Potential Treatment Modalities of Chronic Allograft Dysfunction/Failing Kidneys

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Chronic Allograft Dysfunction

- Progressive graft failure with slowly rising serum creatinine and decreasing GFR
- Independent of acute rejection
- Variable degrees of hypertension and proteinuria
- Features of chronic allograft nephropathy: vascular intimal hyperplasia, interstitial fibrosis, and tubular atrophy
- Most cases of kidney graft loss have an identifiable cause that is not idiopathic fibrosis/atrophy or CNI toxicity - if sufficient clinical and histologic information is available
Causes of Allograft Injury

- **Immunologic (Antigen-dependent)**
  - Cellular immunity
    - Inadequate immunosuppression/noncompliance
  - Humoral immunity
  - Acute rejection
  - HLA-matching
- **Donor-specific antibodies (DSA)**
- **Infections**
  - Cytomegalovirus (CMV)
  - **BK virus**
Causes of Allograft Injury

- Nonimmunologic (Antigen-independent)
  - Organ viability
    - Living vs deceased
    - Donor age/Brain death
    - Prolonged cold ischemia time
    - Ischemia-reperfusion injuries
    - Delayed graft function/acute tubular necrosis
  - Recipient-related factors
    - Hypertension/Hyperlipidemia
    - Non-compliance
    - Obstruction
    - Recurrent disease
  - Treatment-nephrotoxicity due to CNIs
Case #1

- 72 yo female with CKD; etiology of her kidney disease is not clear
- PMH: hypertension, colon cancer in 2000 (s/p partial gastrectomy and bowel surgery as well as chemotherapy), multiple skin cancers, multiple blood transfusions and 2 pregnancies; Panel Reactive Antibody (PRA) 0%
- S/p living-related kidney transplant in 8/2006
<table>
<thead>
<tr>
<th>Date</th>
<th>Scr (mg/dl)</th>
<th>WBC</th>
<th>Hb</th>
</tr>
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<tbody>
<tr>
<td>9/2007</td>
<td>0.9</td>
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<tr>
<td>9/2009</td>
<td>0.75</td>
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<td>13.2</td>
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<tr>
<td>9/2010</td>
<td>0.95</td>
<td>4.3</td>
<td>10.8</td>
</tr>
</tbody>
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*SPEP (done due to mild anemia): two monoclonal bands IgG kappa and IgM kappa: referred to Hematology*
Case #1

- Seen by Hematology in 2010: elevated serum free kappa light chains; skeletal survey: osteopenia, no lytic lesions: MGUS (no need for bone marrow biopsy)
- Scr increased to **1.39 mg/dl** in May 2011 and developed DSA (weak Class I DSAs to A2 and **strong Class II DSAs** to DQ)
Case 1

- Immunosuppression: TAC/MMF/Pred
- Urine p/c ratio: increased to 0.8
- BK viral load was negative
- First a kidney biopsy was done; then due to findings on kidney biopsy a bone marrow biopsy was done few days later - in May 2011
Kidney biopsy H&E

H&E, x50

H&E, x400
Pathology

- B cell rich kappa biased lymphoplasmacytic infiltrate, of unclear significance; Chronic allograft nephropathy, mild to moderate: mild lymphocytic tubulitis, "borderline" suspicious for acute cellular rejection

- IF: The diffuse interstitial capillary staining with C4d suggests the possibility of humorally mediated damage
Bone Marrow H&E

H&E, x50

H&E, x400
Pathology

- Bone marrow biopsy: Hypercellular marrow (50%) with trilineage hematopoiesis, extensively involved (>35%) by indolent CD5- CD10- B cell lymphoma
- **Diagnosis**: lymphoplasmacytic lymphoma or marginal zone lymphoma
Banff 2007 Update

1. Normal
2. Antibody-mediated changes
   - C4d deposition without morphologic evidence of active rejection
   - Acute antibody-mediated rejection
   - *Chronic active antibody-mediated rejection*
3. Borderline changes: “suspicious” for acute T-cell-mediated rejection
4. T-cell-mediated rejection
   - Acute T-cell-mediated rejection
   - Chronic active T-cell-mediated rejection
5. Interstitial fibrosis and tubular atrophy (IF/TA)
6. Other: Changes not considered to be due to rejection

*Solez K, et al. AJT 2008*
Antibody-Mediated Rejection (AMR)

- Antibodies that can mediate rejection include those against:
  - HLA molecules
  - Endothelial-cell antigens
  - ABO blood-group antigens on endothelial cells and red cells
- Most recipients do not have antibodies against HLA molecules before transplantation unless sensitized by exposure to alloantigens through pregnancy, blood transfusion, or previous transplantation
Chronic AMR

- Undetected preexisting donor-specific antibodies or antibodies generated after transplantation (DSA)-deposits on the capillary endothelium - complement activation and coagulation-diffuse C4d staining
- Endothelial injury to glomerular and peritubular capillaries
- Cellular hypertrophy, subendothelial deposition of fibrillar material, expansion and duplication of the glomerular basement membrane, or mesangial-cell interposition (double contours)-transplant glomerulopathy
A. Thickened glomerular capillaries
B. Double contours
C. C4d in peritubular capillaries
D. Subendothelial material

• Capillary C4d+ deposition, presence of circulating DSA, morphologic evidence of chronic tissue injury-**transplant glomerulopathy**, such as glomerular double contours/peritubular capillary basement membrane multilayering/interstitial fibrosis/tubular atrophy/intimal thickening in arteries
Transplant Glomerulopathy

- Occurs in 5-15% of failing and failed grafts
- Up to 20% of protocol biopsy specimens
- Associated with hypertension, varying degrees of proteinuria, progressive functional deterioration and overt graft failure
HLA-Specific Antibodies Developed in the First Year Posttransplant are Predictive of Chronic Rejection and Renal Graft Loss
Lee, Po-Chang; Zhu, Lan; Terasaki, Paul I.; Everly, Matthew J.
Transplantation 2009

- Retrospective case-controlled study from Taiwan
- 278 patients, transplanted between 1991-2004
- 25 patients with failed graft (230 serum samples) and 25 patients with a functioning graft (305 serum samples)
• HLA antibody development within 1-year posttransplant markedly lowers allograft survival

Lee PC, et al. Transplantation 2009
• Kaplan–Meier survival in patients with or without DSA at rejection diagnosis (p = 0.001; log-rank)

• Death-censored allograft survival stratified by % reduction in iDSA at 14 days postbiopsy (p = 0.021; log-rank)

52 patients with acute rejection; 16 (31%) with *de novo* DSA; median follow-up 27.0±17.4 months post acute rejection; *de novo* DSA significant risk factor for allograft loss but prompt DSA reduction was associated with improved allograft survival

Treatment of AMR

- Removal of antibody
- Inhibit activity of antibody
- Decrease production of activity
Treatment of Chronic AMR

- 4 kidney transplant recipients with chronic AMR 1 to 27 years posttransplant: treated with rituximab and IVIG-improved kidney function in all 4 patients; DSAs were reduced in 2 of 4 patients
- Significant decrease in DSA after bortezomib treatment

Fehr T, et al. Transplantation 2009
Walsh RC, et al. Transplantation 2010
Treatment of Chronic AMR

• No controlled trials
• Removal of antibodies by plasmapheresis or immunoabsorption
• High-dose pulses of glucocorticoids
• Increased doses of tacrolimus and MMF therapy
• ACEi/ARB use for proteinuria
• Immunomodulation with IVIG
• Rituximab or antilymphocyte antibody
• Eculizumab (a monoclonal antibody that inhibits the cleavage of C5)
• Bortezomib (a proteasome inhibitor that can inhibit plasma cells)
Case #2

- 52 yo female with CKD presumably due to diabetes
- PMH: type 1 diabetes since age 10, hypertension, CAD-s/p CABG 3 vessel in 2007, PVD, retinopathy, multiple blood transfusion and 4 pregnancies; PRA 0%
- DD kidney transplant (preemptive) in July 2008-0MM kidney
<table>
<thead>
<tr>
<th>Date</th>
<th>Scr (mg/dl)</th>
<th>Albumin</th>
<th>Urine p/c ratio</th>
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<tr>
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<td>0.95</td>
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<td>0.3</td>
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<tr>
<td>7/2010</td>
<td>1.02</td>
<td>3.5</td>
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</tr>
<tr>
<td>12/2011</td>
<td>1.29</td>
<td>3.2</td>
<td>1.7</td>
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Case #2

- Immunosuppression: TAC/MMF/pred
- On lisinopril and pravastatin
- Multiple skin cancers
- Slightly elevated serum creatinine and worsening proteinuria
- BK viral load, SPEP are negative, No DSA
- Kidney biopsy (3.5 years posttransplant)
Case #2

- **Biopsy**: increase in mesangial matrix with mild mesangial hypercellularity; **Nodular glomerulosclerosis-one with KSW nodule**; moderate interstitial fibrosis and mild hyaline arterial and arteriolar sclerosis
- Congo red stain negative for amyloid
- No evidence of acute rejection
- IF: C4d staining negative; negative kappa and lambda staining
- **Diabetic glomerulosclerosis**
Recurrent Disease (True Recurrence): Diagnosis

Biopsy proven disease on native kidney

↓↓

Posttransplant proteinuria or hematuria or elevated creatinine

↓↓

Same biopsy proven disease on kidney transplant
Recurrent Glomerular Diseases (GN)

- Recurrence of primary GN: FSGS, MPGN, IgA nephropathy
- Recurrence of secondary GN: SLE, Henoch-Schönlein, HUS/TTP, anti-GBM disease
- Recurrence of metabolic or systemic disease: diabetic nephropathy, amyloidosis, scleroderma, oxalosis, Fabry disease
Recurrent GN in the Transplant

• The prevalence of GN as the cause of ESRD: 10-25%, higher prevalence in children and white patients

• The prevalence of recurrent GN: 1.9%-31% in different series

• True prevalence of recurrent GN: patients who lost their grafts due to recurrence + patients who have recurrence with a functioning graft

• Cause of graft loss: 1-8.4% of all graft failures
<table>
<thead>
<tr>
<th>Disease</th>
<th>Risk of Recurrence</th>
<th>Graft failure by 10 yrs</th>
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<tbody>
<tr>
<td>IgAN</td>
<td>15-50%</td>
<td>10%</td>
</tr>
<tr>
<td>FSGS</td>
<td>20-40%</td>
<td>20%</td>
</tr>
<tr>
<td>MN</td>
<td>10-40%</td>
<td>15-50%</td>
</tr>
<tr>
<td>MPGN type I</td>
<td>30-50%</td>
<td>15%</td>
</tr>
<tr>
<td>MPGN type II</td>
<td>80%</td>
<td>30%</td>
</tr>
<tr>
<td>ANCA GN</td>
<td>10-20%</td>
<td>5%</td>
</tr>
<tr>
<td>SLE</td>
<td>5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Anti GBM</td>
<td>5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Fibrillary GN</td>
<td>50%</td>
<td>unknown</td>
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<tr>
<td>D- HUS</td>
<td>30-80%</td>
<td>90%</td>
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Fairhead and Knoll. Curr Opin Nephrol HTN 2010
Risk of Long-Term Graft Loss

- 1505 patients with biopsy-proven GN from Australia (1988-1997)
- Most frequent causes of allograft loss at 10 years: 1. Chronic rejection, 2. Death with a functioning graft, 3. Recurrence
- The incidence of allograft loss due to recurrence at 10 years was 8.4% and increased overtime
- Recurrence is more frequent than acute rejection as a cause of allograft loss during first 10 years after transplant

Briganti EM, et al NEJM 2002
Proportion with a Surviving Allograft

- Acute rejection
- Recurrence of glomerulonephritis
- Death with a functioning allograft
- Chronic rejection

Years after Transplantation

NO. AT RISK: 1505 1287 1091 872 717 612 459 350 245 137 48

Briganti EM, et al NEJM 2002
Potential Problems for Identifying Recurrent GN in the Transplant

- Primary disease-native kidney disease-is unknown for many patients
  - Late presentation
  - Primary vs secondary FSGS: difficult to differentiate
- No unified approach for patients with urinary abnormalities and increased serum creatinine after transplantation (histological vs clinical diagnosis)
- Transplant biopsy is not routinely submitted for IF and EM examination
Potential Problems for Identifying Recurrent GN in the Transplant

- Interpretation of the biopsy: DIFFICULT, *de novo* vs recurrent-MPGN vs chronic rejection vs changes already present in the grafted kidney
- Most of the studies are small and retrospective with variable follow-up periods (mostly short-term, inconsistent f/u)
Treatment Options

- No randomized, prospective studies for different treatment regimens
- Plasmapheresis
- Rituxan/Cytoxan
- RAAS blockade
- Retransplantation likely to result in recurrence—especially in FSGS, MPGN and IgA nephropathy
Case #3

• 62 year old AA male; blood group A: PRA 0%
• ESRD-etioloogy is not clear (hypertension/chronic GN)-on peritoneal dialysis since June 2007
• History of prostate cancer-diagnosed in 2007
• Listed for a kidney transplant since May 2006
Case #3

- DD kidney transplant-DCD kidney-on 4/11/2010
- Delayed graft function-continued dialysis until 4/28/2010 (scr is down to 4.8 mg/dl)
- Induction with Thymoglobulin (3 doses)
- Maintenance with tacrolimus + mycophenolic acid + prednisone
Case #3

- Scr is down to 1.86 mg/dl-4 weeks posttransplant
- Scr is up to 2.7 mg/dl in 7/2010 (less than 3 months posttransplant)
- Admitted for a kidney biopsy
Case #3

- Path: consistent with BK nephropathy
  - Viral cytopathic effect - intranuclear inclusion bodies
  - Degenerative tubular epithelial changes with sloughing and cellular and granular casts
  - Variable interstitial nephritis
- Blood BK viral load 4.3 log in 7/2010 - increased to 5.6 log in 8/2010
BK Virus

- 1971: described by Gardner SD and colleagues in Lancet: “isolated from urine after renal transplantation”-named BK virus (the initials of the patient who had ureteric stenosis)
- 1983: first report on tubulointerstitial nephritis (6 year old boy with primary immune deficiency)
- Not truly appreciated until mid 1990’s

Rosen S, et al. NEJM 1983
BK Virus

• Belongs to a family of DNA viruses called polyomaviruses—originally Papovavirus—(includes JC virus, KI, WU and MC viruses)

• Reported in 10-60% of kidney transplant recipients → BK nephropathy in 1-5% of patients → graft loss in up to 60% of patients
BK Virus

- Primary Infection:
  - Childhood nonspecific viral illness-respiratory
- Long-lived latency in uroepithelium and renal tubular cells (not in reticuloendothelial cells-like herpes viruses)
- Antibodies against BKV: 50% of children by age 3, 60-90% by age 10, and 80-90% by age 20
- Reactivation in immunocompromised individuals
Linear Progression of Disease

- Asymptomatic viruria $\rightarrow$ viremia $\rightarrow$ parenchymal damage $\rightarrow$ progressive deterioration of graft function (BK nephropathy), hemorrhagic cystitis, ureteral ulceration/stenosis, and progressive multifocal leukoencephalopathy (PML)
Diagnostic Testing

- **Urine:**
  - Decoy Cells
  - DNA PCR
  - EM-Haufen
  - Urinary cytokines: IL-3 and IL-6 (Opelz et al)
  - Urinary cell mRNA profiles (Suthanthiran et al)

- **Blood**
  - DNA PCR (Quant); PPV ~60% (plasma BK level >10,000 copies/ml-associated with 93% specificity for presence of BK nephropathy- Hirsch HH, et al. 2006)

- **Renal biopsy:** gold standard
Urine “Decoy cells” (intranuclear viral inclusions in tubular epithelial cells)
Screening and Diagnostic Testing for BK

- Linear progression is an opportunity: from viruria (30-40%) to viremia (10-20%) to nephropathy (1-10%) and graft dysfunction/loss.
- Blood and/or urine samples every 3 months for first 2 years, then once a year and in the event of allograft dysfunction.
Treatment of BK Nephropathy

- Careful reduction of immunosuppression and close follow-up for development of acute rejection remains the cornerstone.
- Cidofovir, leflunomide, quinolones, and intravenous immunoglobulin: no randomized prospective clinical trial.
- **No specific antiviral drug treatment**
Evaluation of a Patient with Late Allograft Dysfunction

• Exclusion of “obvious” causes such as obstruction, dehydration, high CNI levels, uncontrolled hypertension, recent new drugs/formulations, noncompliance, and UTI/urosepsis
• Urinalysis, spot urine protein/creatinine ratio, and 24-h urine collection
• BK viral load (blood/urine)
• Kidney biopsy: consider early before significant graft dysfunction
Evaluation of a Patient with Late Allograft Dysfunction

- Adequate biopsy sample to make a correct diagnosis (at least 10 glomeruli and two arteries; two cores of cortex preferably); comparison with time-zero biopsies, if possible

- Light microscopy to assess fibrosis/tubular atrophy/specific stains (PAS and silver stain)

- IF to assess recurrent or de novo GN or C4d deposition

- EM to detect early transplant glomerulopathy or immune deposits
Therapy for Chronic Allograft Dysfunction

- There is no single specific treatment; several therapies and approaches
- Early diagnosis/early intervention: IMPORTANT
- Changes in serum creatinine occur at a late stage
- Serum creatinine might underestimate deterioration in GFR
Therapy for Chronic Allograft Dysfunction

- Optimizing procurement-related factors
- Minimization of donor-recipient mismatch
- Minimization of cold ischemia time
- Aggressive management of hypertension: BP goal <130/80 mmHg
  - Use of calcium channel blockers
- Management of diabetes/PTDM
Therapy for Chronic Allograft Dysfunction

• Treatment of hyperlipidemia-LDL target < 100
• Reduction of proteinuria-ACEi/ARB and or spironolactone use
• Screening and treatment of infections-CMV/BK
• Treatment of recurrent diseases
• Regular assessment of adherence-frequent blood work
• Smoking cessation
Therapy for Chronic Allograft Dysfunction

- Manipulation of immunosuppression
  - More potent immunosuppressive therapy early after transplantation followed by minimization of immunosuppression, especially CNIs, to avoid CNI toxicity and BK nephropathy
  - Treatment of subclinical rejection
  - Monitoring and removal of HLA antibodies
  - Minimization or elimination of calcineurin inhibitors
  - Use of non-nephrotoxic immunosuppressive agents
  - Tolerance induction strategies
Late-Stage Graft Failure

- Balance saving the graft with preparing for the future
- Timely referral for retransplantation
  - Pre-emptive retransplantation: ideal
- Anemia management
- Dialysis Planning
  - Often appropriate for home modalities
Follow-up Case #1

- Treated with 4 doses of Rituximab in June 2011: follow-up with Oncology
- Tolerated the treatment well
- Continues to have frequent skin cancer removals
- Scr 1.08 mg/dl; urine p/c ratio: 0.7
- HLA antibodies immediately after Rituxan treatment: still strongly positive
Follow-up Case #2

- The dose of lisinopril was increased to 40 mg daily
- Spironolactone was added
- Referred back to an endocrinologist for better glucose control
- Weight loss program (BMI of 39)
- Scr stable around 1.2 mg/dl; readmitted with left leg cellulitis
Follow-up Case #3

- Reduction of immunosuppression: MMF was stopped; tacrolimus dose was reduced to a target level of 3-4
- BK viral load continued to be high: switched to cyclosporine—currently on CsA (last level 63) and prednisone (5 mg daily)
- Last BK viral load in March 2012 (2 years posttransplant): 2.6 log copies/ml and scr 1.85 mg/dl; HLA antibodies are negative