma (HCC), with distinct morphological features, genetic traits, and is suggested to be associated with metabolic syndrome. We aimed to search the clinical and pathological importance of steatohepatitic and steatotic features in our HCC series.
Design: Histopathological features, clinical and biochemical data of 151 HCC cases treated in our institution were retrospectively analyzed. The diagnosis of SH-HCC was made, if the tumor was bearing at least three of the "steatohepatitic" features in more than 50% of the tumor, and in multiple tumors if at least one nodule met the above criteria. Cases were reclassified as SH-HCC, SH-HCC<50%, steatotic HCC (SHCC) and classical HCC groups.
Results: The mean age in this series was 54 (range, 11-75). There were 127 male (84%) and 24 (16%) female patients. Etiology was viral in 100 (70.1%), steatohepatitic in 9 (5.9%), viral+steatohepatitic in 16 (10.6%) and unknown in 18 (11.9%) cases. There were 13 SH-HCC (8.6%), 22 SH-HCC<50% (14.6%), 13 SHCC (8.6%), and 103 classical HCC (68.2%) cases. There were no significant differences between the four groups with respect to demographic and biochemical tests, AFP levels, mean BMI, presence of diabetes mellitus and hiper/dyslipidemia. Tumor size, uni- or multifocality, differentiation, nuclear grade, background liver features, presence of viral etiology, presence of microvascular invasion and survival did not show any difference between the groups neither. SH-HCC group had significantly high non-viral etiology (53.8%) (p=0,037) and frequent presence of NASH, but the latter was not significant. SH-HCC<50% group was characterized by significantly higher alcohol etiology (p=0,037), high (77.3%) but insignificant HBV etiology. Steatotic HCC had the highest HCV etiology (30.8%) without any statistical significance. Baring ant amount of SH-HCC did not confer any significant difference from classical HCC with respect to clinicopathological features. When HCCs with and without steatosis (regardless of the presence of SH-HCC component) were compared, cases with steatosis had high BMI (>25 kg/m2) (p=0.037).
Conclusions: Steatosis can exist in HCC in association with viral etiology and/or high BMI but this has no clinical significance. Steatohepatitic features in HCC can also be seen in the presence of viral etiology. When strict criteria used SH-HCC is a variant associated mostly with non-viral etiology but without any prognostic significance.

1693 Associations of Tumor Response to Neoadjuvant TACE Following Liver Transplantation

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Background: Although the mainstay of therapy for hepatocellular carcinoma (HCC) is surgical resection, the majority of patients are not eligible because of tumor extent or underlying liver dysfunction. As a result, liver transplantation for patients with HCC has increased in recent years. Transarterial chemoembolization (TACE) therapy has been commonly used as a bridging therapy for unresectable tumors prior to transplant. However, response to TACE is extremely variable from patient to patient.
Design: Pathology cases of HCC from 2011-2015 were reviewed for those treated with TACE prior to transplantation. 55 cases were identified with full information regarding tumor response to TACE. These were additionally reviewed for patient age, sex, diagnosis, presence of lymphovascular invasion, and differentiation, size, and number of tumors. Degree of tumor response was divided into 3 groups: complete response (CR), no viable tumor; high response (HR), > 50% tumor necrosis; and low response (LR), ≤ 50% tumor necrosis.
Results: The 3 groups were demographically similar (table 1). The presence of multiple tumors was strongly associated with incomplete response to TACE ($p<0.05$). Tumor size was not associated with tumor response group ($p>0.05$). Degree of differentiation could not be assessed in the CR group; however, there was no significant difference in the proportion of poorly differentiated tumors between the LR and HR groups. The presence of microscopic lymphovascular invasion was not associated with tumor response, although there was a trend towards significance in the LR versus HR groups ($p = 0.08$). As with degree of differentiation, the presence of lymphovascular invasion could not be assessed in the CR group.

Tumor Response	Mean Age	Sex (% Male)	Etiology (% HCV)	Fibrosis (% Stage 4)
<=50% necrosis	60.8	81.0%	71.4%	100%
>50% necrosis	57.2	78.9%	73.7%	89.5%
100% necrosis	60.1	86.7%	80.0%	86.7%

Conclusions: Studies examining the role of neoadjuvant TACE have questioned its utility in resection patients. Our findings are somewhat different from those reported previously, which have reported an inverse association of tumor necrosis with tumor size but which do not specifically address the significance of tumor number. Many pathologic features (degree of differentiation and microscopic vascular invasion) as well as the size of the tumor do not appear to predict partial versus CR. However, number of tumors was strongly predictive of CR. These factors may be important in planning neoadjuvant therapy and follow-up prior to transplantation in patients with HCC.

1694 Acute Antibody-Mediated Rejection after ABO-Compatible Pediatric Liver Transplantation: Histopathologic Study with Clinical Correlation

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Background: Acute antibody-mediated rejection (AMR) is an increasingly recognized complication in ABO-compatible liver transplantation (LT). Accurate diagnosis is essential, since if not treated promptly, it leads to graft dysfunction and/or loss. Unfortunately, the histopathologic features are not yet well-defined. This study seeks to characterize the histopathology of acute liver AMR and correlate the features with clinical/laboratory findings.
Design: We performed a retrospective review of all pediatric patients who underwent ABO compatible LT at our institution from 2012 to 2015. Six patients (26 biopsies) were identified with acute AMR based on the following criteria established in other organs: 1. Clinical signs of graft dysfunction; 2. Presence of donor specific HLA antibodies (DSA); 3. Histopathology indicative of acute graft injury; 4. Exclusion of other post-transplant complications. We performed comprehensive histopathologic exams including evaluation of C4d immunohistochemical (IHC) stain.
Results: The most frequent histologic findings were spotty non-zonal hepatocyte necrosis (88%), mixed portal inflammation (85%), pericentral hepatocytes injury/necrosis (80%), bile duct injury (65%), ductular proliferation (46%), and cholestasis (38%). Less common were portal vein endotheliitis (31%), sinusoidal neutrophils (31%), portal edema (27%), and ductopenia (23%). The degree of spotty hepatocyte necrosis was the only histologic change significantly associated with higher levels of DSA ($p<0.05$). Positive C4d IHC staining was seen in only 6 biopsies (26%), but was observed in all patients at one point. Three patients had ACR preceding elevation of DSA, and severity of ACR also correlated with DSA levels ($p<0.05$).
Conclusions: Our results suggest that histopathology of acute liver AMR is variable and overlaps significantly with those seen in other post-transplant complications. Hepatocellular necrosis is the most frequent finding and the only one that correlates significantly with DSA levels. Histopathologic diagnosis of acute AMR is particularly challenging when co-existing with ACR due to overlapping features. ACR severity also correlates significantly with high DSA levels, which suggests the simultaneous occurrence of AMR and ACR, as one immunologic event might trigger another. C4d IHC stain is not a reliable diagnostic modality, given low sensitivity and prior reports of low specificity. Multicenter studies and establishing diagnostic criteria are important next steps for improvement of AMR diagnosis.

1695 Diagnostic Utility of Clusterin Immunostaining in Differentiating Hepatocellular Carcinoma from Tumors of Other Origins

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Background: Clusterin (CLU) is a pleiotropic protein that may function as a tumor promoting factor. We have previously observed a unique pericanalicular staining pattern for CLU in hepatocellular carcinoma (HCC). However, its diagnostic value and expression in tumors from other sites has not been studied.
Design: IHC expression of CLU was evaluated on tissue sections of 33 HCCs, 30 clear cell renal cell carcinomas (CRCC), 14 epithelioid angiomyolipomas (AML), 13

cholangiocarcinomas, 3 balloon cell melanomas and 2 clear cell sarcomas. An additional 992 tumors from various organs (including 17 HCCs and 69 CRCCs) and 28 normal liver were also stained for CLU. The staining patterns were analyzed.
Results: While all normal liver samples showed a weak linear perisinusoidal staining pattern, all 50 [33 TS, 17 tissue microarray (TMA)] HCC cases demonstrated relocalization of CLU, resulting in disruption of the normal pattern. The most common staining pattern in HCC was enhanced and exaggerated pericanalicular staining, which predominated in moderately differentiated HCC (41 cases, 27 TS, 14 TMA]. Cytoplasmic granular staining was observed in all 9 poorly differentiated HCC (PD-HCC). In 5 /9 PD-HCC, luminal accentuation of CLU was observed in areas with glandular differentiation. Negative CLU was observed in sarcomatoid component in 2 /9 PD-HCC. Among the common histologic mimickers of HCC, cytoplasmic and membranous staining was seen in CRCC (79/99), AML (7/14) and cholangiocarcinoma (10/13). Patchy luminal staining was also seen in cholangiocarcinoma (6/13). Weak cytoplasmic with Golgi-like dot staining was seen in adrenal cortical tumors (22/30). Negative CLU was observed in balloon cell melanoma (3) and clear cell sarcoma (2). Cytoplasmic staining was seen in all other tumors, including papillary RCC, pancreatic neuroendocrine tumor, ovarian carcinoma, breast carcinoma, and papillary thyroid carcinoma (PTC). An apical/luminal staining pattern was seen in a small fraction of tumors, primarily in adenocarcinomas with glandular and papillary formation. Membranous staining was also seen in tumors with papillary architecture, mesothelioma and some lung tumors.
Conclusions: Enhanced and exaggerated pericanalicular CLU staining pattern was seen in 82% of HCC and was not observed in any tumors of other origins. This unique staining pattern can be used to distinguish HCC from its histologic mimickers, although this pattern is not well preserved in poorly differentiated HCC.

Neuropathology and Ophthalmic Pathology

1696 Oncogenic Mutations in PI3Kinase in Skull-Based Meningioma

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Background: Meningiomas are the most common intracranial tumour in adults. Identification of SMO and AKT1 mutations in meningioma suggests that some patients with meningioma may benefit from targeted therapies. The frequency of such mutations in clinical cohorts and the presence of other recurrent actionable mutations in meningioma are important to define.
Design: We used high resolution array comparative genomic hybridization to prospectively characterize the patterns of copy number changes in 150 prospective meningioma cases that have been reviewed on our neuropathology service. We then characterized these samples for mutations in AKT1, KLF4, NF2, PIK3CA, SMO, and TRAF7.
Results: Similar to prior reports, AKT1 and SMO mutations were identified in a subset of of non-NF2-mutant meningiomas – ~9% and ~6%, respectively. Notably, we detected oncogenic mutations in PIK3CA in ~7% of non-NF2-mutant meningioma. AKT1, SMO and PIK3CA mutations were mutually-exclusive, but AKT1 and PIK3CA mutations often co-occurred with mutations in TRAF7. PIK3CA-mutant meningioma were enriched in skull-based meningioma and showed limited chromosomal instability, similar to SMO and AKT1(E17K)-mutant meningioma
Conclusions: This integrated genomic analysis of this clinical cohort of meningiomas reveals that in addition to mutations in AKT and SMO, a substantial subset of non-NF2 mutant and skull-based meningioma harbour potentially actionable mutations in PIK3CA.

1697 Targeted Next-Generation Sequencing in the Molecular Profiling of Lower-Grade Gliomas

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Background: There is increasing recognition that the WHO 2007 classification scheme for diffuse gliomas inadequately captures the behavior of these tumors. Recent publications, such as the ISN-Haarlem consensus, suggest a revised classification incorporating molecular parameters. In this retrospective analysis, molecular testing, including a targeted next-generation sequencing-based (NGS) assay, was used to evaluate a series of genes recurrently mutated in gliomas. This report describes the molecular findings of this testing in 32 lower-grade glioma patients and, further, reclassifies the tumors based on the categorization scheme proposed by TCGA.
Design: Patients were selected from those with diagnosed WHO grade II and III gliomas (lower-grade gliomas, LGG) and who had targeted clinical NGS performed on routine formalin-fixed tissue over a three year interval. The targeted NGS panel consisted of 50 common cancer genes and the cases consisted of 23 mixed oligoastrocytomas (MOA) (10 of which were WHO grade III), 6 oligodendrogliomas (OD) (1 WHO grade III, or AO), 2 anaplastic astrocytomas (AA), and 1 "low-grade glioma" lacking further specification. Beyond NGS testing, fluorescent in situ hybridization (FISH) analysis for specific alterations, such as 1p/19q co-deletion and EGFR amplification, in addition to IDH1 R132H immunohistochemistry data, were also available.
Results: Following TCGA's scheme, we obtained 15 *IDH1*-mutant, 1p/19q non-codeleted LGG ("IDHmut, 1p/19q nondel"); 10 *IDH1* wild-type LGG (IDH^{wt}); and 7 IDH1-mutant, 1p/19q codeleted LGG ("IDH^{mut}, 1p/19q codel"). 11 of the 13 grade II MOA fell into the IDH^{mut}, 1p/19q nondel group. This group also contained 3 grade III anaplastic MOA and 1 grade II OD. Consistent with TCGA data, 100% of the tumors in the IDHmut, 1p/19q nondel group also had TP53 mutations; 6 cases belonging to this group also had *ATRX* sequencing performed, which revealed 5 tumors harbored *ATRX* inactivating mutations. Of the remaining MOAs, 1 fell into the IDH^{mut}, 1p/19q codel group and the other fell into the IDH^{wt} group. Conversely, the grade III MOAs were mostly IDH^{wt} (5 of 9 cases). AA and OD largely fell into the IDH^{wt} and the IDH^{mut}, 1p/19q codel group, respectively, except 1 OD, which was found to be IDH^{mut}, 1p/19q nondel. IDH1 IHC was concordant with NGS in all but 3 cases that had IDH1 R132 mutations other than R132H.
Conclusions: Here we show that NGS is a robust platform that can facilitate molecular profiling of histologically challenging LGG cases and demonstrate that the TCGA classification can be applied in clinical practice.

1698 MiR-16, but Not MiR-519, Suppresses Tumor Cell Proliferation in Meningiomas via HuR Inhibition

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Background: Molecular mechanisms underlying meningioma growth remain poorly understood. Dysregulation of microRNAs (miRs) is associated with cell growth in several cancers. This study aimed to assess the role in meningioma of the miRs miR-16 and miR-519, which are known to inhibit the translation of the oncogenic HuR protein.
Design: We investigated the relative expression levels of these miRs in a series of meningioma and normal meningeal tissues. The effects of miR-16 and miR-519 on cell growth, proliferation and HuR level were assessed in vitro using the human malignant meningioma cell line IOMMLee.
Results: Both miR-16 and miR-519 were significantly downregulated in meningioma compared with normal meningeal tissue (miR-16: median, 0.85 vs. 3.29, $P = 0.0003$, effect size = 0.40; and miR-519: median, 0.002 vs. 0.017, $P = 0.006$, effect size = 0.30). Overexpression of either miR in IOMMLee cells significantly reduced cell growth (median area under the curve of 71.4, 49.4, and 13.5 for control, miR-519, and miR-16, respectively; $P < 0.001$) and Ki-67 proliferation index ($P < 0.0001$). The experimental overexpression of miR-16, but not miR-519, was associated with dose-dependent inhibition of cell growth ($P = 0.001$). The number of viable cells significantly correlated with miR-16 transfection concentration (rho = -0.950; 95% CI, -0.986 to -0.827; $P < 0.0001$). The oncogenic protein HuR, whose expression level was significantly higher in grade II than in grade I meningioma ($P = 0.03$, effect size = 0.47), was regulated in vitro by miR-16. Experimental overexpression of miR-16, but not miR-519, lowered HuR protein levels in IOMMLee cells ($P = 0.0001$).
Conclusions: MiR-16 and miR-519 are downregulated in human meningioma tissues. Reestablishing the level of miR-16 in IOMM-Lee cells was found to reduce cell proliferation dose-dependently. The tumor-suppressor effect of miR-16 may be mediated via posttranscriptional regulation of HuR. These results provide new insights into the tumorigenesis of meningiomas, and suggest that the anti-proliferative properties of miR-16 and miR-519 should be considered in the design of novel pharmacological agents.

1699 Pangenomic Analysis of BRAF Genomic Alterations Across All Types of Brain Tumors Reveals Expanded Opportunities for Targeted Therapies

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Background: The striking responsiveness of *BRAF*-mutated melanoma to anti-BRAF targeted therapies has stimulated interest in the development of basket type clinical trials aimed to identify *BRAF* genomic alterations (GA) in many types of non-melanoma cancers. In this study we performed comprehensive genomic profiling (CGP) to search for all classes of *BRAF* GA in a large series of intracranial neoplasms including multiple types of brain tumors (BT) and report multiple instances of successful targeted therapy for these patients with BRAF and MEK inhibitors.
Design: From a series of 51,238 total cases, DNA was extracted from 40 microns of FFPE sections from 2,933 cases of BT. CGP was performed using a hybrid-capture, adaptor ligation based next generation sequencing assay to a mean coverage depth of >600X. The results were analyzed for all classes of genomic alterations (GA), including base substitutions, insertions and deletions, select rearrangements, and copy number changes. Clinically relevant genomic alterations (CRGA) were defined as those identifying anti-cancer drugs on the market or in registered clinical trials.
Results: 142 (4.8%) of the BT featured *BRAF* GA including base substitutions (70%) and fusions (25%) with rare amplifications and other GA types. *BRAF* subs were predominantly found in high grade gliomas and fusions in low grade astrocytomas including pilocytic and pilomyxoid subtypes. *BRAF* GAs were most frequently found in ganglioglioma (60%), pilomyxoid (40%) and pilocytic (40%) astrocytomas. Although the frequency of *BRAF* GA in GBM at 3.6% is relatively low, the large number of GBM submitted for CGP in this study accounted for 42% of the total *BRAF* mutated BT. Base substitutions in *TP53* and *KRAS* were strongly associated with absence of *BRAF* GA. Loss of *CDKN2A/B* and substitution mutation in *ATRX* were strongly associated with