(MGH), Boston, US. However, because of situations around the world, it was not easy to perform the project smoothly. After overcoming many challenges, we have established the telepathology network between MGH and HFH in 2011 and then the 1st Whole Slide Imaging (WSI) scanner in Pakistna has been installed. Current project goal is that MGH supports HFH to be able to support other facilities in Pakistan using the digital pathology. In the paper, we focused on training, establishment of technical and clinical network between two institutions and the implementation of a WSI scanner at HFH.
Design: A pathologist at HFH has spent for two weeks at MGH for the digital pathology training and attending the signing out sessions and conferences. Prior to the pathologist visiting, MGH prepared all necessary equipment and all required software have been installed and tested. After the pathologist returned with equipment to Pakistan, the weekly static image based teleconference has been scheduled. Screen sharing software was selected for teleconference. Also MGH could access the scanned WSI using remote access software prior to the teleconference.
Results: The training sessions for pathologist from HFH were very successful and useful for the project. Starting December 2011, a weekly conference for 1 hour between MGH and HFH has been performed. Pathologist at HFH presents 7-10 variety cases using PowerPoint. All sessions have been recorded as a video and PowerPoint file. The details of WSI based teleconference will be reported. During the conference, we do not use any of patient identifier.
Conclusions: It was most useful for us to have the pathologist at MGH for two weeks. To learn the differences of culture, pathology practice, IT environment, and having communication directly helped us to continue teleconference smoothly and also made us easier to support from US. Working with pathologist and Telemedicine center at HFH, this project is going to be extended to other institution in Pakistan.

1599 Lymph Node Metastasis Status in Primary Breast Carcinoma Can Be Predicted Via Image Analysis of Tumor Histology

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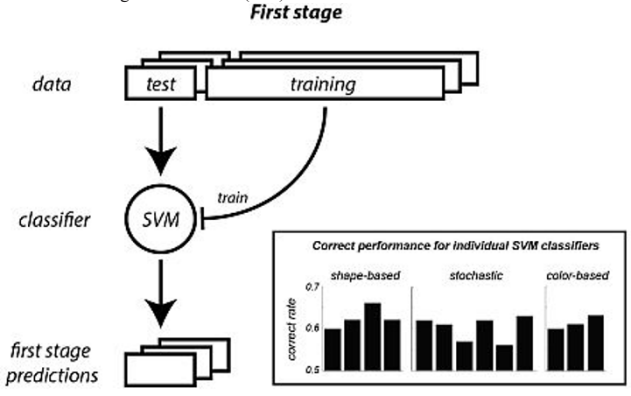
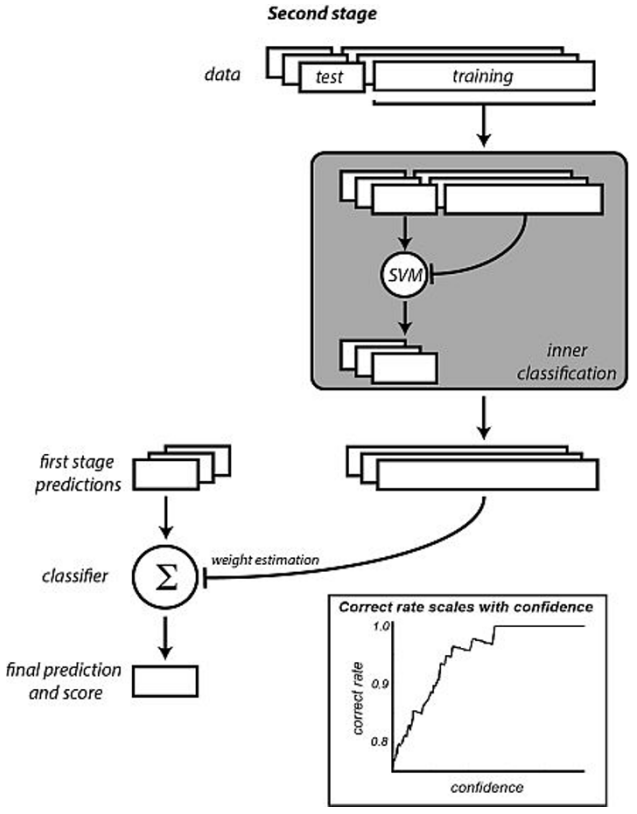
Background: Axillary lymph node metastasis status remains one of the most critical prognostic variables for breast cancer management and patient survival. Methods to improve reliability must be developed to avoid unnecessary surgeries and complications. The objective of our study is to demonstrate that lymph node metastasis status may be predicted via computerized image analysis of primary breast tumor histology.
Design: High-resolution (0.5µm/pixel) whole-slide images were produced from primary breast carcinoma specimens stained with a complete prognostic panel. Cell structures were extracted from these images using a custom segmentation paradigm. The properties of these structures were analyzed using stochastic geometric and chromatic transformations, forming a set of feature distributions that characterized the attributes of the cells in each sample. We constructed predictions individually for each feature distribution using a support vector machine classifier (SVM), and formed a final prediction from the individual predictions in an adaptive manner. Each prediction was accompanied by a confidence score, allowing us to relate the accuracy of the prediction to the certainty of the classification.
Results: We found that this procedure is highly predictive of axillary lymph node metastasis. The system achieved >95% correct rate for the highest scoring cases, which comprised over half the total number of cases we evaluated. Analysis of these cases revealed that N0 predictions correlated with T1 tumors (<2cm) of histologic Nottingham grade (HNG) 1 with low Ki-67 scores (<10). N1 predictions revealed T2/3 tumors of HNG 2/3 and high Ki-67 scores (>20).





Conclusions: We have demonstrated a fully automated procedure to predict metastasis status from histopathological images.

Kidney

1600 Methylmalonic Acidemia: A Megamitochondrial Disorder Affecting the Kidney

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Background: Methylmalonic acidemia (MMA) is an inborn error in the catabolism of branched-chain amino acids and is caused by mutations in the methylmalonyl-CoA mutase (MUT) gene. The MUT enzyme is located in the mitochondrial inner space and has a requirement for 5-deoxyadenosylcobalamin. Although MUT is expressed in many tissues, including the liver, brain and kidney, the patients experience organ specific disease such as basal ganglia dysfunction, pancreatitis and chronic kidney disease. As survival in MMA has increased, renal disease has become very important. Animal models have suggested that mitochondrial dysfunction with megamitochondria formation in selected cell types might contribute to specific disease manifestations but the lack of supporting studies has hampered efforts to discern the pathological features of MMA.
Design: Here we describe light and ultrastructural studies on the native kidney and liver from a 19 year-old patient with vitamin B12 non-responsive MMA, who underwent a combined transplant. She presented as a newborn with coma, metabolic ketoacidosis and massive hyperammonemia; severe MUT deficiency was identified. Stable in the first decade of life, she later developed progressive renal dysfunction.
Results: Kidney sections showed proximal tubular megamitochondria (proximal tubule vacuoles by light microscopy). In electron microscopy studies, the most dramatic changes were restricted to proximal tubules with all mitochondrial profiles shifted to large circular shapes with diminished cristae. There was loss of the plasma membranes of the lateral cellular interdigitations, but the brush border was maintained in many tubules. Measurements of mitochondrial size showed a marked increase of individual mitochondrial area from 0.38 ± 0.036 to 1.71 ± 0.78 μM^2 (SE ±; $p<0.0001$). There was marked interstitial fibrosis and tubular atrophy involving the subcapsular zone, medullary rays and the labyrinth. The liver pathology of mitochondrial enlargement (the basic abnormality in this patient) in MMA has been reported in mouse models and in a single human case, while the detailed renal pathology has not been described in humans.
Conclusions: With this study, we provide evidence that the renal mitochondropathy of MMA is characterized by megamitochondria formation in the proximal tubules of the kidney. Such changes may lead to tubulo-interstitial disease and have implications for treatments directed toward maximizing mitochondrial function in these patients.

1601 Incidental Epithelial Neoplasms Identified in Medical Renal Biopsies

JM Ambruzs, SM Bonsib, PD Walker, N Messias. Nephropath, Little Rock, AR; University of Arkansas for Medical Sciences, Little Rock, AR.

Background: Recent studies have emphasized that nephrectomy specimens removed for neoplasm should also be examined for medical renal disease. However there is little data on epithelial neoplasms in renal biopsies performed for medical reasons. Incidental epithelial neoplasms in renal medical biopsies are uncommon yet often pose a challenge in terms of subsequent clinical investigation and management. We report the largest series examining the frequency, spectrum, and clinical follow-up of incidental epithelial neoplasms identified in renal biopsies performed for medical kidney disease.

Design: We reviewed our experience of native and allograft kidney biopsies from 1/2005 to 6/2012. The biopsies were performed for medical reasons and in no case was the presence of a neoplasm suspected. All biopsies were reviewed by three pathologists, including a uropathologist. Relevant clinical data and follow-up was collected.

Results: 58 (0.17%) unsuspected epithelial neoplasms were identified including 2 in allografts. The mean age at biopsy was 62 years (range 28-85) and the male to female ratio was 2.6:1. All lesions were present on multiple levels with a mean size of 1.2 mm (range 0.2 – 5.2). Forty-four (76%) were low-grade papillary neoplasms including 19 adenomas. Renal cell carcinoma (RCC) was found in 9 samples (16%) of which 3 were papillary, 2 chromophobe, and 1 each of clear cell, clear cell papillary, acquired cystic kidney disease-associated and unclassified. Also found were 2 oncocytomas, 2 high-grade carcinomas favor metastasis, and 1 transitional cell carcinoma. Follow-up was available for 24 cases (mean 26.8 months, range 1–64) including 4 of the carcinomas. One third had radiologic studies including ultrasound, CT scan, PET scan or a combination of these modalities. Of those imaged, 3 identified a mass lesion that warranted surveillance or surgical management. This included a nephrectomy for papillary RCC and surveillance for 2 with acquired cystic kidney disease-associated RCC. One patient with metastatic disease died two months following biopsy.

Conclusions: 1.) This is the largest series of incidental epithelial neoplasms identified in renal biopsies for medical renal disease. 2.) A majority of tumors were low-grade papillary neoplasms. However high-grade tumors were also found. 3.) Tumor classification can be challenging because of the small quantity of tumor often present. 4.) Although uncommon, renal pathologists should consider consultation with a surgical pathologist since the presence of a neoplasm may necessitate a urologic workup.

1602 Diabetic Nephropathy and Fibrillary Glomerulopathy: An Unusual and Problematic Double Glomerulopathy

JM Ambruzs, CP Larsen, FG Silva, PD Walker. Nephropath, Little Rock, AR; University of Arkansas for Medical Sciences, Little Rock, AR.

Background: The *clinical* diagnosis of diabetic nephropathy (DN) may be incorrect in as many as 45% of cases often leading to renal biopsy for definitive diagnosis and exclusion of non-diabetes related renal disease. A significant challenge in the interpretation of these biopsies is the recognition of an underlying or coexisting primary glomerular disease with morphologic features that overlap with those of DN. We report the first clinicopathologic series to date of renal biopsies in patients with coexisting DN and fibrillary glomerulopathy (FG), a rare entity that shares similar clinical demographics and morphologic features.

Design: A search of our database of native renal biopsies from the last 11 years identified 301 cases of FGN (0.89%) and 5289 cases of DN (15.7%). 11 patients with DN had a concomitant diagnosis of FG (0.2%). Standard processing of biopsies included light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM).

Results: Mean age was 60 years (range 41-74) and the female to male ratio was 1.2:1. 8 patients (73%) were Caucasian, 2 were African American and 1 was Native American. Duration of diabetes was 5 to 30 years and 27% had documented retinopathy and/or neuropathy. The most common indication for biopsy was chronic progressive renal failure (45%), nephrotic syndrome (27%), acute on chronic progressive renal failure (19%) and sub-nephrotic proteinuria (9%). The mean creatinine was 2.2 mg/dL (range 1.0-3.5). 4 patients had hepatitis C virus (36%), 1 had prostate carcinoma and 1 had an IgA kappa monoclonal gammopathy of unknown significance. By LM, 10 had diffuse and nodular glomerulosclerosis while 1 showed diffuse mesangial matrix expansion and thickened glomerular basement membranes (GBM). All showed ≥2+ "smudgy" glomerular staining for IgG with no evidence of light chain restriction. Linear, non-branching fibrils were present within the mesangium and, importantly, in the GBM in all cases. Compared to the fibrils normally seen in DN, the fibrils of FG were much larger and easily visualized at 12000X.

Conclusions: Recognition of FG in patients with DN can be problematic given their clinical and morphologic overlap. However it is critical to recognize this co-occurrence given the difference in therapeutic regimen and outcome versus DN alone. This series demonstrates that a glomerular IF pattern of smudgy rather than linear IgG as well as the presence of typical large FG fibrils in both the mesangium and the GBM are the most useful diagnostic criteria leading to a correct diagnosis in these patients.

1603 Histopathologic Spectrum of Renal Biopsies in Patients with Inflammatory Bowel Disease

JM Ambruzs, PD Walker, CP Larsen. Nephropath, Little Rock, AR; University of Arkansas for Medical Sciences, Little Rock, AR.

Background: Renal disease as a complication of inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), has been the subject of case reports describing glomerulonephritis, secondary amyloidosis, and tubulointerstitial nephritis. However no cases series examining IBD and renal disease has been published to date. Our aim was to evaluate a large series of renal biopsies from patients with IBD to determine the spectrum and relative frequencies of IBD-associated renal pathology.

Design: A retrospective review from March 2001 to June 2012 was performed and identified 83 patients with IBD who underwent native renal biopsy. Standard processing of all biopsies included light, immunofluorescence, and electron microscopy.

Results: The cohort included 51 men and 32 women with a mean age of 46 years (range 12-80). There were 45 cases of CD and 38 cases of UC. The most common indication for biopsy was acute or progressive chronic renal failure (62.6%), hematuria (16.9%), and nephrotic-range proteinuria (15.7%). IgA nephropathy was the most common diagnosis (24.1%) followed by interstitial nephritis (19.3%), arterionephrosclerosis (12.0%), acute tubular injury (8.4%), proliferative glomerulonephritis (7.2%), and minimal change disease (4.8%). Twelve additional primary findings were represented in the remaining 24% of cases. Only one case of secondary amyloidosis was identified in a patient with CD. The frequency of IgA nephropathy in IBD was significantly higher than the 8.1% diagnostic prevalence of IgA nephropathy in all other native renal biopsies evaluated at our institution from the same time period (p=<0.0001). This IgA subgroup included 13 with CD and 7 with UC. Of the 16 cases of interstitial nephritis, 7 were classified as acute, 5 as granulomatous, and 4 as chronic. All of the cases of granulomatous interstitial nephritis had current or recent past exposure to aminosalicylates. Exposure to this class of drugs was not universal among the remaining 11 cases.

Conclusions: IBD is associated with a spectrum of renal diseases most commonly affecting the glomerular and tubulointerstitial compartments. Our series shows that IgA nephropathy is the most frequent diagnosis seen in IBD with a significantly higher diagnostic prevalence when compared to all non-IBD native renal biopsies. This may reflect a common pathogenic mechanism. Although many cases of tubulointerstitial nephritis had a history of treatment exposure to aminosalicylates, the possibility of a direct relationship with IBD cannot be ruled out.

1604 Leukemia and Lymphoma-Associated Crescentic Glomerulonephritis

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Background: A variety of glomerulopathies have been reported in association with hematologic diseases. Reports of crescentic glomerulonephritis (GN) occurring concurrently with hematologic malignancies are rare. We present a series of 3 cases of crescentic GN associated with leukemias and lymphomas.

Design: The clinical and pathologic data of 3 patients with hematologic malignancies and kidney biopsies showing crescentic GN were retrospectively reviewed. Biopsies were obtained between 2009 and 2011.

Results: The three cases of crescentic GN associted with leukemias and lymphoma are summarized in Table 1.

Summary of Crescentic GN Cases with Hematologic Malignancies

Case Number	Age/Sex	Malignancy	SCr (mg/dL)	Kidney Biopsy	Serology	Outcome (After Biopsy)
1	48/F	Natural killer (NK) cell leukemia	2.4	Focal crescentic GN, pauci-immune	ANCA negative	DOD in 2 months
2	85/M	Angioimmunoblastic T cell lymphoma (AITL)	4.6	Focal crescentic GN, with linear IgG	ANCA negative, Anti-GBM negative	DOD in 5 months
3	74/F	B cell chronic lymphocytic leukemia (CLL)	N/A	Diffuse crescentic GN, with linear IgG	N/A	DOD in 9 months

SCr: serum creatinine, GN: glomerulonephritis, ANCA: anti-neutrophil cytoplasmic antibody, GBM: glomerular basement membrane, DOD: died of disease, N/A: not available

The kidney biopsies of cases 1 and 2 showed infiltration of kidney tissue by malignant cells while case 3 had no involvement by chronic lymphocytic leukemia. Patients 1 and 2 received several rounds of chemotherapy, and patient 3 was on hemodialysis in the months before death.

Conclusions: In this series of crescentic GN with hematologic malignancies we report 2 cases of anti-GBM GN associated with AITL and B cell CLL and a third case of pauci-immune GN associated with NK cell leukemia. Such lesions may arise in the absence of serologic evidence of disease. These rare lesions portend a poor prognosis for renal and patient survival, with time to death following kidney biopsy ranging from 2-9 months.

1605 Atypical Lymphocytic Infiltrates of the Kidney: Benign or Malignant?

CL Boils, JM Ambruzs, LN Cossey, AA Harris, PD Walker, NC Messias. Nephropath, Little Rock, AR.

Background: Lymphocytic infiltrates are commonly seen on renal biopsies. They may be diagnostically challenging considering that low grade lymphomas can have similar morphology to reactive infiltrates. Immunohistochemical (IHC) stains for CD3 and CD20 can help sort the diagnostic possibilities of reactive, atypical, and lymphoma. Our aim was to determine if there are histologic features that can distinguish between lymphoma, atypical lymphocytic infiltrates (ALI), and reactive lymphocytic infiltrates (RLI).

Design: Our renal biopsy database was reviewed from 2005 to June 2012. 149 cases with atypical infiltrates were included. Multiple histologic parameters were accessed by reviewing H&E stained sections and IHC stains for CD3 (T-cells) and CD20 (B-cells). Percentages of T-cells and B-cells were estimated within lymphocytic infiltrates of concern. Histologic features were compared among those cases classified as lymphoma, ALI, and RLI.

Results: Of these 149 cases, 34 were diagnosed as lymphoma, 20 ALI, and 95 RLI. Similar among these groups was the distribution of the infiltrate as diffuse vs. patchy, cortical and medullary involvement, and tubulitis. Lymphoma cases were more likely to be monotonous (53%) compared to ALI (24%) and RLI (25%), present away from areas of interstitial fibrosis/tubular atrophy (40% vs. 21% and 26%, respectively), involve perirenal soft tissue (77% vs. 28% and 43%), and have a destructive quality (40% vs. 3% and 15%). Of the RLI, the lymphoid infiltrate showed either a mixture

of T- and B-cells or a predominance of T-cells in 96% of cases, with mean percentage of 68% T-cells and 32% B-cells. The atypical cases had mixed or T-cell predominate infiltrates in 70% of cases with mean percentage of 46% T-cells and 54% B-cells. Excluding 3 cases of T-cell lymphomas, the remaining 33 lymphoma cases all showed B-cell predominance, with mean percentage of 13% T-cells and 87% B-cells.
Conclusions: In our series, monotonous cytology, extension into perirenal soft tissue, destruction of renal architecture, and greater discrepancy between CD3 and CD20 populations were more common in lymphoma. However, the morphologic overlap observed between reactive and neoplastic infiltrates is noteworthy. Reactive infiltrates can still show marked destruction of renal architecture. Monotonous infiltrates can show a mixed population of T-cells and B-cells, suggesting a reactive nature. These findings emphasize the importance of having a high index of suspicion based on biopsy findings and using CD3 and CD20 IHC stains for triage in order to determine which atypical lymphocytic infiltrates warrant further hematopathologic evaluation for lymphoma.

1606 Pyelonephritis in Renal Allografts – Biopsy or Cultures?

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Background: We recently encountered four patients with severe allograft dysfunction requiring dialysis in the early post-transplant period with biopsy findings of acute pyelonephritis, but repeatedly negative urine culture results. Despite antibiotics, recovery was slow. Two of them lost their grafts within a year. We retrospectively reviewed our renal allograft biopsies with histologic features of acute pyelonephritis to study degree of correlation between biopsy diagnosis and urine culture results.
Design: We found 53 patients with biopsy diagnosis of acute (with or without chronic) pyelonephritis over a 7 year period.
Results:

Table 1. Patients with biopsy features of pyelonephritis over 7 years.

	Culture positive (n)	Culture negative (n)	Total
Total	35	18	53
Biopsy in 1st year post-transplant	22	14	36
Graft loss within 1 year of biopsy	6/22 (27%)	1/14 (7%)	7/36
Biopsy after 1 year post-transplant	13	4	17
Total graft loss	15/35 (42%)	4/18 (22%)	19/53

In 10/35 culture positive patients, the urine culture turned positive only after the biopsy (after up to 4 months), in 25/35 patients, positive culture results were available before or on the day of the biopsy. Besides the common urinary pathogens, *Staphylococcus epidermidis (n=3), Serratia spp. (n=1), Providencia spp (n=1), Citrobacter spp (n=1), Candida spp (n=5),* were found in culture. *Mycoplasma spp* was positive on urine PCR in one patient. In 14 patients, the colony count was less than 10^5 CFU/ml (5000 to 10,000 CFU/ml), but these were treated as infection. 7 of these 14 recovered graft function (one after Prednisone), 4 had graft loss within one year and three survived with increased serum creatinine. Of the 18 culture negative patients, 5 had subsequent acute rejection episode within the same month, one failed, one patient died and three recovered. Mean baseline serum creatinine of 1.6 mg/dl before biopsy increased to 2.2 mg/dl one year after biopsy in culture positive patients; there was no change (1.8 mg/dl to1.77 mg/dl) in culture negative patients. Graft loss was higher in culture positive group (Table 1). Biopsy findings were similar in both groups.
Conclusions: Low colony counts, isolated low virulence bacterial strains are not uncommon in urine cultures from renal allografts and can be clinically significant. Repeat urine cultures are warranted as culture positivity may occur late during the course. Differential diagnosis of pyelonephritis and acute rejection in transplant setting is difficult and there is currently no single gold standard for confirmation.

1607 Long Term Kidney Graft Injury in Highly Sensitized Recipients

N Carter-Monroe, ED Kraus, AA Zachary, LC Racusen, LJ Arend, RA Montgomery, SM Bagnasco. Johns Hopkins University School of Medicine, Baltimore, MD.
Background: The evolution of pathologic changes over time in highly sensitized renal graft recipients has not been well characterized.
Design: We studied the development of kidney graft injury over 1-9 years post-transplant follow up (FU) in 218 patients transplanted with an HLA-incompatible kidney between 2000 and 2010.
Results: Protocol and "for cause" biopsies were available in 120 pts: 38 M, 82 F; 98 whites, 16 blacks, 6 of other race; median age 45 years; median FU 3.2 years. Median PRA was 95. DSA at transplant were present in 81 pts: 31 class I only, 27 class II only, 23 both. Five pts died (4 with functioning graft), 14 lost their graft. Biopsy proven rejections were detected in 83 pts: antibody mediated rejection (AMR) in 19%, cell mediated rejection (CMR) in 31%, both in 18%, none in 38 pts, 9 pts had BK nephropathy. Rejections were most frequent in the first month (20% CMR, 16% AMR). The average eGFR (ml/min/1.73 m^2) declined significantly ($P<0.001$) from 63 at 3 months to 54 at 1 year, and was 48 at 4 year. After the first year, 56 pts required graft biopsies, revealing CMR in 9 pts, AMR in 11 pts, both CMR and AMR in 3 pts, mixed CMR and AMR in 2 pts, glomerulitis (g≥1) and capillaritis (ptc≥1) but negative C4d in 8 pts, borderline inflammation in 5 pts. There was progressively higher average tubulointerstitial scarring (ci+ct) from 3 to 6 to 12 months ($P<0.001$), and from 1 to 2 to 3 years ($P<0.05$) post transplant. Transplant glomerulopathy (cg ≥1) developed in 54 pts, 14 by 6 months, and 23 by year 1, with proteinuria in 31, and was preceded by capillaritis (g≥1, ptc≥1) with positive C4d in 38%, and with negative C4d in 29%. Capillaritis (g≥1 and ptc≥1) with negative C4d was detected in the biopsies of 25 pts, of which at least 8 had moderate to high strength DSA, potentially indicating episodes of C4d-negative AMR.
Conclusions: Our observations support a role for capillaritis, even with negative C4d, in the development of transplant glomerulopathy. Despite good graft survival, acute and chronic allograft injury due to both AMR and CMR develop over time in incompatible allografts.

1608 Positive SV-40 Staining in Cases of Early PVAN without Nuclear Inclusions

NL Carter-Monroe, SM Bagnasco, ED Kraus, LC Racussen, RA Montgomery, LJ Arend. Johns Hopkins University, Baltimore, MD.
Background: Early histologic diagnosis of polyoma virus BK-associated nephropathy (PVAN) is hampered by lack of identifiable diagnostic viral nuclear inclusions on H&E stains. For these cases, pathologists rely on clinical suspicion of PVAN and/or histologic clues when deciding to order extra tests to demonstrate the presence of polyoma viral replication.
Design: We reviewed pathology reports for 43 renal allograft recipients with at least equivocal staining by SV-40 between 2007 and 2012 and assessed the presence of diagnostic nuclear viral inclusions in tubular epithelial cells (NI) on H&E, as well as the histologic pattern and viral load (VL). Histologic pattern score was based on the system described by Drachenberg et al, (pattern A: viral cytopathic changes with near normal renal parenchyma; patterns B1-B3: 3 levels of viral cytopathic change and tubulointerstitial scarring; pattern C: end-stage PVAN). Two additional patterns were added for cases with equivocal nuclear staining (E) or positive nuclear staining by SV-40 only (S), and evidence of tubulointerstitial scarring and/or inflammation without viral inclusions on H&E. VL was scored to assess the percentage of tubules exhibiting viral replication (1:<1%, 2:1%-10%,3:>10%), as described in the Banff working proposal for PVAN. An additional score of "0" was added for cases with equivocal SV-40 nuclear staining.
Results: A subset of 54 protocol and "for cause" biopsies were reviewed for 43 pts: 31 M, 12 F; 29 whites, 9 blacks, 5 other race; median age 51.4 years. Diagnostic viral nuclear inclusions were seen in 26 (48%) biopsies compared to 28 (52%) showing reactive/regenerative changes or atypia only. Cases without NI on H&E, but definite staining by SV-40, were more likely to have VL1 scores (32%), as compared to cases with NI (11%), with a significant trend towards higher VL scores (VL 2 or 3) in cases with NI ($P<0.002$). Cases without NI were more likely to exhibit histologic pattern E or S (n=27, 96%), whereas 22 (88%) of cases with NI demonstrated histologic pattern B1 and above. No cases demonstrated histologic pattern C. There was no significant difference between cases with or without NI with respect to the presence of inflammation or tubulitis.
Conclusions: Our analysis suggests that routine SV-40 staining may assist in the diagnosis of early stage PVAN in biopsies demonstrating lower viral loads and lack of diagnostic viral nuclear inclusions on H&E staining.

1609 Denervated Renal Graft Explants Have Extensive Damage of the Juxtaglomerular Apparatus and Neural Network

CD Cendrowski, W Li, MT Rooney, PL Zhang. William Beaumont Hospital, Royal Oak, MI.
Background: Renal innervation partially controls the juxtaglomerular apparatus and renal tubular reabsorption. Experimental denervation has been shown to cause large urinary water and sodium losses (up to 3.6 and 8.3 fold from baseline levels, respectively). In humans, a single kidney graft has a glomerular filtration rate only half that of normal and is entirely denervated (even if partial reinnervation is possible later). This study examines the renal innervation system in explanted renal grafts for other possible etiologies of renal dysfunction besides ongoing rejection and chronic changes.
Design: Ten control kidney sections (grossly normal areas taken from nephrectomy specimens for tumor) and seventeen renal transplant explants were included in the study. All sections were immunohistochemically stained with neuron specific enolase (NSE) for evaluating the juxtaglomerular apparatus, CD56 for examining the renal neural network, and calretinin (a marker for calcium influx) for evaluating viability of large renal nerves.
Results: In normal controls, staining with NSE revealed positive granular staining of the juxtaglomerular apparatus, namely the macula densa and specialized afferent arterioles. CD56 staining consistently localized nerve fibers to arterioles, peritubular spaces in the cortex and medulla, and the vasa recta in normal controls. In explants where chronic glomerular and tubular changes were extensive, both NSE staining of the juxtaglomerular apparatus and CD56 staining of the neural network were largely absent in the cortex and medulla. In both normal controls and graft explants, there was weak calretinin staining of large renal nerves, implying at least partial reinnervation of the transplant kidneys.
Conclusions: Explanted grafts appear to have at least partial reinnervation of large nerve fibers. Extensive loss of the juxtaglomerular apparatus and peritubular/perivascular innervation, however, may be additional factors compromising graft nephron regulation of glomerular filtration and tubular reabsorption, in addition to ongoing rejection and chronic injury.

1610 Prognostic Value of Endocapillary Proliferation in IgA Nephropathy Patients with Minimal Immunosuppression

A Chakera, C MacEwen, SS Bellur, L Chompuk, D Lunn, ISD Roberts. Sir Charles Gairdner Hospital, Nedlands, Australia; Churchill Hospital, Oxford, United Kingdom; John Radcliffe Hospital, Oxford, United Kingdom; University of Oxford, Oxford, United Kingdom.
Background: Interpretation of the Oxford Classification study of IgA nephropathy (IgAN), and subsequent validation studies, is confounded by immunosuppression (IS) bias. In these studies, a median of 38% of patients have received IS. In no study does endocapillary proliferation (E score) independently predict outcome. This may reflect bias from higher levels of IS in patients with endocapillary proliferation that is reported

in these studies. In order to determine the true value of E score, retrospective analysis of patient cohorts that have received little or no IS, irrespective of histology, is required.
Design: We performed a retrospective single centre study of patients diagnosed with IgAN. Our unit takes a conservative approach to IS in IgAN and steroid/cytotoxic therapy is rare. Biopsies were reviewed and scored according to Oxford Classification (MEST) criteria. The primary outcome was rate of loss of renal function, dichotomised to slow and fast loss (< and >5ml/min/year), the secondary outcome development of end-stage renal disease (ESRD; CKD stage 5).
Results: 237 patients with IgAN were identified, mean follow up 82 months. 200 had biopsies available for review, of which 44 were inadequate for scoring (<8 glomeruli), leaving 156 patients with a clinical & histological dataset that were included for analysis. Summary of clinical data, expressed as mean (standard deviation): age at diagnosis 42 (15) years, initial eGFR 50 (25) ml/min/1.73m^2, uPCR 250 (281), MAP 107 (16) mm/Hg, delta-eGFR -2.8 (23.5). Only 8/156 patients (5%) received steroid/cytotoxic therapy. In multivariate analysis, including histology & clinical data at diagnosis, the only independent predictors of subsequent ESRD were eGFR (p=0.018) & proteinuria at the time of diagnosis (p=0.004); histology scores did not provide additional prognostic information. Independent predictors of fast loss of eGFR were proteinuria (p=0.008), E (p=0.034) & T scores (p=0.007).
Conclusions: We conclude that in a cohort of IgAN patients receiving little immunosuppression, endocapillary proliferation and tubular atrophy/interstitial fibrosis are independent predictors of rate of loss of renal function. The lack of predictive value of E score in all other clinicopathological studies is most likely a result of IS-associated bias. Our findings provide additional evidence to support IS treatment of endocapillary-pattern IgAN.

Abstract #1611 moved to Genitourinary

1612 The Significance of Immunohistochemical Detection of IgG$_4$ in Membranous Nephropathy

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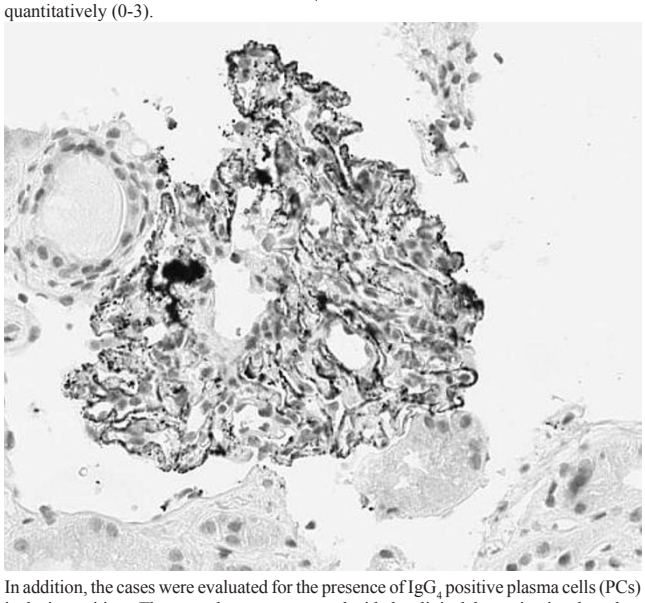
Background: Membranous nephropathy (MN) is a common cause of the nephrotic syndrome in adults. MN is primary (autoantibodies to phospholipase A$_2$ receptor, aldose reductase, superoxide dismutase, or α-enolase) or secondary (cancers, infections, autoimmune diseases, medications). The characteristic finding on pathology is immune complex formation/deposition on the sub-epithelial side of the glomerular basement membrane (GBM), leading to complement activation, podocyte dysfunction, proteinuria, and even progressive loss of renal function. In idiopathic MN, the immunoglobulin G in the immune complexes is predominantly restricted to subclass 4 (IgG$_4$), whereas in secondary causes other subclasses are typically found. While previous studies have identified IgG$_4$ antibodies in patient serum, immunohistochemical characterization of this protein in renal biopsies has not previously been described.
Design: Seventy-seven cases of MN were evaluated retrospectively. Formalin-fixed, paraffin-embedded tissue was stained for mouse monoclonal IgG$_4$ (Cell Marque) and evaluated for presence or absence of IgG$_4$ in the GBM. The slides were scored semi-quantitatively (0-3).



In addition, the cases were evaluated for the presence of IgG$_4$ positive plasma cells (PCs) in the interstitium. These results were compared with the clinical determination, based on review of the patient's medical record, of a primary versus secondary etiology of the MN.
Results: Thirty-three cases had positive IgG$_4$ staining in the GBM, and 44 were negative. Of the positive cases, 29 had no evidence of a secondary etiology. The remaining 4 had a history of a malignancy. Of the negative cases, 34 had a secondary diagnosis, including 21 with class V (membranous) lupus nephritis. The overall positive predictive value of glomerular IgG$_4$ staining was 88% (74% sensitivity). Negative staining had a negative predictive value of 77% (89% specificity). IgG$_4$ positive PCs were detected only in cases of lupus nephritis (11 of 21).
Conclusions: The presence of glomerular IgG$_4$ staining in a case of MN supports a diagnosis of primary disease and may help to limit the workup these patients undergo to rule out a secondary cause. In addition, the presence of interstitial IgG$_4$ positive PCs is highly suggestive of underlying systemic lupus.

1613 Phospholipase A2 Receptor Staining Is Not a Sensitive Indicator of Idiopathic Membranous Glomerulopathy in Children

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Background: Anti-phospholipase A2 receptor (PLA2R) autoantibodies have recently been implicated as a causative agent in most cases of adult idiopathic membranous glomerulopathy (MG). PLA2R staining of renal biopsies in two recent large case series of adults with idiopathic MG showed a sensitivity of 74%/75% for the detection of idiopathic MG. To our knowledge, this is the first case series on PLA2R staining in a pediatric population with MG.
Design: The database at our institution was searched from 2005-2012 for patients age 17 and under with MG and negative ANA serology. Forty-one consecutive cases were identified and clinical follow-up was performed to confirm idiopathic MG (negative testing for autoimmune disease, HBV, HCV, sarcoidosis, and syphilis). Twenty-two patients were included in the study.
Results: Patients showed a 1:1 male to female ratio with average age of 14 years (range 4-17 years). 82% of patients reported proteinuria (avg. 6.8 gm/day) with average creatinine of 0.72 mg/dl (range 0.2-1.3 mg/dl). IgG staining (granular, capillary wall) was present in 100% of patients at 2+ or greater intensity and C3 staining was present in 77%. PLA2R staining was identified in 10 patients providing a sensitivity of 45% (CI 25-67%) for the detection of idiopathic MG. Bovine serum albumin staining was performed in all PLA2R negative cases and showed no positivity. IgG subtypes were performed on five of the PLA2R negative cases with 3/5 showing IgG4 co-dominance and none showing IgG4 restriction. By electron microscopy all cases showed subepithelial deposits with mesangial and subendothelial deposits being present in 50% and 5%, respectively. Staging (Ehrenreich and Churg) showed 41% of patients at stage I, 18% at stage II, and 41% at stage III, with 70% of PLA2R+ patients being stage III.
Conclusions: PLA2R staining within a population of pediatric MG showed a sensitivity of 45% for idiopathic MG which is much lower than previously reported in adult populations. Also, within the PLA2R negative cases no restriction to IgG4 subclass was identified. These PLA2R-negative cases either represent a population of misclassified secondary membranous glomerulopathy in which the secondary etiology is undetectable at the time of renal presentation or an as yet undefined etiology of primary membranous glomerulopathy caused by non-PLA2R antibodies. This series suggests that PLA2R staining lacks sensitivity for the detection of idiopathic MG in children.

1614 Acute Proliferative Glomerulonephritis in Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is the most common cause of end-stage renal disease in the US and its incidence is rapidly increasing. Recent papers have defined IgA dominant infection-associated proliferative glomerulonephritis (GN) in diabetic patients and its associated poor prognosis; however few if any large series have looked at the prognosis and spectrum of proliferative GN in patients with DN.
Design: Our database was searched from 2001 thru 2011 for patients with diagnosed DN and proliferative GN (intra- or extracapillary hypercellularity). A total of 78 consecutive cases were included. All cases were viewed by at least two renal pathologists.
Results: The mean age was 59 years with a 1.5:1 male to female ratio. Indication for biopsy was often multiple with acute renal failure/elevated creatinine and rapid increase in proteinuria/nephrotic syndrome being the most common. A history of recent infection was reported in 33 patients with urinary tract infection, cellulitis and pneumonia the most common. Proliferative GN was present in all patients, often with "shredding" of the KW nodules. By immunofluorescence 39/78 patients showed IgA dominance while 17/78 and 5/78 displayed IgG and IgM dominance, respectively. Of the 33/78 patients with clinical history of infection 19/33 were IgA dominant. C3 staining was present in 71/78 patients often at ≥2+ levels. Lambda was the dominant light chain in 33/78, with 25/78 having equal lambda/kappa staining. By electron microscopy 76/78 patients displayed immune complex deposition with 69/78 showing mesangial deposits and 38/78 and 34/78 patients displaying subendothelial and subepithelial deposits, respectively. Presently, follow-up data is available for 35/78 cases (average 44 months). No significant difference in clinical outcome was identified (p=0.74) between IgA dominant and non-IgA dominant patients with 63% and 57% proceeding to renal replacement therapy or death, respectively.
Conclusions: To our knowledge, this series is the largest to date to explore the prognosis and scope of proliferative GN in DN. Follow-up data revealed a similar rate of progression to renal replacement therapy or death for IgA dominant and non-IgA dominant patients. Also, of the 33/78 patients with history of recent infection, DN, and proliferative GN, 58% displayed IgA dominant staining while 42% did not. These findings suggest that regardless of heavy-chain dominance, proliferative GN in DN has a poor clinical outcome and that infection-associated proliferative GN in DN is not restricted to the IgA dominant type.

1615 IgA Deposition in Diabetic Nephropathy

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Background: Diabetes mellitus (DM) is the most common cause of end-stage renal disease in the USA and is becoming an epidemic. Recent papers have defined IgA dominant infection-associated glomerulonephritis (GN) in DM however, little is published on the scope and prognosis of IgA dominant/co-dominant deposition in patients with diabetic nephropathy (DN).

Design: Our database was searched from 2001 thru 2011 for patients diagnosed with DN and IgA dominant/co-dominant deposition. The biopsies were received from multiple medical centers across the USA and showed a fair representation of all nephrology practice settings. A total of 132 consecutive cases were included. Cases were viewed by two renal pathologists.
Results: The mean age was 59 years with a 2:1 male to female ratio. Indication for biopsy was often multiple with rapid onset proteinuria/nephrotic syndrome (67%), acute renal failure (37%), and hematuria (17%) being the most common. 36/132 patients had a known history of recent infection, with osteomyelitis, foot ulcer, and cellulitis being the most common. A subset of patients showed endocapillary or crescentic proliferative GN (39/132 patients). Classification of DN via Tervaert et al showed 102/132 class III. IgA dominant/co-dominant staining was present in all patients, usually at ≥2+ intensity (81%). IgM (27%) and IgG (11%) staining was less common and C3 staining was present in 70% of patients, most commonly at ≥2+ levels. Light chains were often lambda predominant (61%) or equal intensity for kappa and lambda (26%). By electron microscopy 99% of patients displayed mesangial deposits with only 16% of patients showing capillary wall deposits. Currently, follow-up data is available for 46/132 patients (mean 45 months) showing 57% of patients have progressed to renal replacement therapy (RRT) or death. Progression to RRT or death among patients with proliferative GN (57%) and without (57%) was the same.
Conclusions: To our knowledge this is the largest series to investigate IgA dominant/co-dominant deposition in DN. In our series, DN with IgA dominant/co-dominant deposition was not uniformly associated with an underlying infection or proliferative GN. Also, prognosis was the same in patients with and without proliferative GN. This data suggests that while IgA dominant/co-dominant deposition in the setting of DN may have several different etiologies, prognosis is universally guarded.

1616 Histopathological Response Patterns Following Treatment of Acute Renal Allograft Rejection

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Background: Biopsy evaluation plays a key role in the diagnosis and grading of acute rejection and chronic changes. To date there are few descriptions of the histological outcomes of anti-rejection therapy. This study aimed to evaluate and compare post-rejection treatment biopsies with index biopsies to assess treatment response patterns.
Design: A retrospective review of 713 transplant biopsies from 2009-11 yielded 30 cases of acute rejection with biopsies performed to evaluate the response to therapy. Biopsies were obtained within 15-223 days (mean 54.6) after an index rejection biopsy. Banff 2007 criteria were used to classify acute cell mediated rejection (ACMR) and/or acute antibody mediated rejection (AAMR). The post treatment histological response was graded as: 1-complete resolution; 2-near complete if ACMR downgraded to borderline/ C4d staining reduced to ≤ 10 % of peritubular capillaries (PTC) in AAMR; 3-partial: ACMR downgraded by at least one grade/ C4d staining reduced by 50%; 4.-persistent without improvement. Features of new onset chronic changes including interstitial fibrosis and tubular atrophy (IFTA) and other chronic changes in tubules, interstitium, vessels and glomeruli were recorded.
Results: The cases were grouped based on type of rejection in the index biopsy into AAMR, AACMR, and Mixed AAMR/ACMR. The histological resolution responses are shown in Table 1.

Histological response	AAMR (n=4)	ACMR (n=12)	Combine AAMR/ACMR (n=14)	
			AAMR Changes	ACMR Changes
1 Complete resolution	50%	66.8%	14.3%	64.3%
2 Near complete resolution	25%	16.6%	42.8%	7.1%
3 Partial resolution	25%	16.6%	14.3%	14.3%
4 Persistent rejection	0%	0%	28.6%	14.3%
New onset IFTA	25%	33.3%	50%	
New onset glomerulopathy	0%	0%	7.1%	
New onset vasculopathy	0%	0%	28.6%	

Six of 16 (37.5%) cases with residual inflammation in post treatment biopsies showed higher grade of tubulitis as compared to interstitial inflammation. Combined AAMR and ACMR cases showed higher grades of new onset IFTA, glomerulopathy and vasculopathy.
Conclusions: Our results in AAMR and ACMR show that complete histological resolution was achieved in only 50-67 % of cases and there was new onset of IFTA in one third of the biopsies. Combined AAMR/ACMR rejections had lower rates of complete resolution of the AAMR changes. Persistent rejection and the development of transplant glomerulopathy and vasculopathy were only observed in the combined AAMR/ACMR rejections.

1617 The Subcapsular Blue Strip Width: A New Marker for Evaluating the Residual Potential Nephrogenesis in the Newborn Kidney

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Background: The multipotent cap mesenchymal cells located in a blue-appearing strip in H&E-stained sections and located under the renal capsule represent the nephron progenitor population of the newborn kidney.
Design: 30 kidneys from 15 consecutive preterm newborns of 19-38 weeks of gestation at birth, were routinely processed. Histological sections were stained with H&E. In each kidney, the mean width of the mesenchymal pluripotential cells located under the renal capsule, appearing as a "blue strip" was measured by a semi automatic segmentation method based on combination of color and texture information. A comparison with human based measurement was also performed as well as the radial glomerular count, representative of the entity of the previous nephrogenesis.
Results: A marked interindividual variability was observed in the amount of pluripotential/stem cells detected in the preterm kidneys. The width of the "blue strip" did not correlate with the gestational age of preterms at birth. Significant differences regarding the residual nephrogenic potential was observed among preterms of the same gestational age. No correlation was found between the blue strip width and the values obtained with the radial glomerular count. Finally, the semi automatic method performed as well as the human measurement but it allowed avoiding problems related to interindividual evaluation.
Conclusions: Measurement of the amount of pluripotential renal cells appears a simple and effective new tool for the evaluation of the residual potential nephrogenesis in newborn kidneys. The blue strip width should be considered complementary to previous methods, including the radial glomerular count, that give a reliable information on the previous nephrogenesis. The absence of any correlation between the blue strip width and the glomerular count (future and past of nephrogenesis) allows to hypothesize that nephrogensis should not be considered as a progressive linear process at constant speed, but as a process that could start very fast in the first period of gestation and progress at a lower speed in the final period, or vice versa.

1618 Medullary Injury in the Human Renal Biopsy: Assessment of Epithelial Mass

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Background: Renal tubulointerstitial injury assessment is often restricted to the cortex. The outer medulla has two major zones: outer stripe (OS) and inner stripe (IS). OS cellular mass is mostly formed by proximal tubules and is limited. IS consists of an epithelial cell mass (EPCM) mostly formed by thick ascending limbs and collecting ducts. Delineation of this zone depends on recognizing corticomedullary junction connective tissue/vascular components, adjacent OS, and vasa recta. With increasing injury, EPCM diminishes with thick ascending limb atrophy/loss (TA); the collecting ducts are relatively preserved. To characterize injury in these regions, we conducted a morphometric study.
Design: Consecutive native renal biopsies (n=22) were examined; the sole inclusion criteria was the availability of medulla (primarily outer medulla). Trichrome, PAS, and cytokeratin (CK) immunostained (AE1/AE3) slides were digitally scanned. For the entire cortex and entire medulla, EPCM was quantitated using a positive pixel count algorithm tuned to detect CK brown and trichrome red. Furthermore, pathologist visual assessment was recorded for %TA and % composed of EPCM.
Results: Cortical and medullary EPCM declined together, with linear regression showing direct relationships between cortical and medullary EPCM by trichrome ($r=0.69$ between cortex and medulla, $p<0.0001$) and CK ($r=0.68$, $p=0.0007$). The EPCM (mean±standard deviation [SD]) of the cortex and medulla, respectively, were 60±14% and 46±12% on trichrome;49±9% and 47±10% on CK, and 48 ± 28% and 24 ± 18% on pathologist assessment. The OS and IS width was 1.7±0.7 and 4.1±2.5 mm (mean±SD), respectively. Weak but statistically significant correlations were found between increasing IS width and cortical %TA ($r=0.43$,$p=0.046$). Conversely, both IS and OS width were inversely correlated with trichrome EPCM ($r=-0.44$,$p=0.040$ for OS width versus entire medullary EPCM and $r=-0.48$,$p=0.023$ for IS width versus entire medullary EPCM).
Conclusions: This study demonstrates relationships between diminishing cortical and medullary EPCM. Furthermore, expansion of OS and IS are both associated with reduced medullary epithelial cell mass. Thus, as epithelial cell elements are lost, reactive/fibrotic responses causes zonal expansion. Analyzing and quantitating medullary injury may provide a unique perspective to examine human chronic kidney disease.

1619 Medullary Injury in the Human Renal Biopsy: Fibrosis Assessment

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Background: The assessment of renal tubulointerstitial injury is important for both native and transplant kidneys; however, past studies have primarily focused on the renal cortex. To study medullary fibrotic injury, interstitial fibrosis (IF) and tubular basement membrane (BM) mass were quantitated in both the renal cortex and medulla.
Design: The sole inclusion criteria was that medullary tissue be available for evaluation. For 22 consecutive native renal biopsies, a whole slide slide scanner was used to obtain whole slide images (WSIs). IF was quantitated on trichrome stains and collagen III immunohistochemistry using a positive pixel count algorithm applied to the WSIs. The algorithm was also used to quantitate the % composed of BM material on a PAS stain. IF was also measured by subtracting the PAS BM% from the trichrome (Trichrome%–PAS%, referred to as T–P) in order to account for BM material also detected on trichrome staining. Pathologist visual assessment of %IF was also provided.
Results: Trichrome and T-P IF% showed a wide range, from 20-59% and 2.4-44% for all tissue, respectively. Image analysis of trichrome and T-P WSIs correlated for all anatomic compartments ($r=0.74$–0.99, P all <0.0001). Visual measures also showed a wide range, from 15-90% for all tissue. Visual measures showed significant correlation with all of the trichrome and T-P measures except for 2 comparisons: the all tissue visual versus the all tissue T-P method and cortex visual versus the medulla T-P method. Collagen III showed a range of 9.5-47% for all tissue. Collagen III deposition correlated between compartments ($r=0.74$, $P=0.0001$ for all tissue vs. cortex, $r=0.89$, $P<0.0001$ for all tissue vs. medulla, and $r=0.71$, $P=0.0003$ for cortex vs. medulla). However, collagen III did not show a significant relationship with any of the other measures of IF.

Conclusions: Trichrome and T-P image analysis correlated between the cortex, medulla, and entire tissue; and visual assessment of these compartments also correlated with these measures. In this study, collagen III deposition correlated between compartments but did not show correlation with other IF measures, possibly suggesting that additional components are important in extracellular matrix composition. Overall, medullary measurements may show utility in larger studies prospectively correlating medullary IF with renal function in both human and animal models; and medullary measurements could prove useful in drug studies, clinical trials, and evaluation of biopsies containing only medulla.

1620 A High-Risk Variant of the ApoL1 Gene Correlates with Increased Interstitial Fibrosis and Tubular Atrophy among African Americans with Arterionephrosclerosis

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Background: Previously we found that blood pressure levels and proteinuria did not account for morphological lesions in arterionephrosclerosis attributed to hypertension, suggesting other factors may play a role. Recently a variant of the ApoL1 gene that is commonly seen in African Americans (AA) but very rare in Caucasians (C) was implicated in hypertension-attributable end stage kidney disease. In normal kidney, ApoL1 is expressed in podocyte, proximal tubular epithelia and arteriolar endothelium. In kidney disease, the localization and expression level of ApoL1 change. However, the mechanism of this increased disease risk and correlation with histopathologic changes in the kidney are unknown.

Design: All clinical renal biopsies with a histological diagnosis of arterionephrosclerosis 1988-1999 were identified. Excluding insufficient biopsy samples, 46 biopsy samples were analyzed for the presence of the high risk ApoL1 gene variant. We then compared genotype results with pathological lesions, serum creatinine and proteinuria.

Results: Our population included 13 C (5 male/8 female) and 33 AA patients (25 male/8 female), on average 54.4 ± 14.8 yrs. Amongst AA patients, 12 had 0 risk alleles, 12 had 1 risk alleles and 9 had 2 risk alleles. The 13 C patients all had 0 risk alleles. Amongst patients with 0 risk alleles, C and AA had similar clinical and morphology features. Serum creatinine, proteinuria, total global glomerulosclerosis (GS) or types of GS (obsolescent, solidified or disappearing), segmental GS, mesangial expansion, periglomerular fibrosis, arterial and arteriolar injury did not differ in AA with or without risk alleles. However, there was more severe tubular atrophy in those AA with 2 risk alleles than those with 0 risk alleles (37.2 ± 25.0 *vs.* 13.3 ± 14.7%, $p<0.05$). Similarly, interstitial fibrosis was more severe in AA with 2 risk alleles than those with 0 risk alleles (43.9 ± 27.7 *vs.* 17.1 ± 17.8%, $p<0.05$).

Conclusions: Homozygosity for a high-risk variant of ApoL1 in patients with arterionephrosclerosis correlates with the extent of interstitial fibrosis and tubular atrophy in biopsy specimens, but is not correlated with glomerular, arterial or arteriolar injury.

1621 A Proposed Pathologic Classification System for ANCA-Associated Glomerulonephritis Is Not Effective in Patients with Estimated Glomerular Filtration Rate of <15 at Presentation

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Background: A classification system has been proposed for glomerulonephritis associate with anti-neutrophil cytoplasmic autoantibodies (ANCA-GN) (Berden at al. J Am Soc Nephrol 21:1628-36, 2010), based on ≥50% sclerotic glomeruli (Sclerotic), ≥50% normal glomeruli (Focal), ≥50% crescents (Crescentic) or none of these (Mixed). We evaluate the effectiveness of this classification in a cohort of patients with very severe disease.

Design: Clinical and pathologic features were evaluated in 115 patients with ANCA-GN and estimated GFR <15ml/min/m^2 at presentation; and correlated with outcome. Pathologic evaluation included classification by the Berden system based on % sclerotic glomeruli, % normal glomeruli and % crescents; and semi-quantitative scoring of the pathologic features in Tables 1 and 2 (0-4+ scale). The primary outcome was death or dialysis within 12 months.

Results: The classes were no different in age, sex or presenting eGFR. There was no significant difference ($p=0.3$) in % of patients reaching ESRD after 12 mo. Pathologic analysis showed that, in these patients with severe clinical disease, all classes had similar degrees of substantial tubulointerstitial injury reflected in the chronicity index ($p=0.2$) (Table 1) as well as specific tubulointerstitial scores (Table 2). However, the activity index did vary among the classes ($p<0.001$).

Table 1

Class:	n:	Activity Index	Chronicity Index	% ESRD after 12 mo
Focal	7	3.9±1.7	4.3±3.7	28.6%
Mixed	35	5.1±1.8	5.7±2.5	42.9%
Crescentic	51	8.7±2.6	6.6±3.5	56.9%
Sclerotic	22	6.6±3.5	6.8±3.7	45.5%
p		p<0.01	p=0.2	p=0.3

Table 2

Class:	% Nornal Glomeruli	% Crescents	% Global Sclerosis	Glomerular Necrosis	Interstitial Leukocytes	Interstitial Fibrosis	Tubular Atrophy
Focal	62%	27%	9%	0.9+	1.0+	1.4+	1.4+
Mixed	20%	26%	19%	1.0+	1.4+	1.8+	1.8+
Crescentic	13%	75%	16%	1.9+	2.0+	2.0+	2.1+
Sclerotic	6%	53%	65%	1.4+	1.7+	2.0+	2.1+
ANCA:							
MPO-ANCA	18%	53%	26%	1.5+	1.6+	1.9+	1.9+
PR3-ANCA	15%	52%	24%	1.4+	1.8+	1.8+	1.9+

Conclusions: Pathologic classification of ANCA-GN that is effective in predicting outcomes in patients with a broader range of clinical presentations may not be as effective in patients who present with very severe impairment of GFR. The comparable tubulointerstitial injury indicated that all had sustained substantial renal impairment even though they has different classes of glomerular injury.

1622 Utility of Immunofluorescence and Electron Microscopy in Renal Transplant Biopsies

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Background: Renal biopsy is the gold standard to diagnose allograft rejection versus other causes of graft dysfunction. However, the role of immunofluorescence (IF) and electron microscopy (EM) in renal transplant biopsy diagnosis has not been well established. We therefore assessed the utility of IF and EM in this setting.

Design: We reviewed 267 transplant biopsies performed on 199 patients at Vanderbilt University Medical Center from 2003 to 2005. Pre-biopsy clinical assessment was performed by five experienced transplant nephrologists and pre-biopsy diagnosis and/or differential diagnoses were recorded on a pre-biopsy worksheet.

Results: 152 of 267 (57%) diagnoses were accurately predicted by the pre-biopsy differential diagnosis. 62 (23%) diagnoses were not predicted by clinical pre-biopsy assessment. 53 diagnoses (20%) were included in the differential diagnosis, but at least one additional significant finding was missed. Acute rejection was clinically suspected in 125 cases (47%), of which 65 (52%) were histologically confirmed, 43 (34%) showed a different histologic diagnosis, and 17 (14%) had rejection with at least one other major diagnosis. Of those cases where biopsy did not confirm clinically suspected rejection, major biopsy diagnoses were chronic allograft nephropathy (CAN) ± transplant glomerulopathy (TGP) in 46%, acute tubular injury in 31%, polyoma virus nephropathy (PVN) in 9%, thrombotic microangiopathy (TMA) in 6%, lupus nephritis (LN) in 5%, calcineurin inhibitor toxicity in 2% and minimal histologic abnormalities in 2%. The most common unpredicted diagnoses were TMA (22 cases, 8%, all unpredicted), de novo or recurrent glomerulonephritis (GN) (41 cases, 21%, unpredicted in 19) and PVN (11 cases, 6%, unpredicted in 9 cases). Clinical management and treatment strategy were altered according to biopsy results in 54% of cases.

Conclusions: Despite overall accurate clinical prediction of dignosis, renal biopsy showed unexpected findings in a significant number of cases. In addition, clinical suspicion of rejection was not confirmed in 34% of cases, thus resulting in avoidance of potential immunosuppression, or requiring a decrease in immunosuppression in patients with PVN. Thus, we conclude that IF and EM are valuable in assessment of the kidney transplant biopsy. Our data support that IF should be done routinely at least the first time the transplant is biopsied, with EM added as indicated by clinical history or abnormal LM/IF findings.

1623 Toward a Working Definition of C3 Glomerulopathy by Immunofluorescence

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Background: In the past, membranoproliferative glomerulonephritis (MPGN) was subdivided into types 1-3 according to light microscopic and ultrastructural findings. Based on new understanding of the role of alternative pathway (AP) complement dysregulation, the term C3 glomerulopathy (C3G) now encompasses DDD (type 2) and those forms of type 1 and 3 with isolated deposits of C3. Precise immunofluorescence (IF) criteria for C3G remain to be defined. Our aims were to: 1) test hierarchical IF criteria with varying stringency for C3G; 2) determine if "C3 only" is a practicable criterion; 3) apply these criteria to analyze the incidence of C3G in types 1 and 3 MPGN.

Design: A total of 818 biopsies coded as MPGN pattern in the Columbia Renal Pathology Laboratory from 1998-2002 were retrospectively reviewed. After exclusion of those cases with clear etiology (such as hepatitis C, cryoglobulinemia, and dysproteinemia), we identified 444 cases of primary MPGN types 1-3. We retrospectively analyzed detailed IF reports and coded cases using the following criteria: Glomerular deposits of: C3 only (Group 1); C3 dominant and ≤1+ IgM only (Group 2); C3 dominant and at least 2 orders of intensity stronger than any combination of IgG, IgM, IgA, C1q (Group 3).

Results: The findings are summarized in tabular form.

Primary MPGN Subtype	Number of cases	IF Group 1 n (%)	IF Group 2 n (%)	IF Group 3 n (%)	IF Groups 1-3 n (%)
Type 1	291	15 (5%)	11 (4%)	38 (13%)	64 (22%)
Type 2(DDD)	56	23 (41%)	10 (18%)	12 (21%)	45 (80%)
Type 3	97	8 (8%)	13 (13%)	13 (13%)	34 (35%)

The most restrictive criterion of "C3 only" captured only 41% of DDD (compared to 5% of type 1 and 8% of type 3), whereas adding the most liberal definition identified 80% of DDD (compared to 22% of type 1 and 35% of type 3). The 20% unaccounted DDD had stronger intensity of Ig staining, but never exceeding the intensity of C3.

Conclusions: 1) "C3 only" is an impractical definition of C3G. 2) A less restrictive approach that allows for low-level Ig trapping or deposition is needed. 3) C3G is more common in MPGN type 3 than type 1. These criteria provide a framework for future correlations with functional and genetic measures of AP dysregulation in MPGN.

1624 Correlation of Urine Red Cell Morphology and Renal Biopsy Findings

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Background: Hematuria may indicate serious disease such as infection, renal disease, and malignancy. Examination of the urine sediment, including detailed analysis of red blood cell morphology, may be useful in discriminating the source of hematuria.

Specifically, dysmorphic red blood cells are associated with glomerulopathy; various sensitivities and specificities have been reported depending upon the end point of the study. We report the association of urinary dysmorphic red blood cells with biopsy-confirmed glomerulopathy.
Design: Between 2008 and 2012, 162 patients with renal biopsies had prior RenalVysion™ analysis, which included cytologic examination of the cellular elements of urine using Papanicolau and acid hematoxylin-stained concentrated urine specimens with cellular enhancement. A total of 16 patients were excluded owing to lack of glomeruli on renal biopsy or lack of red blood cells observed during urine cytologic examination, with a final study group of 146 patients. We evaluated the correlation of dysmorphic red blood cells in the urine with subsequent diagnosis of glomerulopathy by renal biopsy.
Results: We found that 76 of 108 patients with biopsy-confirmed glomerulopathy had dysmorphic red blood cells in the urine; in addition, one of 38 patients without glomerulopathy had dysmorphic red blood cells. Using biopsy-confirmed glomerulopathy as the end point for this analysis of dysmorphic red blood cells, sensitivity was 70.3%, specificity was 97.4%, positive predictive value was 98.7%, and negative predictive value was 53.6%.
Conclusions: Detection of dysmorphic red blood cells in urine is a sensitive and specific marker of glomerulopathy. This finding is best utilized in conjunction with the patient's clinical history, urine cytology findings (including casts, tubular cells, and inflammatory cells), urine chemistry, and serum chemistry.

1625 Renal Cortical Necrosis Is the Most Common Histopathological Finding in Obstetric Acute Kidney Injury in a Developing Country

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Background: Obstetric acute kidney injury is not uncommon in a developing country and is a significant cause of maternal morbidity and mortality. Poverty, lack of awareness and poor accessibility to obstetric care are the probable reasons. This study was done to analyze the spectrum of histopathological changes seen in pregnant women biopsied for acute kidney injury (AKI).
Design: All native kidney biopsies reported over 18 months (April 2011 to September 2012) in the renal pathology division of a tertiary care referral centre in southern India were analyzed. Biopsies from 85 centers, from rural as well as urban regions across India are processed here. AKI was the indication in 307 biopsies (11.3%) out of 2695 native kidney biopsies during the time period. Obstetric AKI was found in 39 patients (12.7% of all biopsied AKI). Age, clinical presentation and histopathological diagnosis were analyzed in patients biopsied for obstetric AKI.
Results: The age range was 19 to 34 years, with a mean of 24.3 years. Acute renal failure occurred in association with septic abortions or puerperal sepsis in 10 patients (25.6 %), preeclampsia or eclampsia in 10 patients (25.6 %), postpartum hemorrhage in 6 patients (15.4 %), hemolytic uremic syndrome in 4 patients (10.2 %), HELLP syndrome in 3 patients (7.7 %) and 2 patients (5.1 %) each for intrauterine death of fetus, abruptio placentae and retained products of conception. Renal histology showed cortical necrosis (patchy or diffuse) in 20 patients (51.3 %), extensive tubular necrosis in13 patients (33.3 %) and thrombotic microangiopathy in 6 patients (15.4 %). Renal cortical necrosis was reported in 26 out of the 2695 native kidney biopsies (0.96%). Obstetric complication was the most common cause (76.9%) of renal cortical necrosis in our study.
Conclusions: Cortical necrosis which is extremely rare in the western world is a common histopathological finding in patients with obstetric AKI in a developing country.

1626 Comparison of Staining Methods for Scoring Renal Fibrosis

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Background: The best morphologic predictor of outcome for most renal diseases is the degree of interstitial fibrosis (IF). Given this fact, it is of utmost importance that the technique used be accurate and highly reproducible between pathologists. We sought to compare the different stains available for estimation of fibrosis in an effort to determine which one has the best correlation with renal function and the best inter-observer agreement.
Design: Twenty cases with varying degrees of fibrosis were selected in which the indication for biopsy was chronic kidney disease and there was no evidence of acute injury on biopsy. Each case was stained with MT, Jones methenamine silver (JMS), PAS-Trichrome (PT), collagen III immunohistochemistry (Col), and polarized Sirius red (SR). These 100 slides were blindly reviewed and scored by 6 pathologists for degree of severity (none, mild, moderate, severe) and percentage of fibrosis (0-100%). Inter-observer correlation and agreement were evaluated for each stain. We also performed a functional correlation between the percentage of fibrosis and the calculated eGFR for each stain.
Results: Most stains had excellent quantitative scoring interobserver agreement. Interobserver correlation was higher with MT (r=0.72-0.94) and JMS(r=0.79-0.95) than for PT (r=0.59-0.90) and Col (r=0.69-0.90). SR had the least agreement (r=0.32-0.70). Interobserver agreement for grading the degree of fibrosis was highest for MT (κ=0.68) followed by JMS (κ=0.57), PT (κ=0.52), Col (κ=0.51), and SR (κ=0.27). All 5 stains showed correlation with eGFR as follows: TM, r^2=0.72; JMS, r^2=0.69; PT, r^2=0.69; Col, r^2=0.61; SR, r^2=0.40.
Conclusions: The degree of interstitial fibrosis is a routine but important component of renal biopsy evaluation as this is considered the most important single morphologic predictor of outcome. Nevertheless, there is a paucity of studies addressing the accuracy or reproducibility of the various techniques available for studying this important feature. We confirm here that the most commonly used technique, estimation of fibrosis with MT, shows the best interobserver agreement and correlation with eGFR. Sirius red had the least sensitivity and reproducibility in our hands. JMS, PT, and Col had only slightly lower agreement and eGFR correlation and thus would also be acceptable for routine use.

1627 Phospholipase A2 Receptor Staining (PLA2R) Is Very Rare in De Novo Membranous Glomerulopathy in the Renal Transplant

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Background: Membranous glomerulopathy (MG) is one of the most common glomerulonephritides involving the renal transplant. Since many patients never have a tissue diagnosis of their native kidney disease, it is often not possible to definitively determine whether MG in the transplant setting is a recurrent or de novo process. Therefore, we sought to determine the utility of PLA2R staining for the detection of recurrent MG. We also compared the morphologic features of the two groups in order to determine if there is increased evidence of antibody-mediated rejection in the de novo group, as some have recently reported.
Design: 105 cases of MG occurring in renal transplant biopsies were identified. Only biopsies from patients with a tissue diagnosis of the primary native renal disease were included in this study and included: 12 MG, 3 diabetes mellitus, 3 focal segmental glomerulosclerosis, 3 polycystic kidney disease, 1 IgA nephropathy, 1 anti-GBM antibody disease, and 1 with renal congenital abnormalities. There were 12 biopsies from 11 patients with recurrent MG and 12 biopsies from 11 patients with de novo MG.
Results: De novo MG occurred at mean 43 months post transplant (range 2-190 months) and recurrent MG at mean 63 months post transplant (range 1-131 months). 10/12 (83%) recurrent MG and 1/12 (8%) de novo MG biopsies showed positive glomerular staining for PLA2R giving PLA2R a sensitivity of 83% (95% CI 51-97%) and specificity of 92% (95% CI 60-100%) for recurrent MG. 2/12 (17%) de novo and 1/12 (8%) recurrent biopsies showing the presence of microcirculation inflammation (MCI). Peritubular capillary (PTC) C4d staining was negative in all cases. Cell mediated transplant rejection was seen in 2/12 (17%) de novo and 2/12 (17%) recurrent MG. 1/12 (8%) de novo MG and 0/12 (0%) recurrent MG had BK nephritis. Mesangial deposits were present in 1/12 (8%) recurrent and 5/12 (42%) de novo. There was one case of recurrent MG with a follow-up biopsy which showed negative PLA2R staining at 1 month post transplant (stage 0) and 3+ positive staining at 16 months post transplant.
Conclusions: Recurrent MG is strongly correlated with PLA2R positivity with a sensitivity of 83% and specificity of 92% for recurrent MG. There was no morphologic evidence of an association between antibody mediated rejection and de novo MG as both groups had a similar degree of MCI and PTC C4d staining. Most interestingly, PLA2R staining was almost always negative in de novo MG, suggesting a different mechanism in this unique form of MG.

1628 APOL1 Risk Variants in Collapsing Lupus Glomerulopathy

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Background: Collapsing glomerulopathy (CG) is a devastating renal disease affecting African Americans (AA) which has been reported in association with numerous etiologies, the most well known being HIV (HIVAN). Recently, an association was found between the presence of *APOL1* risk alleles and HIVAN. CG also occurs in the setting of systemic lupus erythematosus (SLE) as a part of the spectrum of so-called lupus podocytopathy. We sought to determine if Collapsing Lupus Glomerulopathy (CLG) was also associated with the presence of APOL1 risk alleles.
Design: A total of 546 renal biopsies were identified in the case file of our institution from AA patients with SLE. Two renal pathologists confirmed the diagnosis of CG. Additional features examined include the ISN/RPS Classification, activity score, chronicity score and the presence of microcystic tubular dilatation and arteriosclerosis. DNA was extracted from archived biopsy tissue and genotyped for *APOL1* risk alleles using TaqMan assays. The pathologists were blinded to the *APOL1* genotype at the time of evaluation.
Results: A total of 26 cases of CLG were identified. *APOL1* strongly associated with CLG (c^2=24.8, P<0.001). In a recessive model, *APOL1* risk alleles conferred 5.4 fold higher odds of developing CLG (c^2=20.6, P<0.001, Odds ratio CI_{95}=2.4 – 12.1). *APOL1* risk alleles were also found to be associated with non-necrotizing crescents (c^2=7.1, P=0.008, OR= 1.6, CI_{95}=1.2 – 2.3) and microcystic dilatation (c^2=12, P=0.001, OR= 2.2, CI_{95}=1.4 – 2.3). Other morphologic features were not found to be associated with *APOL1*.
Conclusions: We found that CLG is strongly associated with the presence of *APOL1* risk alleles and we suspect that this initial study actually under represents the strength of the association. There is extensive morphologic overlap between CLG and proliferative lupus nephritis (PLN) resulting from the morphologic similarity between a florid collapsing lesion and cellular crescent formation. Given this overlap and the higher incidence of "crescents" in biopsies from patients with 2 *APOL1* risk alleles, it is plausible that some of the cases categorized as PLN might actually represent CLG. *APOL1* genotyping of AA patients with SLE might prove helpful in the future to identify patients at risk for CLG, an entity with a poor prognosis which is often resistant to treatment.

1629 Expression of CD71 in Mesangial Cells of IgA Nephropathy and Proliferative Parietal Epithelial Cells of Immune Complex Crescentic Glomerulonephritis

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Background: The transferrin receptor (CD71) is an integral membrane protein that mediates the uptake of transferrin-iron complexes. CD71 has been shown to be abnormally expressed in a variety of immune-related diseases. The mechanisms of CD71 involving in the process of immune-related diseases are unclear. This study

aims to evaluate immunohistochemical expression of the CD71 in IgA nephropathy and crescentic glomerulonephritis and assess its value in the diagnosis of some glomerulonephritis.

Design: The renal biopsy tissue sections of 28 IgA nephropathy (IGAN), 16 non-IgA immune complex crescentic glomerulonephritis (ICCGN), 13 Pauci-immune crescentic glomerulonephritis (PICGN), 19 acute kidney injury (AKI) were immunostained for CD71. The number of immunoreactive glomerular mesangial, endothelia and epithelial cells was scored as 0-3. Staining intensity was graded as 0 -3+ The total immunoreactivity score (IRS) of immunostaining was calculated by adding the percentage score (0 to 3) of immunoreactive cells to the intensity score (0 to 3).

Results: The number of CD71 positive mesangial cells and the intensity of immunostaining were significantly increased in IGAN compared with ICCGN, AKI and PICGN ($P < 0.01$). The differences was quantified by calculating the IRS (Table 1).

Table 1: Total Immunorectivity Score No. (%) of CD71 in Mesangial Cells.

Score	0	2	3	4	5	6	
							Total Case No.
IGAN	0	1(4)	2(7)	5(18)	14(50)	6(21)	28
AKI	4(21)	13(69)	1(5)	1(5)	0	0	19
ICCGN	4(25)	10(62)	2(13)	0	0	0	16
PICGN	3(24)	8(62)	1(7)	1(7)	0	0	13

The number of CD71 positive proliferative parietal epithelial cells and the intensity of immunostaining were significantly increased in ICCGN compared with PICGN ($P < 0.001$). The differences was quantified by calculating the IRS (Table 2).

Table 2: Total Immunorectivity Score No.(%) of CD71 in Parietal Epithelial Cells.

Score	0	2	3	4	5	6	
							Total case No.
ICCGN	0	0	2(12)	2(12)	8(51)	4(25)	16
PICGN	4(31)	7(53)	1(8)	1(8)	0	0	13

No increased expression of CD71 was observed in glomerular endothelial cells in all study groups.

Conclusions: Increased expression of CD71 in mesangial cells IGAN supports the conclusion of previous study that CD71 serves as an IgA receptor mediating mesangial deposition of IgA complexes in IGAN. An enhanced expression of CD71 in proliferative parietal epithelial cells in ICCGN suggests that CD71 could also play an important role in triggering the immune activation involving crescent formation. CD71 staining may serve as a useful marker in aiding diagnosis of IGAN and ICCGN.

1630 Adenovirus Nephritis in Renal and Other Solid Organ Transplant Recipients

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Background: Adenoviral (AdV) infection in an immunocompromised host carries a mortality rate approaching 80%. It is seen most frequently in bone marrow transplant recipients, where it causes pneumonia and disseminated infection, but in solid organ transplant (SOT) recipients it can involve the graft. Among abdominal organ recipients, small bowel grafts are most frequently affected, presumably due to the presence of a virus reservoir in the mucosa-associated lymphoid tissue. However, other grafts, including kidney, may also be involved. AdV graft infection leads to graft loss in most instances. Therefore, an awareness of the pathology associated with such infections is important in order to allow early detection and specific treatment.

Design: We reviewed 3 SOT recipients with AdV kidney involvement from 2 institutions. We sought to compare the diagnostic morphology and the clinical and laboratory findings.

Results: 2 patients received renal transplants (both adults, 1 male and 1 female) and 1 heart transplant (5 years old boy). Biopsies were performed for renal failure with hematuria in 2 renal grafts and in 1 native kidney from a heart transplant recipient with a clinically stable allograft. Immuno stain (IHC) for AdV was positive in both grafts and in 1 native kidney. There was a variable degree of tubulocentric necrosis with a vaguely granulomatous mixed inflammatory infiltrate associated with rare cells with cytopathic effect. There was also lymphocytic infiltrate simutaing T-cell rejection with admixture of eosinophils. In the heart allograft, AdV was detected by IHC in the absence of necrosis. All patients had AdV (+) serology but, in 1 adult patient, the viral load was low and presumed to be clinically insignificant. All patients were subsequently treated and cleared AdV infection, as evidenced by follow-up biopsies, with no loss of the grafts.

Conclusions: AdV infection can involve allografts and native kidney in SOT recipients. Infection is associated with variable necrosis and acute inflammation in addition to a rejection-like infiltrate. Hematuria in non-renal SOT recipients may be associated with AdV nephritis and clinically-silent graft involvement. Detection of AdV nephritis may be associated with subclinical non-renal graft involvement. Prompt diagnosis (aided by IHC), with specific treatment, can prevent graft loss. Positive serology, with a low but detectable viral load, may be associated with clinically significant graft involvement in some patients.

1631 Correlation of Histological and Clinical Parameters in Patients with Renal Biopsy Diagnosis of Diabetic Nephropathy

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Background: The pathologic diagnosis of diabetic nephropathy (DN) in the renal biopsy is based on a constellation of morphologic findings that include glomerular changes such as tuft enlargement, basement membrane thickening, mesangial expansion and nodular mesangial sclerosis. Extraglomerular features of DN include increased tubular basement membrane thickness, interstitial fibrosis, arteriolar hyalinosis and intimal fibrosis of arterioles and interlobular arteries. Commissioned by the Renal Pathology Society (RPS), Tervaert et al. (JASN 21:556, 2010) published a pathologic classification system of DN based predominantly on glomerular lesions to grade DN. The goal of our study is to correlate the severity of morphologic findings of DN to clinically documented duration of disease and to the course of clinical parameters of kidney function and other laboratory data throughout this period.

Design: Renal biopsies from 30 patients with the sole biopsy diagnosis of either mild, moderate or severe DN were retrospectively selected from our biopsy repository and evaluated for the presence and severity of glomerular, interstitial, vascular and tubular lesions. The biopsies were then scored according to the RPS classification of DN. The patient's clinical charts and laboratory data bases were evaluated for documented duration of disease, course of serum creatinine and BUN values, severity of proteinuria, presence of hypertension and course of serum glucose and Hb A1c levels. The histological findings and respective RPS DN scores were then correlated to the duration of disease, the course of serum creatinine, glucose, HB A1c and urine protein levels throughout the clinically documented disease period.

Results: We find that longer clinical duration of diabetes correlates positively with higher RPS class lesions in the biopsies. Higher RPS class biopsies show also increased % interstitial fibrosis, arteriolar hyalinosis and higher levels of proteinuria. Moreover, we find that interstitial fibrosis independently correlates with vascular hyalinosis and the duration of diabetic disease.

Conclusions: Our findings show that increased severity of interstitial and vascular pathologic changes in DN correlate with more severe glomerular lesions and therefore higher RPS classes. Moreover, increase in interstitial fibrosis correlates independently with higher degree of vascular hyalinosis. Our findings raise the question whether vascular hyalinosis plays a role in progression of diabetic nephropathy or could be a potential marker of disease progression.

1632 Transplant Glomerulopathy, Pathogenesis and Evolution

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Background: Transplant glomerulopathy (TG) is a frequent finding in renal allografts. TG often leads to progressive graft dysfunction and loss. The pathogenesis and evolution of TG, while not well defined, appears to be complex involving alloimmune and non-immune mechanisms that may act separately or overlap. How much antibody-mediated mechanisms, as evidenced by C4d in tissue and/or circulating donor specific antibodies (DSAs), participate in its development remains unsettled.

Design: Renal Tx biopsies with TG in 2010 and 2011 were reviewed. The collected data included morphologic changes of TG including C4d tissue deposition, concurrent lesions including rejection and chronic injury, and type and levels of donor-specific anti-HLA class I and II antibodies. The preceding diagnostic and follow-up biopsies were subjected to a similar review.

Results: Out of a total 845 transplant biopsies in 603 recipients during the study period, TG was first noted in 41 index biopsies (4.9%) in 41 patients. Among these 41 biopsies, 31 displayed glomerular capillary C4d staining, and the staining was global diffuse in all of them (Group 1). Glomerular C4d was not seen in the remaining 10 biopsies (Group II). Comparison of Group I and II was made for C4d in peritubular capillaries (55% vs 50%); antibody-mediated rejection (39% vs 3%); cell-mediated rejection (16% vs 0.17%). DSA data *at time of biopsies* were available in 7 patients, with 5/5 (100%) positive for Group I and 1/2 (50%) for Group II. Within Group I, there were 17 preceding biopsies with, 9 (53%) showing C4d positive glomeruli and 14 follow-up biopsies with 12 (86%) showing C4d positive glomeruli. Within Group II, there were 8 preceding biopsies, with 4 (50%) showing C4d positive glomeruli, and 6 follow-up biopsies with all 6 (100%) showing C4d positive glomeruli.

Conclusions: TG was found in 4.9% of renal allograft biopsies in a single institution. Although absence of glomerular C4d is noted in a significant portion of TG, virtually all cases of TG are related to DSA during its course, confirming an exclusive pathogenetic role of DSA. A differential pathogenesis for DSA is possible, since a significant portion of TG occurs as an isolated finding without associated cell- or antibody-mediated rejection and C4d is absent in peritubular capillaries in up to a half of the C4d + TG. Glomerular C4d may serve as a sensitive surrogate marker for the development of TG, long before morphologic changes.

1633 Urinary Polyomavirus-Haufen Shedding in Mouse and Man: A Proof-of-Concept Study for a Non-Invasive Urine Biomarker for Polyomavirus Nephropathy

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Background: Polyomavirus Nephropathy (PVN) is the most significant viral renal allograft infection with 4% incidence. A definitive diagnosis is only established by renal biopsy. Recently we described a novel, non-invasive urinary assay to diagnose PVN, i.e. the "polyomavirus (PV)-Haufen-Test," with positive and negative predictive values of >95% for definitive biopsy confirmed PVN. This test has great diagnostic potential.

Hypothesis: 1) PV-aggregation and Haufen formation depend on a high concentration of Tamm-Horsfall protein (THP) that is only present in primary urine found in injured renal tubules. Such THP concentrations are not detected in secreted secondary urine. 2) Urinary PV-Haufen are found in a mouse model of PVN but not in control animals. Thus the presence of PV-Haufen in voided urines is specific for intrarenal disease, and PV-Haufen are reliable diagnostic biomarkers.

Design: Part A - association of PV-Hauden and THP: A1) Immunohistochemistry of PVN cases (n=3) with double labeling to detect PV and THP in renal tubules. A2) Immunogold electron microscopy of urinary PV-Haufen to detect Haufen-bound THP (n=3). A3) Immunoprecipitation studies on urinary PV-haufen (n=6). A4) Dilution curves altering THP concentrations in fluids mimicking primary and secondary urines and evaluating for PV-aggregation and Hafuen formation (n=5).

Part B - THP concentrations in voided urine samples (with concurrent kidney biopsies; n=12).
Part C - Mouse model of PVN: Search for urinary PV-Haufen in mice with PVN (n=5) and control animals without PVN (n=5).
Results: Part A: A1) In PVN, intratubular PV aggregates show abundant THP. A2) Urinary PV-Haufen are intimately admixed with THP. A3) Immunoprecipitation of urinary PV-Haufen shows abundant coprecipitation of PV and THP. A4) PV Aggregation and PV-Haufen formation is THP dose-dependent and only occurs with high THP concentrations of >1mg THP/ml fluid mimicking primary urine in injured tubules. **Part B**: THP concentrations in voided urine samples are low, median THP 4.5 microgram/ml urine, range: 0.7-19.5.
Part C: All mice with PVN (florid disease stage B) shed abundant PV-Haufen in voided urine samples; PV-Haufen are not detected in control animals.
Conclusions: PV-Haufen formation occurs in the setting of very high THP concentrations found in injured renal tubules exceeding voided urine THP concentrations by 50 fold. A new mouse model of PVN shows typical urinary PV-Haufen in diseased animals. Urinary PV-Haufen are novel dignostic biomarkers for intrarenal PVN.

1634 Ultrastructural Changes in 5/6 Nephrectomy Rats Correlate with the Progression of Ablative Nephropathy

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Background: Chronic kidney disease (CKD) is a worldwide health problem with a rising incidence and poor outcomes. 5/6 nephrectomy (Nx) is an established model of ablative nephropathy with progressive focal segmental glomerular sclerosis (FSGS). Despite well-documented light microscopy changes, no detailed information about ultrastructural changes in progressive FSGS is available. The aim of the current study was to characterize electron microscopy findings in 5/6 Nx rats at different stages of FSGS.
Design: Sprague Dawley rats underwent 5/6 Nx and were monitored until week 23 after the ablative surgery. Serum (SC) and urine creatinine, hematuria and proteinuria were measured weekly. Kidney morphology (including electron microscopy) was evaluated at 3, 8 and 23 weeks after the ablative surgery.
Results: 5/6 Nx rats had progressive proteinuria, hematuria, SC increase and FSGS. Ultrastructurally, the glomerular basement membrane (GBM) thickness was increased at late, but not early stages of FSGS (153±10 nm, 158±9 nm, 151±6 nm and 190±16 nm in control, 3, 8 and 23 weeks after the ablative surgery, respectively). No evident changes in the GBM texture were seen. Cytoplasmic swelling of the glomerular capillary loop endothelial cells was noted. Segmentally, glomerular capillary loop endothelial cell fenestration was decreased. Podocyte foot processes did not show relevant effacement even at late FSGS stages. The GBM thickness significantly correlated with SC (R^2=0.721, p<0.0001), hematuria (R^2=0.627, p<0.0004) and to a lesser degree with urinary protein/creatinine ratio (R^2=0.312, p<0.024).
Conclusions: 1) The GBM thickness increases with the progression of FSGS in 5/6 Nx rats. 2) Progressive swelling and loss of fenestration in the glomerular capillary loop endothelial cells indicates cellular damage, probably secondary to increased glomerular hyperfiltration/hyperperfusion injury. 3) Our findings may be useful for understanding the pathogenesis of ablative nephropathy and FSGS in humans.

1635 Fibroblast-Specific PAI-1 Depletion Increases Macrophages but Not Kidney Fibrosis after Unilateral Ureteral Obstruction

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Background: Plasminogen activator inhibitor 1 (PAI-1) is a serine protease implicated in pro-fibrotic kidney disease. PAI-1 inhibits matrix breakdown and plays important roles in chemotaxis and proliferation of inflammatory and wound-healing cells. Systemic PAI-1 knockout mice have decreased interstitial renal scarring in response to ureteral obstruction. A multitude of cell types in the kidney express PAI-1 under stress. This study was designed to determine the effect of fibroblast-specific PAI-1 depletion in mice after ureteral obstruction.
Design: We created mice with floxed PAI-1 and bred to tenascin C Cre mice to knock down PAI-1 in fibroblasts after administration of tamoxifen. Unilateral ureteral obstruction (UUO) was performed in *PAI-1$^{loxP/loxP}$*/Cre (n=4) and control mice (Cre or *PAI-1$^{loxP/lox}$, n=8)*, and both kidneys were harvested after 10 days. The efficiency of the inducible fibroblast specific PAI-1 knockout was measured by double staining for PAI-1 and GFP, which binds to tenascin C. Interstitial fibrosis was measured by Sirius red staining. PAI-1, collagen I and III mRNA was determined by real time PCR. Fibroblast and macrophage infiltration were assessed by FSP-1 and F4/80 staining.
Results: 76-87% of GFP positive cells, i.e. fibroblasts, were PAI-1 negative in *PAI-1$^{loxP/loxP}$*/ Cre mice while control mice showed PAI-1 positivity in all interstitial cells, indicating effective knockdown of PAI-1 in this model. *PAI-1$^{loxP/loxP}$*/Cre also had less PAI-1 mRNA in obstructed kidneys, 54.7% compared to control mice. F4/80 positive cells were increased in *PAI-1$^{loxP/loxP}$*/Cre *vs.* control (43.7 ± 2.6 *vs.* 23.1 ± 3.7/HPF, p<0.05). However, fibroblast cell number was not different between the two groups (10.7 ± 7.6 *vs.* 18.6 ± 11.0/HPF, p NS). Further, fibrosis, assessed by Sirius red positive area, collagen I and III mRNA, did not differ between the two groups.
Conclusions: Our studies demonstrate efficacy of fibroblast-specific PAI-1 depletion in mice. Macrophage accumulation in obstructed kidneys is markedly increased in the absence of PAI-1 signaling from fibroblasts. Interestingly, this increase in macrophages is not accompanied by change in fibrosis or number of fibroblasts. Whether the phenotype of macrophages is altered when fibroblast PAI-1 is diminished, or whether PAI-1 in cells other than fibroblasts crucially modify ultimate fibrosis, awaits further study.

1636 Podocyturia (PCU) and Biopsy (Bx) Podocyte (PC) Globotrioasylceramide (GL-3) Accumulation Correlate with Proteinuria in Patients with Fabry Disease (FD)

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Background: Renal failure is a major FD complication. BX studies suggested that PC injury parallels age and urine protein/creatinine ratio (UPCR) in young FD patients. We hypothesized that PCU may correlate with proteinuria and likely of pathogenetic significance. We studied PCU and PC GL-3 accumulation in two cohorts of FD patients with a wide range of age and renal function.
Design: Urine from 12 FD patients (M/F=7/5), age 34[14-66] years, median[range], were processed to prepare cytospin slides and stained for PC (Podocalyxin, PCX) and parietal cell (Claudin 1, CL1) markers. PCX+/CL1- cells were identified as PCs and PCX+/CL1+ cells as parietal cells with PC phenotype. Cells with small/apoptotic and normal size nuclei were counted separately. TUNEL staining was performed for apoptosis. All counts were corrected for urine creatinine (Cr). The findings were correlated with age, UPCR, urine albumin/creatinine ratio (UACR) and glomerular filtration rate (GFR). Bxs from 36 FD patients (M/F=25 /11) age 23[4-63] years were studied by electron microscopy stereology to estimate PC GL-3 volume density [Vv (Inc/PC)]. Results were correlated with age and UPCR.
Results: GFR was 85±22 ml/min/1.73 m^2 in the PCU cohort and 109±23 in the biopsy cohort. UPCR was 0.1[0.03-1.1] mg/gCr in the PCU cohort and 0.1[0-3.1] in the biopsy cohort. There were 670-62000 PCX+ cells/gCr in urine samples, 49-88% of them PCs. 24±12% of PCs had small nuclei. TUNEL confirmed apoptosis in majority of PCX+ cells with both small and normal size nuclei. Among the different cell types counted only PCX+/CL1- cells with small nuclei (PCX+/CL1-S), representing apoptotic PCs correlated with UACR *(r=0.73, P*= 0.007*)* and UPCR (*r*= 0.75, *P*=0.005). PCX+/CL1-S cell numbers also correlated with age(*r*=0.70, *P*=0.01). Although females (56±13 years) were older than males (26±13 years) in our cohort (p=0.002), by multiple regression analysis (MRA) only PCX+/CL1-S, and not gender or age, showed a trend to independently predict UPCR (R^2=0.72, p=0.07). Bx Vv(Inc/PC) similarly correlated with UPCR (*r*=0.36, *P*=0.032). MRA showed that both age and Vv(Inc/PC) independently predicted UPCR (R^2=0.52, p=0.0003).
Conclusions: Our studies suggest that urine apoptotic PCs progressively increase with age in FD patients, correlate with proteinuria, and thus, of pathogenetic significance and may become a useful non-invasive FDN biomarker. Our Bx study similarly showed a relationship between PC involvement in FD and proteinuria, confirming the above conclusion.

1637 Plasminogen Activator Inhibitor-1 (PAI-1) Affects Parietal Epithelial Cell (PECs) Transition

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Background: Glomerular PECs may migrate to the glomerular tuft and serve as potential podocyte stem cells, expressing some podocyte markers. However, whether such visceral location PECs can be functional podocytes or are more mesenchymal and profibrotic is not established. Our previous data show that PAI-1$^{-/-}$ mice are protected against development of sclerosis and podocyte injury. In this study, we explored whether the transition of PECs is modulated by the expression of PAI-1.
Design: We studied NEP25 mice, in which selective podocyte injury can be induced by injection of the toxin LMB2, that were bred to PAI-1$^{-/-}$ mice (NEP25xPAI-1$^{-/-}$, n=10) and compared to toxin injury in mice with intact PAI-1 (NEP25xWT, n=6). At day 20 after LMB2 injection mice were sacrificed and renal changes were analyzed. Mouse PECs were cultured and injured with angiotensin II (Ang II), or exposed to supernatant from intact or toxin-injured NEP25 podocytes.
Results: At day 20 after LMB2 injection, NEP25xPAI-1$^{-/-}$ mice had significantly attenuated glomerulosclerosis compared to NEP25xWT mice (sclerosis index 1.73± 0.09 *vs.* 2.14±0.18, 0-4 scale, p<0.05). Synaptopodin positive cells were increased in NEP25xPAI-1$^{-/-}$ *vs.* NEP25xWT mice (15.1±1.8 *vs.* 6.7±1.0 /glomerulus, p<0.01). Glomerular visceral epithelial location cells co-expressing CD44 and synaptopodin were significantly increased in NEP25xPAI-1$^{-/-}$ mice compared to NEP25xWT mice (4.8±0.4 *vs.* 0.9±0.1/glomerulus, p<0.001). However, NEP25xWT mice had significantly more glomerular CD44 positive cells than NEP25xPAI-1$^{-/-}$ mice (14.3±1.0 *vs.* 21.5±2.9/glomerulus, p<0.05), suggesting that more PECs were activated and transdifferentiated to mesenchymal type cells. Cultured mouse PECs expressed similar PAI-1 protein at baseline and after Ang II. Treatment with a dominant negative PAI-1 mutant protein (without proteolytic inhibition activity but with intact VN binding) reduced PEC expression of PAI-1 26.5% (P<0.05)**,** inhibited PEC migration and abolished Ang II-accelerated PEC migration. When PECs were treated with supernatant from LMB2-injured primary cultured NEP25 mouse podocytes, the expression of CD44, a marker of activated PECs, was increased 26.4%.
Conclusions: PAI-1 deficiency in PECs inhibits PEC migration in vitro. However, in vivo NEP25xPAI-1$^{-/-}$ mice had more parietal podocytes and less sclerosis compared to NEP25xWT mice. These results support that systemic PAI-1 deficiency promotes PEC transition with associated less sclerosis, perhaps by promoting more functional podocyte-like rather than profibrotic type transition of PECS.

1638 T-bet+ Lymphocytes and IgG4+ Plasma Cells Correlate with Poor Clinical Outcome in Plasma Cell Rich Acute Cellular Renal Transplant Rejection

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Background: We previously reported the existence of IgG4+ plasma cells in many, but not all, cases of plasma cell rich acute cellular rejection (ACR). Both total plasma cell load and IgG4+ plasma cell load is significantly increased in biopsy specimens with less favorable clinical outcome. Here, we assess the regulatory T cell (Foxp3+), NK cell (CD56+), and Th1 cell (T-bet+) load in transplant kidney biopsies with plasma cell rich ACR and in cases with concurrent antibody-mediated rejection (ACR/AMR).

Design: Renal transplant biopsies were selected for the following study groups: plasma cell rich ACR (n=20), plasma cell rich ACR/AMR (n=7), control ACR (n=8), and control ACR/AMR (n=5). Only cases without concurrent glomerular or tubulointerstitial disease, other than acute rejection, were considered for the study. Immunostaining for Foxp3, CD56, and T-bet was performed on formalin-fixed and paraffin-embedded tissues and cell density quantitatively assessed using computer-assisted morphometric analysis. These new data were correlated with our previously quantified inflammatory cell burden (IgG4, CD20, CD3, CD8, CD68) and Collagen-III for the same sample set, and with clinical outcome (less favorable outcome defined as dialysis or Creatinine > 2.0).

Results: A significant increase in the density of T-bet+ cells is observed in plasma cell rich rejection biopsies compared to control biopsies (p=0.003) and there is a trend toward increased Foxp3+ cells in plasma cell rich rejection biopsies compared to control biopsies (p=0.09). No significant difference in CD56+ cell density is seen among the groups. Total T-bet+ cell load is increased in biopsy specimens with less favorable clinical outcome (p=0.028), and a positive correlation between T-bet+ and IgG4+ plasma cell load is observed for cases where IgG4+ plasma cells are identified (r=0.35, p=0.07). No trend is identified between the presence of IgG4+ plasma cells and the other parameters (CD56+, FoxP3+ cells), and these other parameters do not correlate with clinical outcome.

Conclusions: These findings establish the existence of significant numbers of Th1 cells and regulatory T cells in many, but not all, cases of plasma cell rich ACR. Data support a positive correlation between the presence of Th1 cells and IgG4 plasma cells and suggest a correlation between the presence of these particular immune cells and less favorable clinical outcome.

1639 Immunohistochemical Markers Indicate Transdifferentiation of Tubular Epithelial Cells into Histiocytic Cells in the Presence of Monoclonal Casts/Crystals and Myoglobin

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Background: We recently described a case of possible histiocytic differentiation of tubular epithelial cells in association with amyloidogenic monoclonal light chains accumulated in the tubular epithelium (Hemminger *et al. Am J Surg Pathol 36:1253, 2012)*. We found that tubular cells carrying the amyloid were positive for both histiocytic and tubular epithelial markers. We seek to further characterize and expand our studies to include other reactive tubular changes, including myeloma cast nephropathy, crystalline tubulopathy, and myoglobin cast nephropathy.

Design: From our archives, we selected a subset of cases (3 myeloma cast nephropathy, 1 monoclonal crystalline tubulopathy, 2 myoglobin cast nephropathy) based on the overall slide quality, biopsy size and quality of the casts and associated inflammatory cell reaction. Serial sections were performed and four separate immunohistochemical stains were applied to each case: CK18 and AE1/3 to highlight tubular epithelium and CD68 and CD163 to highlight monocytes and macrophages. After determining that many tubular cells associated with the casts/crystals were positive for both epithelial and monocytic stains, we proceeded to perform the following double stains to simultaneously highlight the tubular epithelium and monocytes/macrophages: CK18 with CD163; CK18 with CD68; AE1/3 with CD163; AE1/3 with CD68. The monocyte markers were stained red and the epithelial markers brown.

Results: Numerous interstitial cells were positive with CD68 and CD163, highlighting the interstitial macrophages. Interestingly, in myeloma cast nephropathy, the tubular luminal cells surrounding cast material were mostly histiocytic; however, several showed staining with both epithelial and histiocytic markers. In contrast, the myoglobin casts were surrounded by cells positive mostly for epithelial markers; only a few double-stained cells were noted. In the crystalline tubulopathy case, several cells containing crystals were positive with both markers. Ultrastructural examination confirmed the cells associated with the cast material and tubular crystals to have both histiocytic (lysosomes, Golgi) and epithelial (cell junctions, microvilli) differentiation.

Conclusions: Our findings lend further support to the hypothesis that tubular epithelial cells are capable of transdifferentiating into histiocytic cells when in the presence of cast material representing an inflammatory stimulus.

1640 Renal ALECT2 Amyloidosis: A Clinicopathologic Study of 17 Patients

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Background: Amyloidosis derived from leukocyte chemotactic factor 2 (ALECT2) is a newly identified form of amyloidosis that primarily affects the kidney and it is now the third most common type of renal amyloidosis. Only one clinicopathologic series of 10 ALECT2 patients has been reported so far. Here, we describe the clinical features, pathologic findings, and outcome of 17 patients with renal ALECT2.

Design: We identified 17 cases of ALECT2 from our pathology archives, between 2007-2012. In all cases, amyloid deposits were Congo-red positive and showed apple green birefringence when viewed under polarized light. Amyloid typing was done by laser microdissection/mass spectrometry in all cases.

Results: The cohort consisted of 9 males and 8 females with a mean age at diagnosis of 67 yrs (range 56 to 81). All 17 patients were Hispanic and all 12 with available data were of Mexican origin. All patients presented with chronic renal insufficiency. Mean serum creatinine at renal biopsy was 2.9 mg/dL (range, 1.3-6.6). Proteinuria ranged from 0.04-11 g/day (mean 3.8 g/day). Mean serum albumin was 3.5 g/dL. Peripheral edema was present in 31% of patients, full nephrotic syndrome in 19%, and microhematuria in 19%. Histologically, all cases showed extensive interstitial involvement. Glomerular and vascular involvement were each present in 76% of patients and were mild in most patients. None of the cases showed glomerular amyloid spicule formation on silver stain or electron microscopy. The percentage of glomeruli with global sclerosis ranged from 0-92% (mean 44.6%). Tubular atrophy and intersitial fibrosis affected >50% of the cortex sampled in 59% of cases. Concurrent diabetic glomerulosclerosis was present in 3 patients and concurrent membranous glomerulopathy in 1 patient. Follow up data were available in 15 patients, two of whom died shortly after biopsy. After a mean follow up of 26 months (range, 5-60 months) in the remaining 13 patients, 6 (46%) progressed to ESRD. The time from biopsy to ESRD ranged from 1 week to 33 months (mean 12.7 months)

Conclusions: ALECT2 should be suspected in older individuals of Mexican origin who present with renal impairment and bland urinary sediment, regardless of the degree of proteinuria. Renal outcome is poor with close to half of patients progressing to ESRD within 2 years. Renal ALECT2 is characterized histologically by extensive interstitial involvement with less extensive and less frequent glomerular and vascular involvement.

1641 AA Amyloidosis in a Patient with Common Variable Immunodeficiency Disease; Report of a Case

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Background: Common variable immunodeficiency disease (CVID) is a primary immunodeficiency disease caused by failure of B cells to differentiate into immunoglobulin secreting plasma cells resulting in hypogammaglobulinemia and recurrent sinopulmonary pyogenic infections. AA amyloid fibrils are derived from serum amyloid-associated proteins synthesized in response to systemic inflammatory conditions and deposited in various tissues including the kidney. There are only three cases reported in literature with CVID associated with severe systemic AA amyloidosis.

Design: A 40 year old male patient with a history of recurrent pneumonia was found to have hypogammaglobulinemia in 2005 during a severe urticaria workup. He was lost to follow up and 7 years later developed nephrotic range proteinuria, gastrointestinal symptoms and lymph node enlargement. That led to further investigations and multiple system biopsis.

Results: A renal biopsy revealed AA amyloidosis confirmed by immuno fluorescence. Biopsies of the gastrointestinal tract revealed amyloidosis and absent plasma cells on CD 138 immunohistochemical stain. A lymph node biopsy showed follicular hyperplasia, absent plasma cells on CD138 and kappa, lambda stains and focal vascular amyloid deposition.

Conclusions: Secondary AA amyloidosis is extremely rare in CVID and may be related to chronic and recurrent infections in this group of patients. In our case the pathological findings prompted further investigations leading to a conclusive diagnosis of CVID, highlighting the importance of further analyzing CVID at the pathological level.

1642 Kidney Disease in Obese Patients: A 12 Year Renal Biopsy Study

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Background: Renal biopsies are performed in obese patients with clinical renal disease which may be directly related to obesity or secondary to associated or unassociated medical conditions. Obesity related glomerulopathy (ORG) is a pathologic process attributed to hyperfiltration podocyte injury in which glomerular hypertrophy, perihilar segmental sclerosis, and partial foot process effacement lead to subnephrotic proteinuria in patients with excess body mass.

Design: Native kidney biopsies from 2000 to 2012 were retrospectively reviewed from patients with obesity, defined as body mass index greater than 30kg/m^2. 32 cases were excluded including those with less than 5 glomeruli. Glomerular diameter was measured using a standard micrometer in 1-7 glomeruli (mean 4) in glomeruli cut through the hilum. The clinicopathologic characteristics are analyzed.

Results: Of 6702 total native kidney biopsies, 287 (4%) were obtained from obese patients (mean: weight 122kg [range: 74-236kg], BMI 40.3kg/m^2 [range: 30-66.5]). Associated factors such as insulin resistance (31%, n=80), hypertension (60%, n=153), and obstructive sleep apnea (9%, n=22) were also frequent. The main indication for biopsy was proteinuria in 93% (n=237), nephrotic (102) and subnephrotic (135). Of these patients, 52% (n=123) also had renal insufficiency, defined as Cr >1.5mg/dL. Typical lesions of ORG were seen in 41% of cases: focal segmental glomerulosclerosis (FSGS) 28% (n=72) - perihilar variant (n=22), and glomerulomegaly alone 13% (n=33). Of patients without hypertension or diabetes, glomerulomegaly alone was the most common finding in 44% (n=8/18). Diabetic nephropathy was seen in 22% (n=56) of all obese patients and 70% of the obese diabetic patients, immune complex disease 15% (n=39), tubulointerstitial diseases 5%, vascular diseases 5%, thin basement membranes 5%, minimal change disease 3%, idiopathic FSGS 2%, and collapsing glomerulopathy 2% with varying tubulo-interstitial scarring and vascular sclerosis. Glomerulomegaly as defined by glomerular diameter greater than 180 μm was present in 84% (n=215) of cases (mean 224+/- 34 μm), borderline in 4% (n=10), and of normal size in 11% (n=29) (mean 157 +/- 15 μm).

Conclusions: Obese patients may have multiple comorbidities contributing to renal injury and the development of proteinuria. Presumably hyperfiltration-induced glomerular hypertrophy was seen in 84% of cases, which may contribute towards

podocyte injury and proteinuria regardless of underlying disease. Kidney biopsy is important for accurate diagnosis and potentially guiding therapy in this difficult patient population.

1643 Diverse Renal Lesions in Obesity: Clinical and Pathologic Findings

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Background: Obesity related glomerulopathy (ORG) is a pathologic entity primarily mediated by hemodynamic changes, where glomerular hypertrophy, perihilar segmental sclerosis and variable foot process effacement are noted manifesting subnephrotic proteinuria in patients with obesity. Obese patients, at risk for developing ORG, may develop other glomerular, tubulointerstitial (TI) or vascular disease partly due to associated medical conditions. Herein we summarize the clinicopathologic characteristics of these renal lesions.

Design: Native kidney biopsies from 2000-2012 were retrospectively reviewed from patients with obesity, defined as body mass index greater than 30kg/m^2. 32 cases were excluded including those with less than 5 glomeruli. Glomerular diameter was measured using a standard micrometer in 1-7 glomeruli (mean 4) in glomeruli cut through the hilum. Renal pathologic lesions detected by light, immunofluorescence, and electron microscopy were evaluated.

Results: Of 6702 total native kidney biopsies, 287 (4%) were obtained from obese patients. Proteinuria was the indication for biopsy in 93% of all obese patients, 11% had hematuria. Of the remaining 255 biopsies, 215 (84%) showed glomerulomegaly as defined by glomeruli greater than 180 μm in diameter, mean 224 μm +/- 34 mm. Renal lesions (other than secondary FSGS or glomerulomegaly alone) were present in 154 cases. Over 1/3 (56 cases) had diabetic nephropathy (DN) due to concomitant diabetes. The remainder had immune complex (IC) mediated disease 15% (6 IgA nephropathy, 10 lupus nephritis, 14 membranous glomerulonephritis (GN), 4 post infectious GN, 2 fibrillary GN, 1 C1q nephropathy, and 1 immune complex NOS), TI disease 4% (7 active interstitial nephritis, 2 acute tubular injury), thrombotic microangiopathy 2%, minimal change disease 3%, collapsing glomerulopathy 2%, thin glomerular basement membranes (GBM) isolated or with superimposed disease 5%, other non-specific changes 5%. Of the 27 hematuric patients, 48% (n=13) had either IgA nephropathy (6) or thin GBM (7). Proteinuria was highest in patients with idiopathic FSGS (mean 8g/24hrs) and IC GN (mean 7.4g/24hrs) and was subnephrotic in obesity-related FSGS (61%), glomerulomegaly-alone (82%), and TI diseases (80%). Presenting creatinine levels were highest in TI diseases (mean 8.4mg/dL) and DN (mean 2.5mg/dL) who were also older patients; DN (mean 54 yrs), TI diseases (mean 50 yrs), all others (mean 41yrs).

Conclusions: Diverse kidney pathology superimposed on ORG is present in obese patients with clinical renal disease. Renal biopsy is helpful for accurate diagnosis, prognosis, and treatment.

1644 Differential Expression of C4d and IgG4 Immunohistochemical Markers in Lupus and Non-Lupus Membrabous Glomerulonephritis

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Background: Systemic lupus erythematosus membranous glomerulonephritis (SLE-MGN) is sometimes difficult to distinguish from non-lupus membranous glomerulonephritis (NL-MGN) and represents about 20% of clinically significant renal disease in SLE. By Light Microscopy (LM), membranous lesions of SLE-MGN without superimposed proliferative GN are often indistinguishable from NL-MGN. Unlike in NL-MGN, immune complex deposits (ICDs) in SLE-MGN are not restricted to glomerular basement membrane (GBM) and may also be found in the mesangium, tubular basement membrane (TBM), and vasculature/interstitium (V/I). The study aims to review differential expression of two immunohistochemical markers (IHC), namely C4d and IgG4, in SLE-MGN and NL-MGN.

Design: 27 patients between 2006-2012 were retrospectively reviewed. Out of these, 15 patients (age ranges from 21-51 years; all females) had SLE-MGN and 12 patients (age ranges from 19-74 years with M:F ratio 6:5) had NL-MGN (including idiopathic and secondary MGN). At the time of diagnosis, all SLE-MGN patients had extra-renal manifestations of SLE and positive serology. Nephrotic range proteinuria was present in all 27 patients. All renal biopsies were studied by routine LM, electron microscopy (EM) and immunofluorescence (IF), with IHCs performed for C4d and IgG4 for the localization of ICDs in the GBM, mesangium, TBM, and V/I.

Results: Both SLE-MGN and NL-MGN were similar in terms of morphology, showing membranous pattern of glomerular involvement, with thickening of the peripheral capillary loops, and basement membrane spikes and vacuoles. The results of IHCs are shown in the table. In 3/15, 5/15, and 7/15 of SLE-MGN cases (but no NL-MGN), granular staining for C4d was noted in the mesangium, TBM, and V/I, respectively. Of note, GBM IgG4 deposition was almost exclusively prevalent in NL-MGN (100%), in contrast to SLE-MGN (7%).

Conclusions: IgG4 staining may aid in distinguishing NL-MGN from SLE-MGN in some cases where the diagnosis of SLE is equivocal. Additionally, C4d highlights the GBM ICDs in both SLE-MGN and NL-MGN. However, C4d-positive granular staining in TBM and vascular wall is almost only seen in SLE-MGN, also aiding to separate SLE-MGN from NL-MGN. Future studies to include a larger cohort are suggested to verify these results.

	SLE-MGN		NL-MGN	
	C4d	IgG4	C4d	IgG4
GBM	15/15 (100%)	1/15 (7 %)	12/12 (100%)	12/12 (100%)
Mesangium	3/15 (20%)	1/15 (7 %)	0/12 (0%)	0/12 (0%)
TBM	5/15 (33%)	0/15 (0%)	0/12 (0%)	0/12 (0%)
V/I	7/15 (47%)	0/15 (0%)	0/12 (0%)	0/12 (0%)

1645 Renal Involvement by Hematopoietic Neoplasms

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Background: Renal manifestations of some hematopoietic disorders are well-recognized. Specific associations such as immunoglobulin cast nephropathy and light chain deposition disease (LCDD) with multiple myeloma (MM) or monoclonal gammopathy of undetermined significance (MGUS) are extensively characterized. Direct renal involvement by a hematopoietic neoplasm is rarely described.

Design: A retrospective analysis of all kidney biopsies examined at Saint Louis University from 2000 to 2012 was performed. The renal manifestations were categorized, and the incidence of each category was calculated. Patients with renal involvement by the underlying hematopoietic neoplasms were identified. Presenting clinical and laboratory findings were obtained. Pathology material was reviewed.

Results: Out of a total of 4522 kidney biopsies, 130 recorded a hematopoietic disorder (69% with MM or MGUS). Of these, 121 were native kidneys, and 9 were allografts. The mean age at presentation was 64. The male:female ratio was 1.55:1. Indications for biopsy included (from most common to least) renal insufficiency, proteinuria, nephrotic syndrome, and hematuria. On biopsy, 47 (36%) had hypertensive change, 28 (21%) cast nephropathy, 24 (18%) amyloidosis, 17 (13%) diabetic nephropathy, 16 (12%) immunoglobulin deposition disease, 11 (8%) focal segmental glomerulosclerosis. Less frequent biopsy diagnosis includes acute tubular injury, interstitial nephritis, fibrillary glomerulonephritis, membranous glomerulonephropathy, acute rejection and calcineurin inhibitor toxicity. One patient had neoplastic plasma cells (kappa-restricted) involving the kidney. Two patients had post transplant lymphoproliferative disease (PTLD) in the form of lymphoma. One patient with myelofibrosis had extramedullary hematopoiesis (EMH) in the allograft kidney.

Conclusions: Renal manifestations of hematopoietic disease are not uncommon. It is not surprising to find a high percentage of cast nephropathy, amyloidosis and LCDD in our patient pool with high percentage of MM or MGUS. Renal infiltration by a hematopoietic neoplasm is rare: in this study, only one MM patient had renal infiltration by neoplastic plasma cells, and only two transplant patients had renal PTLD. Though neoplastic hematopoietic infiltration of the kidney appears rare, its true incidence is unknown. A large multicenter study or national registry is needed to accurately assess its incidence. In addition, one renal allograft showed EMH in the setting of myelofibrosis. It is important to be aware of this rare occurrence, since EMH can mimic acute cellular rejection as well as acute interstitial nephritis.

1646 Hyaline Arteriolosclerosis in Glomerular Afferent and Efferent Arterioles: Are the Deposits Hard or Soft, Stationary or Mobile?

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Background: Hyaline deposits (HD) in glomerular afferent (AA) and efferent (EA) arterioles (the latter being unique to diabetes) are thought to cause glomerular occlusion in diabetic nephropathy and possibly hypertension. This requires HD to be rigid and accumulate over time, but our studies in 25 diabetics and 14 controls suggest they are compressible and mobile. We also found HD in EA in 15% of controls showing that serial paraffin sections can reveal new facts about HD. Furthermore, 2 diabetics and 4 controls also had PolyBed 812 embedded toluidine blue (TB) stained 1μ serial sections that exposed smaller HD not seen in paraffin sections (unpublished observations). One such 19 yr old male control had even more HD, apparently from hypotension due to a torn kidney in an auto accident. He was stable after kidney resection with normal urine output for 7 days when life support was withdrawn due to brain damage, thus allowing comparison of size and location of HD in resected kidney (Rkid) versus autopsy kidney (Akid). Standard stains of 1μ sections confirmed that TB stains accurately reflected HD morphology.

Design: HD were compared in 1μ serial sections of 15 complete glomeruli from each kidney. HD were called small, medium or large according to how many thirds of wall width were involved. Mean HD length was measured in μ, and mean % of wall circumference with HD was estimated to the nearest eighth (22.5 °).

Results: Mean number of glomeruli with HD in AA, EA, and Bowman's capsule/either convoluted tubule wall was 15/14/9 in Rkid and 9/9/3 in Akid. Mean length (μ) of HD in AA/EA was 17.3/23.9 in Rkid and 12.3/17.6 in Akid. Mean circumference of wall (%) with HD in AA/EA was 27/56.8 in Rkid and 25.6/33.3 in Akid. % of large HD in AA/EA was 53/50 in Rkid and 33/33 in Akid. HD in Bowman's capsule/either convoluted tubule wall were found at the vascular pole, often near HD in AA or EA. Exam of 100 glomeruli in PAS stained 2μ paraffin sections in Rkid found 3 HD in AA and 1 HD in EA. No HD were noted in surg path or autopsy reports of Rkid and Akid.

Conclusions: The relatively simple 1μ serial sections revealed far more HD than were previously known to exist. HD were seen in almost every glomerulus in 1 transiently hypotensive control Rkid despite being absent in surg path reports. The number and size of these HD in Rkid were reduced by about 1/3 in Akid after 7 days of hemodynamic stability, suggesting rapid movement of HD through interstitial spaces.

1647 Utility of Whole Slide Imaging Algorithms in the Assessment of Renal Allograft Biopsies: Does Automated Analysis Provide a Better Assessment of Donor Specific Antibody Than Human Scoring?

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Background: Antibody mediated rejection (AMR) in renal transplants is often attributed to donor specific antibodies (DSAs). Circulating DSAs lead to complement split product C4d deposition along peritubular capillary endothelium, as highlighted by C4d immunohistochemistry (IHC). The extent of C4d deposition has been scored according to the Banff criteria (C4d1-minimal,C4d2-focal,C4d3-diffuse). However,

the relationship between C4d staining extent and circulating DSA quantity has not been fully characterized; thus, we sought to determine the correlations amongst human scoring, whole slide image (WSI) analysis, and DSA-specific mean fluorescence intensity (MFI) levels.

Design: Renal allograft biopsies with a confirmed DSA were selected from our files. The initial C4d scoring was verified on repeat pathologic review of the C4d IHC stained slides. These cases were scanned using an Aperio WSI scanner and analyzed with the Aperio microvessel density algorithm, which measured 18 vascular parameters per case. HLA class I and II DSAs for each biopsy were identified and a cumulative, DSA-specific MFI was calculated.

Results: C4d scoring and WSI analysis were compared to the cumulative MFI value (range: 2,600–385,000) for each case. The cumulative MFI was found to be moderately correlated with human C4d scoring (r=0.557,p=0.0071). The cumulative MFI only weakly correlated with automated WSI analysis, with median vessel perimeter being the strongest correlating parameter (r=0.367,p=0.0935). In order to achieve a more accurate reflection of the MFI data, the cases were then stratified into 4 ranks: "non-contributory", "low", "intermediate", and "high." This ranked MFI was also found to be moderately correlated with human C4d scoring (r =0.643,p=0.0011) and showed improved correlation with automated WSI analysis. Amongst the WSI analysis output parameters, median vessel perimeter and median vascular area were most correlated with ranked MFI (r=0.547,p=0.0084 and r=0.523,p=0.0125, respectively). Weaker correlations were seen with median lumen area and mean vessel wall thickness (r=0.505,p=0.0165 and r=0.386,p=0.0759, respectively).

Conclusions: Human scoring of C4d deposition provided a better correlation with DSA MFI than automated image analysis. However, more sophisticated WSI equipment and algorithms may lead to more accurate assessments in the future. Ultimately, improved histology examination and DSA detection could lead to enhanced recognition and therapy of AMR.

1648 Podocytic Infolding in Glomerular Basement Membrane: Clinicopathological Study of 31 Cases

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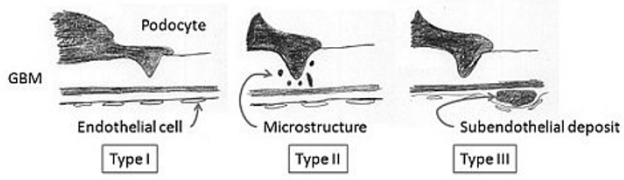
Background: Recently, podocytic infolding into the glomerular basement membrane (GBM) observed by electron microscopy (EM) has been noted as a unique pathological finding. In relation to this, various deposition in the GBM including microstructure such as microtubule and microsphere structures around the podocyte and subendothelial deposits were also observed in. However the clinicopathological significance of these phenomena is not well known.

Design: Among 3230 renal biopsies performed in our hospital from 1995 to 2011, we have identified 31 cases with podocytic infolding (depth over 100nm) into the GBM according to the EM findings. Before analysis, we classified them into three groups; podocytic infolding only (group I), podocytic infolding with microstructure (group II) and podocytic infolding with subendothelial deposit (group III). In addition to the clinicopathological analysis, we measured GBM thickness, infolding depth and their ratio in EM observation.



Results: The median patients' age was 60 years (range 8-84). 19 patients were men and 12 women. All 31 patients showed proteinuria and nephrotic syndrome, but none showed macrohematuria. Two patients showed increased serum creatinine levels (sCr) (>1.14mg/dl). The diagnoses were as below; 23 of 25 cases were membranous nephropathy (MN) and collagen disease in group I (n=15) and II (n=10), and all cases were MN in III (n=6). The median urinary protein excretion and sCr were less in group II than I and III, (p value 0.0694, 0.1209 respectively). In immunofluorescence study, we found negative for immunoglobulin and complement in two cases. In EM findings, podocytic infolding was accompanied with GBM thickening in 29 of 31 cases. The median infolding depth/GBM thickness were 500/1000nm in group I, 322/808nm in group II and 400/1085nm in group III. The median ratio were 51.7% in group I, 38.5% in group II and 36.7% in group III. The median size of microstructure in group II was 100nm in diameter. In group II, podocytic infolding situated within lamina rara externa in all cases.

Conclusions: Podocytic infolding with microstructure(group II) has different clinicopathological features from that without microstructure. The microstructure in podocytic infolding may have a finding in recovery stage from glomerular damage.

1649 Curcumin Enhances Mesangial Repair by Stem Cells in Light Chain-Mediated Glomerular Injury

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Background: Light chain deposition disease (LCDD)-associated glomerulopathic light chains (GLCs) induce glomerular injury characterized by increased mesangial extracellular matrix (ECM) and, in the early stages, mesangial cellular proliferation. Repair of the damaged mesangium by stem cells is complicated by the need to dispose of the increased ECM present. Curcumin has been proven to enhance apoptosis in this setting. The present study was designed to evaluate the effect of curcumin on the altered and expanded ECM.

Design: Human mesangial cells (HMCs) were incubated with LCDD-GLCs purified from the urine of patients with kidney biopsy proven LCDD. HMCs were seeded in glass bottom plates and incubated in the 6D living cell platform until about 40% confluent. HMCs were made quiescent and then incubated with the G-LCs (10 ug/ml) for 4 days. Then these cells were added curcumin (10uM) for 4 days. Annexin-V FITC and propidium iodine were used to evaluate apoptosis. The entire process was monitored using the 6D imaging system. Controls included GLCs-treated HMCs without incubation with curcumin and camptothecin (10μM) to enhance apoptotic events as a positive control.

Results: LCDD-LCs induced apoptosis in mesangial cells and participated in the ECM production, as previously documented. Curcumin enhanced the apoptosis of mesangial cells and clearing of the ECM that LCDD-LCs generated. This resulted in effective seeding of the mesangium by the stem cells and eventual production of new, biochemically normal ECM by the stem cells leading to mesangial healing.

Conclusions: Curcumin enhances mesangial cell apoptosis and contributes to the repair of the damaged glomerular by the stem cells by facilitating removal of the abnormal matrix present. Stem cells are unable by themselves to effectively clear the expanded ECM. Therefore, the role of curcumin is important in mesangial repair.

1650 Diabetic Nephropathy with an Atypical Clinical Course: A Potentially Treatable, Second Disease Is Commonly Found on Renal Biopsy

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Background: Diabetes mellitus (DM) is now a world wide epidemic and diabetic renal disease is a significant cause of morbidity and mortality. Increasingly, renal biopsies are performed on atypical cases of diabetic nephropathy (DN) to look for treatable secondary causes of renal injury. The aim of this study was to determine the nature and prevalence of medical renal diseases occurring on a background of diabetic nephropathy (DN).

Design: Our surgical pathology database was searched for all non-transplant renal biopsies with DN over the last eleven years. 5289 had a diagnosis of DN accounting for 15.7% of all renal biopsies from that time period. These cases were evaluated for diagnoses in addition to DN. Each case was examined by light microscopy, immunofluorescence microscopy and electron microscopy using standard techniques.

Results: Clinical indications for biopsy included: acute or rapidly progressive renal failure and/or, increased proteinuria and/or hematuria with or without RBC casts. A second renal condition was found in 47.2% of cases in addition to DN. Of the 47.2%, primary glomerular disease was the most common secondary diagnosis (45.3%) including: IgA nephropathy (7.8%), crescentic glomerulonephritis (GN) (4.3%) and acute proliferative GN (4.3%). Lupus, amyloid, fibrillary GN, minimal change disease, membranoproliferative GN and others were found in ≤ 5%. Tubulointerstitial conditions were also common with acute tubular injury in 40.34% followed by acute interstitial nephritis in 8.9%. Other conditions such as microscopic polyangiitis, IgG4 sclerosing disease, crystal nephropathy, cholesterol emboli et al were also seen (n ≤ 55 each).

Conclusions: The differentiation between DN alone and DN with other primary renal diseases is important when the clinical course is atypical. In this, the largest series to date and from centers across the US, we found that 47% of patients with an atypical course for DN have another medical renal disease with a second primary GN being the most common. This study supports the use of renal biopsy in patients with DM and an acute change in renal parameters to determine the presence of potentially treatable causes of altered renal function.

1651 Injured Proximal Tubular Epithelium Can Dedifferentiate into Vimentin Positive Cells in Human Kidneys

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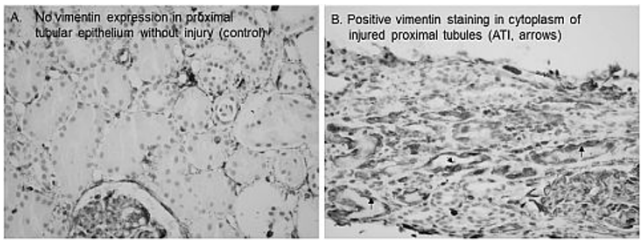
Background: Injured proximal tubules have been shown to dedifferentiate into cells which express vimentin in animal models. However, the dedifferentiation capacity of injured proximal tubules in human kidneys remains unknown. In this study, we compared the immunohistochemical expression of kidney injury molecule-1 (KIM-1), a specific marker of proximal tubular injury, with expression of vimentin in renal allograft biopsies with acute tubular injury (ATI).

Design: Human renal tissue from either indicated allograft biopsies with ATI (n=26, group 2) or protocol allograft biopsies (n=17, group 1) was stained with KIM-1 (AKG7 monoclonal antibody, provided by Dr. Joseph V. Bonventre, BWH, Boston, MA) and vimentin (monoclonal antibody, Dako). KIM-1 and vimentin stains were graded from 0 to 3+ in the proximal tubular epithelium[/underline]. Serum creatinine, KIM-1 and vimentin scores were statistically evaluated by linear regression analysis.

Results: Serum creatinine, KIM-1 scores and vimentin scores were all significantly higher in the ATI cases (3.655±0.388 mg/dL, 1.962±0.188 arbitrary units (AU), and 1.269±0.219 AU) than in control protocol biopsies (1.318±0.061 mg/dL, 0.324±0.095 AU, and 0.000±0.000 AU). Overall (n= 43), serum creatinine was significantly correlated with KIM-1 expression (R=0.746, P=0.0001) and vimentin (R=0.659, P=0.0001). There was also a significant correlation between KIM-1 scores and vimentin scores. In group 2, 61% (17/26) of cases had vimentin expression which was one score level weaker than the respective KIM-1 expression (e.g. vimentin 2+ with KIM-1 3+), whereas 26% cases showed equal levels of expression for both biomarkers.



Conclusions: Injured proximal tubules in humans also undergo vimentin dedifferentiation as shown in animal models. Vimentin dedifferentiation occurred essentially parallel to the tubular injury, confirmed by the correlation of positive staining with KIM-1 and vimentin. However, slightly delayed vimentin expression, demonstrated by weaker vimentin scores relative to the respective KIM-1, raises the possibility that strong vimentin dedifferentiation in the tubular epithelium may indicate a non-reversible tubular injury.

1652 Non-Nephrotic Range Proteinuria in Asymptomatic Children

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Background: Persistent mild proteinuria in otherwise asymptomatic children may be the initial presentation of significant renal disease. The clinical management and the threshold for performing a renal biopsy can be difficult to determine. Retrospective review of such cases may provide insight into the anticipated histologic abnormalities and their clinical course may suggest therapeutic guidelines.

Design: Renal biopsies from asymptomatic children with non-nephrotic range proteinuria {urine protein creatinine ratio (uP/Cr) < 2}, ± microscopic hematuria, were identified in our pathology database over a ten-year period (2000-2010). Of these, adequate biopsies with nonspecific diagnoses were further evaluated for clinicopathological parameters.

Results: 52 patients with asymptomatic non-nephrotic range proteinuria were identified and 24 (46%) had non-diagnostic pathology. Other diagnostic categories included FSGS (19%), Alport's syndrome (11%), nonspecific immune complex-mediated disease (7.7%), IgA nephropathy (5.7%), membranous nephropathy (3.8%) and thin basement membrane disease (5.7%). The mean uP/Cr in the "non-diagnostic" category patients was 0.8 (range 0.05-1.9). 9 patients had associated persistent microscopic hematuria. All had normal renal function with mean GFR of 149±41 ml/min/1.73 $m^{2,}$ negative serological studies and normal serum complements. Histological findings were unremarkable except for minimal global glomerulosclerosis (< 3%) in seven patients. Interestingly, 4 cases demonstrated diffuse foot process effacement (FPE) which in light of only mild proteinuria was interpreted as asymptomatic minimal change disease (MCD). Only one such patient subsequently developed a full clinical picture of MCD in a couple of weeks, requiring steroid therapy. 50% of the patients received angiotensin converting enzyme inhibitors. On follow up (mean follow up 47 months; range 1-118 mo), all patients had stable renal function, 14 (58%) had resolution of proteinuria and 10 (42%) had reduced, yet persistent proteinuria (mean uPr/Cr 0.45; range 0.05-1.38); 3 developed hypertension requiring treatment.

Conclusions: Asymptomatic pediatric patients with non-nephrotic range proteinuria and non-specific renal biopsy findings have a benign clinical course. Ultrastructural diffuse FPE in such a setting may represent evolving MCD and requires close clinical follow up.

1653 Pediatric C1Q Nephropathy Stains for Sox9 and Belongs to Focal-Segmental Glomerulosclerosis (FSGS)

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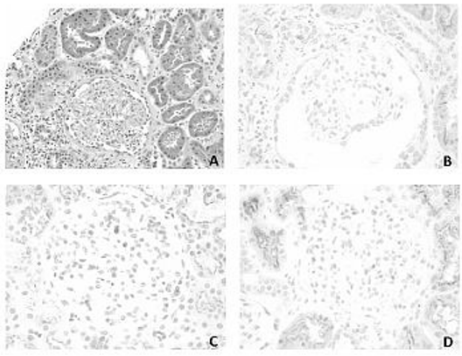
Background: C1q nephropathy is a controversial entity with distinctive immunopathologic features: dominant or co-dominant C1q staining in glomerular mesangium. By histology, this group of diseases presents as minimal change disease (MCD) or focal glomerulosclerosis (FSGS). Many authors favor latter but without confirmation due to lack of a reliable molecular marker for FSGS. Increasing evidence indicates that FSGS is due to an irreversible podocyte damage by activation of TGF- mediated apoptosis and initiating fibrogenesis to sclerosis. Sox9 is a transcriptional factor and one of the downstream targets of TGF-. Studies have been showed that Sox9 stains positive in FSGS, but negative in MCD. Thus Sox9 serves as a molecular marker for detecting FSGS. Using immunohistochemitry stain for Sox9 in pediatric C1q nephropathy, the purpose of this study is to confirm that C1q nephropathy is a FSGS but not MCD.

Design: Pediatric patients who had diagnosis of C1q nephropathy with histological features of FSGS/MCD in Children's Hospital of Michigan during 2004-2012 were included in present study. Immunohistochemistry stain for Sox9 was performed in paraffin slide in each case. Sox9 staining (nuclear staining) in podocytes was recorded as positive or negative.

Results: Nine patients had been diagnosed C1q nephropathy in the study time frame and 5 patients had available tissue for performing immunohistochemistry stain for Sox9. Among these, 4 patients had FSGS by histology, 2 of which were "very focal". One remainder patient had no detectable segmental sclerosis and was considered to be MCD. The Sox9 staining in podocyte was positive in all FSGS patients (4/4, 100%) including those with "very focal" lesions. The Sox9 staining was also positive in MCD patient.



Conclusions: Our data confirms that C1q nephropathy is an entity belongs to FSGS. The positive staining Sox9 in the MCD patient probably relates to sampling issue or an on going evolution of MCD to FSGS. Study in more cases is required to confirm the present findings.

1654 The Diagnostic Utility of Ki-67 Staining in Acute Renal Tubular Injury

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Background: Acute tubular injury (ATI) is one of the most common structural changes that can lead to acute renal failure. However, renal histological abnormalities are often subtle and may not be detectable. A reliable marker is needed to support the clinical findings of ATI. Ki-67 is a nuclear non-histone protein expressed in all phases of active proliferating cells. Renal tubular cell proliferation is increased following ATI. Thus, we hypothesize to use Ki-67 proliferation index (percentage of proliferating cells) to aid the diagnosis of ATI.

Design: Twenty kidney biopsies with the diagnosis of ATI and 20 kidney biopsies with no light microscopic tubular injury or glomerular abnormalities (18 thin basement membrane disease and 2 minimal change disease) were retrospectively selected. Ki-67 stain was performed on all 40 cases and the proliferation indices were calculated to evaluate tubular epithelial cell proliferative activities. Two-proportion Z-test was utilized to test the statistical significance between the two groups.

Ki-67 proliferation index in ATI and Non-ATI groups

	Marked Increased (>10/HPF)	Increased (5-10/HPF)	Rare (<5/HPF)	Negative
ATI	6/20	13/20	1/20	0/20
Non-ATI	0/20	0/20	4/20	16/20

Results: The Ki-67 index was increased or markedly increased in 19 out of 20 ATI cases (95%) with one case showing rare positive nuclear staining. In 20 Non-ATI cases, the Ki-67 index revealed no increased cell proliferation. Only 4 Non-ATI biopsies showed rare positive staining and the remaining 16 Non-ATI cases had negative staining. The Ki-67 index was significantly increased in ATI group compared with Non-ATI group ($p < 0.05$).

Conclusions: This study indicates that the Ki-67 stain of renal tubular epithelial cells is a useful ancillary tool to diagnose ATI. It can be used as a supportive marker for kidney biopsies from patients with acute renal failure but no significant morphological changes.

1655 M2 Macrophages in Early Lesions of Crescentic Glomerulonephritis

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Background: T cells, macrophages and neutrophils are implicated in the pathogenesis of crescentic glomerulonephritis (CGN). However, the initial events leading to the perforation of glomerular capillary walls are poorly characterized. The goal of this study was to examine early lesions and characterize the effector cells at the site of initial injury.

Design: We identified 23 kidney biopsies with early disease, including pauci-immune CGN (n=10), anti-GBM CGN (n=5) and immune complex mediated CGN (n=8). Early lesions were defined as segmental fibrinoid necrosis without crescents, and early cellular crescents occupying less than 50% of Bowman's capsule circumference. All biopsies were examined using standard light, electron and immunofluorescence microscopy. Additionally, immunohistochemical staining of paraffin sections for macrophages (CD68, MRP8/14, CD163), T cells (CD3), B cells (CD20) and NK cells (CD56) was performed in each case.

Results: Light microscopy demonstrated frequent mononuclear cells and rare neutrophils at foci of glomerular capillary wall injury. Electron microscopy confirmed mononuclear cells as the predominant cell type at areas of glomerular basement membrane attenuation and rupture. Numerous CD68+ macrophages and rare CD3+ T cells (1-2/per glomerulus) were evident at these foci by immunohistochemistry. CD20+and CD56+ cells were not detected. The overwhelming majority of macrophages were M2 type (CD163+) with few M1 (MRP8/14+) macrophages. The findings were similar in each category of CGN.

Conclusions: The frequent localization of M2 macrophages in early lesions of CGN is an intriguing observation that has not been previously described. This finding suggests an important role of M2 macrophages in the evolution of capillary injury in CGN.