Introduction to Kidney Transplantation-2
Evaluation of graft dysfunction
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Evaluation of Graft Dysfunction

- Differential dependent on time after transplant
  - Immediate (during hospital stay)
  - Short term (up to ~6 months)
  - Long term (beyond 6 months)

- Delayed graft function
  - Need for dialysis within 7 days of transplant for any cause (hyperkalemia, CHF, uremia)
  - Essentially ATN (ischemic injury, perfusion damage, reperfusion injury)
  - Long term impact debated
Case 1

- 44 Caucasian with ESRD from IgAN
- 1st transplant 1993 - failed due to chronic allograft nephropathy
- Pre-emptive 2nd transplant from brother
- Basiliximab induction, Rapamycin/Mycophenolate
- Moderate post-op pain and ileus but on IVF
- Creat 6.7 → 2.7 → 3.1 → 3.7
- UOP preserved, Rapamycin level 7
- What’s wrong and what testing?
Case 1: Renal Ultrasound

Excellent perfusion, no hydronephrosis, very small peritransplant collection
Case 1: Renal biopsy

Normal Kidney

N.B. Began oozing fluid through biopsy needle skin insertion point immediately after biopsy
Urine leaks and Ureteral Stents

• Urine Leak
  – filtered urine and creatinine reabsorbed leading to high serum creatinine with normal biopsy and ultrasound
  – Chemical peritonitis leads to pain, ileus

• Site of leak
  – Pelvis (trauma of surgery)
  – Ureter (trauma)
  – Anastamosis to bladder
  – Diagnosis- send fluid creatinine, potassium

• Ureteral Stents
  – Reduce incidence of leaks
  – Reduce obstruction (clots or strictures)
  – Increase incidence of UTI
  – Increased cost due to removal (GU)
    • Overall reduction in GU complications is small but each event is costly
Urologic Complications

• Occur in 1-3% of transplants

• Ureteral strictures (usually further out)
  – Ischemic (ureter supplied by lower pole artery)
  – Viral (BK virus infection)
  – Rejection of ureteral/vasculature
  – Managed with stent placement → surgical repair

• Bladder outlet obstruction
  – BPH in men after foley removal
  – Neurogenic bladder in men/women (DM)

• Ureteral Obstruction
  – Blood clots
  – Kidney stones
  – “Lymphoceleles”
  – Fungus balls
Ureteral obstruction due to lymphocele
Case 2

• 41 year old with CRF ?etiology- +proteinuria, negative serologies except +ACL
• LURTx (boyfriend) 10 days ago
• No antibodies detected against donor pre-Txp
• Thymoglobulin → Prograf/Cellcept
• Creat 1.3→ 1.8, Prograf level- 6.7-8.3
• Hct 32, Plat 140 (<130 <= 61), LDH 337, Haptoglobin 308
• Renal U/S unremarkable
• Diagnosis?
Case 2- Pathology

Case 2- Thrombotic Microangiopathy

- Differential diagnosis
  - Calcineurin inhibitor nephrotoxicity
  - Antibody mediated rejection
  - Antiphospholipid antibody syndrome
  - Recurrent disease (i.e. familial HUS)
  - Reperfusion injury (deceased donors)
- ESRD due to HUS- 29% recurrence rate
- *de novo* rate- 0.8%; 4.6/1000 patient years
- Increased relative risk of combine sirolimus with calcineurin inhibitor
Case 2- Thrombotic Microangiopathy

- Endothelial damage/ activation of clotting cascade
  - Localized thrombus formation
  - Micro-circulatory abnormality
  - Organ dysfunction
  - ADAMTS 13 levels normal

- Systemic form ~50-60%
  - Hemolysis, thrombocytopenia, +/- mental status changes/fevers
  - Graft loss ~20-40%
  - Rx- Controversial!! Plasmapheresis, stopping CNI, steroids, rituximab (anti-CD20)

- Localized form ~30-40% (graft loss very rare)
  - Renal only disease
  - Stopping CNI temporarily is usually sufficient
  - Can switch to another CNI (Tacrolimus $\rightarrow$ Cyclosporine) or to rapamune

- Renal limited form may be seen in kidneys of other solid organ recipients (up to 40% of lung transplant patients biopsied for CKD)

Case 2- Other features of CNI toxicity

• Acute
  – Reduced renal blood flow (vasoconstriction)
  – Tubular toxicity (vacuolization)
  – Association with genes controlling intracellular concentration of CNI in kidney
    • ABCB1 gene of DONOR associated with 9 fold RR of dx of CNI toxicity

• Chronic
  – Stripe like Interstitial fibrosis
    • >90% of patients have 25% or more fibrosis after 2y
  – Secondary FSGS glomerular lesions

• Renal failure after non-renal solid organ txp
  – 20% with GFR <30 after 10 years, ~8-10% on HD
Case 3

- 70 year old man with CRF from hypertension
- Pre-emptive renal transplant with thymoglobulin induction, Prograf/Mycophenolate
- Creat 6 → 3.5-4 after 4 days without improvement despite good oral intake and normal tacrolimus levels
- No improvement with hydration
- Renal U/S- increased “RI”, no hydrenephrosis
Case 3
Case 3
Case 3-Subcapsular hematoma
Elevated Resistive Index (Resistance Index)

- (Systolic-Diastolic)/ systolic flow
  - Assumes reduction in diastolic flow due to increase in vascular resistance
  - Other contributors - pulse pressure (aortic stiffness, using beta-blockers), intraparenchymal pressure
- More important (and specific) is complete absence of diastolic flow
- DDX for RI ~1
  - Hyperacute rejection/severe antibody mediate rejection
  - Renal vein thrombosis
  - Subcapsular hematoma
  - VERY elevated Prograf levels
  - ?severe thrombotic microangiopathy/reperfusion injury
In chronic setting, increased RI predicts worse renal outcomes.

601 renal transplant recipients imaged with calculated RIs followed for 3 or more years.

RI >0.8 best predictor of 50% decline in renal function or death (better than proteinuria, BP, donor type, second transplants)

Radermacher et al. *NEJM* 2003, 349;115-24
Other vascular complications

• Transplant renal artery stenosis
  – Early- due to kink, edema, surgical error
  – Late- fibrosis, atherosclerosis, rejection
  – Pseudo-TRAS– iliac artery stenosis
• Renal artery thrombosis
• Iliac artery dissection
  – Before or after anastamosis
• Renal vein thrombosis
  – Iliac vein thrombosis
  – Increase risk with pediatric donors
• Renal vein stenosis
Renal Vein Thrombosis
Case 4

- 28 yo woman with ESRD from reflux
- 1st txp failed in 2 years from rejection
- Panel reactive antibodies- 90%
- Received ABO incompatible txp from HLA identical brother
- Zenapax/Prograf/Cellcept/Prednisone/Ritu ximab
- Creat 1.0→ 6 with anuria on POD #8
- U/S- absent diastolic flow
Case 4
Antibody Mediated Rejection (AMR)

- Antibody types
  - HLA antibodies
  - ABO antibodies (isohemagglutinins)
  - Anti-MICA, Anti-MICB, Anti-angiotensin receptor Ab

- Early AMR
  - risk ~0% if no prior sensitizing events
  - ~5-10% of all rejections
  - In 140 transplants at CPMC, AMR occurred only in patients with prior DSA, pregnancy, txp, or PRBC
  - excellent prognosis with recurrence rate ~20% or less and 98% 1 year graft survival

- Late AMR - worse prognosis
  - Patients have developed donor specific antibodies despite immunsuppression regimen
Antibody Mediated Rejection

• Diagnosis/Assessment
  – Measure DSA titer
  – Detection of C4d deposition on biopsy
  – Graft dysfunction and severity of injury

• Treatment
  – Steroids +/- anti-T cell therapy
    • 30-50% of AMR has concomittant cellular rejection
  – Plasmapheresis/IVIG (100 mg/kg)
  – High dose IVIG alone (effective for low titers)
  – Rituximab?
  – Anti-C5 Ab (eculizumab)
  – Anti-C1 Ab
AMR and C4d staining

Colvin R. et al
Cellular rejection

- T cell mediated
- Banff 97 criteria
  - Borderline: tubulitis without interstitial inflammation
  - 1A/B: tubulitis (5-10 or >10 cells per tubule)
    - >25% interstitial inflammation
  - 2A/B: endotheliitis/endovasculitis
    - Lymphocytes in vessel wall (B if occludes 25% of lumen)
    - Interstitial inflammation not necessary
  - 3: transmural infarction
Treatment of Cellular Rejections

• Depends on:
  – Severity of rejection, interstitial disease, prior drug levels/compliance,
    • 2A or worse: Thymoglobulin or OKT3
    • Borderline/1A: Steroid boost alone
    • 1B: steroids or thymoglobulin depending on degree of renal dysfunction, prior immunosuppression levels, degree of interstitial fibrosis (i.e. is it worth accepting to toxicity of potent meds to make this kidney work)
Impact of Cellular Rejection on Outcomes

• Early
  – If creatinine returns to normal → no impact
  – If creatinine not to baseline → worse outcome
    • Reflects degree of fibrosis
    • May reflect incomplete treatment of rejection

• Late
  – Tends to have worse outcomes
  – Labs checked less often → more advanced fibrosis
  – Immunologically different in compliant patients who reject late
  – Non-compliant patients may not have recurrent rejection but have recurrent non-compliance
Allograft Dysfunction - Late

- Chronic rejection/acute rejection
- Chronic drug toxicity
- Recurrent glomerular disease
- BK virus interstitial nephritis
- All the diseases that everyone else gets (to be covered in separate lectures in future)
Simplified model of CAN

Donor: age, htn, dm, nephron mass

Drug toxicity, HTN, Hyperfiltration, DM, proteinuria, rejection

Brain death, hemodynamic stability, perfusion techniques, CIT,
Post transplant renal function and change in creatinine from month 6 - 12 predict graft survival


A: Creatinine at 6 months
>100,000 transplants performed 1988-1998 among survivors >1 yr
Donor/recip characteristics, creatinine, and graft loss at follow up
Does not account for causation, but excellent at predicting

C: Δ creatinine b/w 6 and 12 months