POST RENAL TRANSPLANT HYPERTENSION

Sushma Bhusal
12.9.14
Case Presentation

- **CC:** 35 yo Hispanic Female, renal transplant patient, presented on 11/10/14 with nausea, vomiting, epigastric pain, elevated BP x 2 days

- **HPI:**
  - Discharged 2 weeks prior after being treated for similar reasons
  - Recurrent episodes of DKA and Hypertensive urgency
PMH/PSH

- ESRD S/P DD kidney transplant 6/6/12
- DM1
- HTN
- Infected R atrial thrombus secondary to Endocarditis (2007)
- Mild CAD
- Anxiety
- Recurrent UTIs including graft pyelonephritis (5/2013)
Medications

- Clonidine 0.2mg/q24hr patch
- Enalapril 5mg daily
- Labetalol 200mg TID
- Prednisone 5mg daily
- Bactrim 800-160mg MWF
- Tacrolimus 1mg q12
- Pantoprazole 40mg daily
- AISS
- Lantus 30u qhs
- Retin-A 0.025% on face and neck nightly
Case Presentation

- **Allergies:** NKDA
- **Family History:** Non contributory
- **Social:** Non smoker, no tobacco/alcohol use
Physical Exam

- Vitals: BP **211/014**, HR 87, RR 20, O2 sat 100% 2LNC
- Gen: *lethargic*, easily arousable, ANO X 3
- HEENT: oral mucosa *dry*
- Lungs: clear to auscultation bilaterally
- Heart: regular rate and rhythm, S1, S2 normal, 2/6 murmur over LUSB
- Abdomen: soft, *epigastric tenderness*, positive bowel sounds, no graft tenderness
- Extremities: no edema
Urine Studies:
UA: Small ketones
  No blood
LE, Nitrate: Neg
Tacro: 3.1

CXR:
Enlarged heart, Subsegmental ateleactasis.

VBG: 7.36 / 39 / 59 / 22 /
Hospital Course

- Hyperkalemia treated with insulin, Zofran for nausea, Labetalol for BP
- Transferred to ICU for persistent elevations in BP (SBP 200s)
- In the ICU, started on Cardene drip
- Symptomatically improved, BP better
### BP Trend

<table>
<thead>
<tr>
<th>Date</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/10/14</td>
<td>179-211</td>
<td>88-90</td>
</tr>
<tr>
<td>11/11/14</td>
<td>147-224</td>
<td>85-100</td>
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<tr>
<td>11/12/14</td>
<td>142-190</td>
<td>78-93</td>
</tr>
<tr>
<td>11/13/14</td>
<td>164-198</td>
<td>85-98</td>
</tr>
<tr>
<td>11/14/14</td>
<td>170-204</td>
<td>70-107</td>
</tr>
<tr>
<td>11/15/14</td>
<td>131-170</td>
<td>71-87</td>
</tr>
<tr>
<td>11/16/14</td>
<td>145-149</td>
<td>75</td>
</tr>
</tbody>
</table>
Hospital Course

- Color Doppler US done
- Underwent TRAS CO2 arteriogram, angioplasty and stent on 11/14/14
Pre and Post PTA/stent

Pre-Stent

Post-Stent
Carbon dioxide arteriogram with stent

• There was a moderate-severe stenosis roughly 0.5 cm distal to the origin.

• Renal artery pressures were assessed proximal and distal to the stenosis. Systolic pressure was 92 distal to the stenosis and 130s in the external iliac artery, indicated a hemodynamically significant stenosis.

• Stent placed, RS SBP post stent: 133

• Reduction in stenosis from 90% to 40%
POST RENAL TRANSPLANT HYPERTENSION
Epidemiology

• CVD: leading cause of morbidity and mortality in transplant patients

• Annual risk of fatal and non fatal CV events 3.5-5%, 50 fold higher than gen population

• Before 1983, 1/2 of transplant patients had HTN

• 80-90% patients post transplant develop hypertension

• Incidence increased after the advent of CNIs

Kasiske et al. HTN after kidney transplant AJKD 2004
Mario F Rubin: Advances in CKD 2011
Mangray et al AJKD 2011
Arias et al. NDT 2012
Thomas et al. Current HTN Rep 2013
Burden of post transplant HTN

- Minnesota, 1976-2002, 1666 patients
  - 1,295 patients with a functioning graft and complete data at 1 year
  - 160 patients (12.4%) had normal BP
  - 470 patients (36.3%) had prehypertension
  - 443 patients (34.2%) and 222 patients (17.1%) had stage 1 and stage 2 HTN despite treatment with antihypertensive medication

Kasiske et al. HTN after kidney transplant AJKD 2004

- Paoletti et al Transplantation 2009
  - BP controlled only in 5% pts, 30% Nocturnal HTN

- Carpenter et al. Clinical Transplant 2012 FAVORIT study
  - 4000 pts, BP uncontrolled 69%
HTN and Graft Failure

- Collaborative Transplant Study 1987-1995
- Multicenter Observational Study 262 centers, 29,751 patients
- Also continuous inverse relationship between SBP > 120 and duration of graft function

Figure 2. Association of allograft survival and systolic blood pressure at 1-year posttransplant (P < .0001). (Adapted from Weir et al. J Am Soc HTN 2011)
Donor Risk Factors

- HTN
- Family h/o HTN
- Older age
- Gender
- Overall quality of allograft
- Donor genetic variants: SNPs within genes that code for ABCC2, ABC1 and CYP3A5 and APOL1 a/w DGF, CNI toxicity and early graft failure

*Thomas et al. Current HTN Rep 2013*
Donor - Recipient Interactive Factors

• Delayed Graft Function

• AMR: DSA and non DSA (AT1-AA)

• IF/TA, TMA, Recurrent Glomerular Disease

• Complications of Surgery and transplant biopsy: TRAS, AVF, Page Kidney

Thomas et al. Current HTN Rep 2013
Dragun et al. NEJM 2005
# Etiology

## Table 1. Causes of Posttransplant Hypertension

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
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</thead>
<tbody>
<tr>
<td>Organ donor characteristics</td>
<td>Cadaveric</td>
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<tr>
<td></td>
<td>Hypertensive (subarachnoid bleed)</td>
</tr>
<tr>
<td></td>
<td>Older</td>
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<tr>
<td>Renal allograft dysfunction</td>
<td>Rejection</td>
</tr>
<tr>
<td></td>
<td>Delayed graft function</td>
</tr>
<tr>
<td></td>
<td>Chronic allograft nephropathy (IFTA)</td>
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<tr>
<td>Retained native kidneys</td>
<td></td>
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<tr>
<td>Renal artery stenosis</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td>Calcineurin inhibitors</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Posttransplant hyperparathyroidism</td>
</tr>
</tbody>
</table>
Post-transplant hypertension

Recipient factors:
- Genetics
- Pre-existing HTN
- CKD
- Age
- DM
- Hormone-producing tumors

Donor factors:
- Genetics
- Nephron mass
- Quality of kidney
  - SCD versus ECD
- Age
- Sex

Donor-recipient interactions:
- DGF
- AMR

Surgical and biopsy complications:
- TRAS, AVF, Page kidney

Management Strategies:
1. Lower vascular tone – ACEi/ARB, CCB, other vasodilators
2. Lower sympathetic tone – β-blocker, alpha blockers and centrally-acting agents
3. Salt Retention and volume overload – Loop diuretics and thiazides
4. Decrease rate of fibrosis – ACEi/ARB
5. Improve cardiac outcomes – β-blockers, ACEi/ARB
6. Evaluate secondary causes such as OSA, complications of transplant surgery or biopsy
7. Consider drug tolerance and co-morbidities
8. BP control: Assess using combination of Clinic BP, 24 ABPM as needed and consider SBPM as alternative to 24 ABPM
9. KDIGO 2012 guidelines define target BP of <130/80 mmHg in the kidney transplant patient; balance long term versus immediate post-transplant goals

1. Increased vascular tone with increased vasoconstrictors (endothelin-1, TXA2, AG II) over vasodilators (nitric oxide)
2. Increased sympathetic tone
3. Na retention via increased activation of RAAS, NCC, and ENaC
4. Increased fibrotic factors leading to interstitial fibrosis and tubular atrophy

1. Increased sensitivity to vasoconstrictors and activation of GC receptors on vascular smooth muscle
2. Mineralocorticoid receptor activation with Na and water retention

CNI

GCs
TRANSPLANT RENAL ARTERY STENOSIS
Epidemiology

• Potentially reversible cause of HTN (1-5%), patient morbidity and allograft dysfunction

• Variable prevalence 1%-23%

• 12.4% vs 2.4% with and without routine Doppler screening

• Occurs between 3 months to 2 years after transplant

  - Bruno et al JASN 2004
  - Arias et al. NDT 2012
  - Mangray et al AJKD 2011
Etio-Pathogenesis TRAS

- Stenosis at anastomosis site
- Localized stenosis: pre or post anastomotic site
- Multiple or diffuse stenosis
  - Bruno et al. JASN 2004
  - Arias et al. NDT 2012
Stenosis at anastomosis site

- Trauma to donor or recipient vessels during harvesting, clamping / suturing
- Torsion, kinking, angulation of artery
- Hemodynamic mechanism in end to side anastomosis
- Arise early after transplant
  - Bruno et al. JASN 2004
  - Arias et al. NDT 2012
Etio-pathogenesis: By site

- Localized stenosis: pre or post anastomotic site
  - Subtle intimal flaps or subintimal dissections: intimal scarring and hyperplasia
  - Donor specific Abs
- Multiple or diffuse stenosis
  - Atherosclerotic disease
  - Late immune mediated endothelial damage
  - Prolonged cold ischemia time

Bruno et al. JASN 2004
Arias et al. NDT 2012
Retrospective cohort of prospectively collected data of 999 transplanted patients 2005-2012

**Inclusion criteria:** Both deceased and live donor transplants, simultaneous pancreas-kidney transplant

**Exclusion criteria:** ABO and HLA incompatible who underwent Ab removal pre-transplant

**Immunosuppressive regimen:**
- 1 gm Methylpred at surgery and 1 week steroids
- Induction: anti CD52(alemtuzumab) or anti CD25(daclizumab/basiliximab)
- Maintenance: Tacro for alemtuzumab gp, tacro+MMF for anti CD25 gp
Routine Color Doppler perioperatively, Allograft dysfunction, 3 mths post transplant

Clinical suspicion, unexplained allograft dys or suggestion of TRAS on CDU

MRA/CTA

IADSA

Willicombie et al Am J of Transplantation 2014
Screening: TRAS

CDU
847

MRA
828/847 (97.8%)

CTA
14/847 (1.7%)

IADSA
5/847 (0.6%)

IADSA
238/847 (28%)

TRAS
137/238 (57%)

Willicombie et al Am J of Transplantation 2014
## Results: Association between DSA and TRAS

<table>
<thead>
<tr>
<th></th>
<th>TRAS-</th>
<th>TRAS +</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low level preformed DSA</td>
<td>66/710 (9.3%)</td>
<td>13/137 (9.5%)</td>
<td><em>p = 0.81</em></td>
</tr>
<tr>
<td>Denovo DSA (of those without preformed DSA)</td>
<td>55/644 (8.5%)</td>
<td>15/124 (12.1%)</td>
<td><em>P=0.28</em></td>
</tr>
<tr>
<td>De novo class II DSA</td>
<td>31/644 (4.8%)</td>
<td>12/124 (9.7%)</td>
<td><em>p=0.052</em></td>
</tr>
<tr>
<td>De novo class I DSA</td>
<td>35/644 (5.4%)</td>
<td>6/124 (4.8%)</td>
<td><em>p=0.96</em></td>
</tr>
</tbody>
</table>
Clinical Features

- Difficult to treat HTN
- Deterioration of renal function
- Pulmonary Edema
- Vascular murmur in iliac fossa

References:
- Bruno et al. JASN 2004
- Arias et al., NDT 2012
Pathogenesis of Reno-vascular HTN

- Clinical Counterpart of experimental model 1K, 1C Goldblatt’s hypertension
Diagnostic Procedures

- Lab tests
  - Plasma Renin Activity, in basal conditions or administration of ACEI
  - Serum potassium

Bruno et al JASN 2004
Non Invasive Procedures

Color Doppler Ultrasound:
- Sen 87-94 %, Sp 86-100%
- Extra renal (PSV) and Intrarenal approach (Parvus-Tardus phenomenon)
- Resistive Index (S-D)/S

Contrast Enhanced US:
- Identification of renal artery not needed, not angle dependent

 Bruno et al JASN 2004
 Arias et al. NDT 2012
Google images
Non Invasive Procedures

Isotope Renography
- basal / RAAS stimulation
- sensitivity 75%, spec 67%

Spiral CT
- No arterial puncture
- Less contrast needed

MRA
- Sen 67-100%, Sp 75-100%

Bruno et al JASN 2004
Arias et al. NDT 2012
Google images
Invasive Procedures

- Renal Arteriography: Gold standard
  - Large volume contrast, thromboembolism
  - Groin hematomas, pseudoaneusyms, AV fistulas

- CO2 Angiography

Bruno et al JASN 2004
Arias et al. NDT 2012
Management

Medications

Surgical
Conservative Therapy

• Stable renal function, no hemodynamically significant stenosis via Doppler (PSV < 180 cm/s, RI > 0.50)

• Dietary and Lifestyle modifications

• Anti-hypertensives

  • Bruno et al JASN 2004
Anti-hypertensives

- **Diuretics:** Thiazides vs Loop

- **CCBs: Dihydropyridine**
  - Less additive AV conduction delay with B blockers
  - No appreciable drug-drug interactions with CNIs

*Mario F Rubín Advances in CKD, 2011*
*Weir et al JASoc HTN 2011*
Anti-hypertensives

• **B blockers**
  - Decreases myocardial demand
  - Counters sympathetic activity
  - Non selective B blockers desired

• **ACE/ARBs**
  - Reduced BP, intraglomerular HTN, proteinuria
  - Counteracts CNI induced HTN

• Others: Alpha blockers, Minoxidil

*Mario F Rubin Advances in CKD, 2011*
*Weir et al JASoc HTN 2011*
ACE Inhibitor or Angiotensin Type 1 Receptor Antagonist Therapy Is Associated with Prolonged Patient and Graft Survival after Renal Transplantation

Heinze et al JASN 2006

- Retrospective open cohort study, 2031 patients (ACE-I 781 vs non ACE-I 681)

- Methods:
  - Patient and graft survival were compared between patients (38%) with vs without ACE/ARB (31%)
  - Data were analyzed with and without propensity score models
Figure 2. Kaplan-Meier estimates of functional (death censored) graft survival (log rank: $P = 0.57$).

Figure 3. Kaplan-Meier estimates of actual graft survival counting death as event. ACEI/ARB therapy was associated with longer graft survival (log rank: $P = 0.002$).
Nifedipine Vs Lisinopril: Midtvedt et al. Transplantation 2001

Single center, double blind, RCT

Methods:

• 154 transplant patients with HTN (DBP >=95) during 1st 3 weeks post transplant

• 123 pts completed 1 yr Rx (69 Nifedipine/54 Lisinopril) and 64 completed 2 yr Rx (39 nifedipine/25 Lisinopril)

• Baseline GFR measured in a stable phase 2-5 weeks, 1,2 yrs

Results:

• Baseline GFR rates similar (46 +/- 16 ml/min vs 43 +/- 14 ml/min)

• Changes in GFR from baseline statistically significant after 1 and 2 yrs (9.6 ml/min Rx difference, p 0.0001 and 10.3 ml/min, p 0.0017)
Surgical Interventions

- Primary Transluminal Angioplasty
- PTA with Stent
- Surgical Revascularization
Treatment of TRAS by PTA and/or Stenting: Study in 63 patients in single institution

Marini et al. Transplantation Proceedings 2011

Methods:
- Retrospective observational study 2150 allograft renal transplants, 62 patients underwent endovascular for TRAS > 75%
- Parameters included technical success, BP, antihypertensives, Cr levels

Results:
- PTA/stent placement success 90.3%
- 79 PTAs with 11 stents: primary interventions, 6 PTAs and 4 stents, follow up 39 months
- Cr 2.8+-1.7 (pre) vs 2.1+-1.2 (post) (p<0.001)
- SBP 147.2+-18.7 mmHg vs 131.6+-14.2 mmHg (p<0.001), Antihypertensives no. 2.3+-1.1 vs 1.6+-1.6(p<0.0001)
- Patency rates 95 +/- 2.8% at 1 month, 87.9 +/- 4.3% at 3 months, and 85 +/- 4.7% at 12 months. Secondary patency was 100% with no restenosis on follow-up
- Allograft survival after primary and secondary PTA/stenting was 97% at 1, 93% at 3.89% at 5, and 85% at 10 years
Long-Term Outcomes of Patients Treated with Primary Stenting for Transplant Renal Artery Stenosis: A 10-year Case Cohort Study

• Methods:
  • Prospective, observational case-cohort study
  • 744 pts, 18 pts underwent PES for TRAS > 60%, control 726, no TRAS
  • Outcome: Death censored graft failure and all cause mortality, BP

• Results
  • Technical success for PES 100%, mean follow up 7.1 ± 3.7 and 6.9 ± 2.4 years in the study and control groups
  • 4 pts in study and 113 pts in control group reached primary outcome
  • Reduction in stenosis resulted in immediate improvement in BP control and graft function (p<0.01), persisted through 6 year follow-up(p<0.05) Restenosis one pt (5.6%)
• Single Center retrospective study, 2008-2011
• 12 pts with TRAS (vessel dia < 5 mm), underwent EVI with DES
• TRAS detected within Yr 1 (83%), 100% had HTN, allograft dysfn (100%), edema (58%)
• Procedure success: 100%, follow up 16+/−10 mnths
• BP improved 156/82 to 138/73 (p < 0.05)
• Se Cr improved 3.1+/− 1.3 to 2.3+/−0.5 (p = NS)
• Renovascular disease, established renal disease, HTN induced in pigs x 6 weeks
• All pigs: PTRAS
• Randomized 3 gps: RVD + PTRAS vs RVD + PTRAS + ETA blockade + vs RVD + PTRAS + ETA/B, ex vivo studies on stented kidneys

• Results:
  • PTRAS resolved renal stenosis, attenuated hypertension, and improved renal function
  • ETA block: + microvasc rarefaction, renal injury, greater recovery of renal func
  • ETA/B: blunted the therapeutic effects of PTRAS alone or PTRAS followed by ET-A blockade.
Take Home Points

• Resistant HTN in a post transplant patient indicative of Renal Artery Stenosis even when Color Doppler may be normal

• Dedicated vascular US needed for early and accurate diagnosis of TRAS
THANK YOU
## Results: Rejection

<table>
<thead>
<tr>
<th></th>
<th>TRAS-</th>
<th>TRAS +</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Prescreening rejection</td>
<td>71/710 (10%)</td>
<td>18/137 (13.1%)</td>
<td>(p=0.34)</td>
</tr>
<tr>
<td>Overall rejection-free survival</td>
<td>64.7%</td>
<td>80.9%</td>
<td>(p=0.33)</td>
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<tr>
<td>ACR-free survival</td>
<td>87.0%</td>
<td>83.3%</td>
<td>(p=0.61)</td>
</tr>
<tr>
<td>AMR-free survival</td>
<td>35/644 (5.4%)</td>
<td>84.2%</td>
<td>(p=0.59)</td>
</tr>
<tr>
<td>TG-free survival</td>
<td>92.4%</td>
<td>77.4%</td>
<td>(p=0.087)</td>
</tr>
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</table>
Screening: Rejection and DSA

• All rejection episodes biopsy proven (Banff 07 classification)

• Patients routinely screened for DSA at 1, 3, 6 and 12 months and yearly thereafter

• If non sensitized: LABScreen mixed beads, single Ag beads if sensitized

• DSA to HLA-A, -B, -Cw, -DR, -DQ and -DP

Willicombie et al Am J of Transplantation 2014
Allograft survival by DSA and intervention status in patients with TRAS

![Graph showing allograft survival by DSA and intervention status in patients with TRAS.](attachment:graph.png)

<table>
<thead>
<tr>
<th>Intervention Status</th>
<th>DSA-no intervention</th>
<th>DSA+ no intervention</th>
<th>DSA- intervention</th>
<th>DSA+ intervention</th>
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<tbody>
<tr>
<td>No Intervention</td>
<td>10</td>
<td>8</td>
<td>97</td>
<td>22</td>
</tr>
<tr>
<td>With Intervention</td>
<td>6</td>
<td>4</td>
<td>67</td>
<td>15</td>
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<tr>
<td></td>
<td>6</td>
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</table>
Glucocorticoids

- Incidence 15%, highest in pre Tx HTN
- Common if Pred > 20 mg
- MOA: Increased sensitivity to vasoconstriction and partial activation of mineralocorticoid receptors: Na and H2O retention
- The activation of GC receptors on vascular smooth muscle leading to increased tone plays an important role in the development of acute HTN in a mouse model
Pathophysiology of CNIs

Figure 1. Calcineurin inhibitors and hemodynamic effects.