Proteinuria post Kidney Transplantation

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Clinical Scenario

- **HPI:** 69 y/o WM with h/o HTN, Anemia, DVT s in BLE now on Coumadin, CKD5 due to ?HTN s/p HD since 9/06 with unknown h/o of proteinuria, who underwent Cad Ktx 10/25/10 now presents with Cr 1.4-1.6.

- Patient was found to have a spot P:Cr of .32gm at 34 days post-transplant -> 2.4gm at 71 days -> 4.13gm at 89 days.

- Serologies negative: ANA, HIV, Hep panel, C3/C4
Objectives

- Proteinuria: Native Kidneys vs Allograft?
- Does proteinuria declines post renal transplantation? How fast?
- What are propose for mechanisms for decline proteinuria.
- Is proteinuria an independent predictor of graft loss, cardiovascular events and survival?
Proteinuria

Native Kidneys vs Allograft Pathology?
Characteristic of Proteinuria

- Degree of proteinuria after transplantation is a powerful predictor of both allograft and patient survival.

- Proteinuria not only a marker for allograft pathology, but promote progression by causing tubular damage.

- Proteinuria is associated with increased cardiovascular events.
Causes of Proteinuria in the early Post-Transplantation Period

- Delayed Graft Function (DGF)
- Acute Rejection (Cellular and/or Humoral)
- Calcineurin-Inhibitor Nephrotoxicity and mTORs inhibitors
- Thrombotic microangiopathy/HUS
- Rapid Recurrence of Native Renal Disease (esp. FSGS, amyloidosis)

Roodnat et al, Transplantation 2001
Proteinuria following LD Renal Transplantation

- Prospective study evaluating 14 living donor renal transplantation

- 7 pts received pre-emptive transplants and 7 received transplant after HD for 3-24 months.

- Random Upr:Cr was obtained pre-transplants and 7-14 days until proteinuria resolved completely.

- IS: Tacrolimus, MMF, and Corticosteroids +/- thymoglobulin or Simulect.

- No patients was on anti-hypertensive drugs that might decrease proteinuria.

D’Cunha et al, AMJ of Transplantation 2005
Improve Renal Function

D’Cunha et al, AMJ of Transplantation 2005
Resolution of Proteinuria

Figure 3: The random urine protein to creatinine ratio (UPr:Cr) pre-transplant and nadir post-transplant in the seven patients on dialysis prior to transplantation.

Figure 4: The random urine protein to creatinine ratio (UPr:Cr) pre-transplant and nadir post-transplant in the seven preemptive transplant recipients.

In the two patients who had pre- and post-transplant DTPA...
Decrease of proteinuria post transplantation.

All pts Upr:Cr normalize to <0.2 mg/dl at a mean of 4.5wks post transplantation.

D’Cunha et al, AMJ of Transplantation 2005
Proteinuria in all forms of Renal transplantation

- 115 pts who had Renal Txpl at Mayo Clinic from Jan. 1999 to Dec. 2004

- 24 Hr urine protein excretion was measured ≤ 3 months before transplantation, 3wks and 1 year post-transplantation, and every year subsequently.

- Immunosuppression generally comprised antithymocyte globulin induction + triple therapy with prednisone, tacrolimus, and mycophenolate mofetil.

- Protocol biopsies were performed immediately after graft implantation, and 4 mo, 1yr, 2 yrs, and 5yrs post-transplant.

- 85 pts received preemptive transplantation, while 30 pts received dialysis for less than 3 months.

Myslak et al, AMJ of Transplantation 2006
Causes of Proteinuric in the Native Kidneys

Table 2: Causes of native kidney disease in the study population and corresponding levels of pre-transplant proteinuria

<table>
<thead>
<tr>
<th>Cause of kidney failure</th>
<th>Number of patients (%)</th>
<th>Pre-transplant proteinuria (mg/day) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>14 (12%)</td>
<td>4934 ± 2811 (66–9780)</td>
</tr>
<tr>
<td>Glomerular disease</td>
<td>45 (39%)</td>
<td>5305 ± 610 (188–20446)</td>
</tr>
<tr>
<td>FSGS</td>
<td>8 (7%)</td>
<td></td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>10 (9%)</td>
<td></td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>7 (6%)</td>
<td></td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>5 (4%)</td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>3 (3%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12 (10%)</td>
<td></td>
</tr>
<tr>
<td>Failing kidney allograft</td>
<td>19 (17%)</td>
<td>2602 ± 2316 (137–9141)</td>
</tr>
<tr>
<td>ADPKD</td>
<td>5 (4%)</td>
<td>636 ± 364 (133–1019)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (4%)</td>
<td>2789 ± 1947 (558–5166)</td>
</tr>
<tr>
<td>Other</td>
<td>22 (19%)</td>
<td>1531 ± 1785 (50–5977)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (4%)</td>
<td>2356 ± 2338 (82–6167)</td>
</tr>
</tbody>
</table>

Myslak et al, AMJ of Transplantation 2006
Proteinuria at 3wks & 1yr

Myslak et al, AMJ of Transplantation 2006

1500 mg/day
Urine protein excretion before and after transplantation

<table>
<thead>
<tr>
<th>Urine protein level (mg/day)</th>
<th>Pre-transplant N (%)</th>
<th>Post-transplant (3 weeks) N (%)</th>
<th>Post-transplant (1 year) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–150</td>
<td>5 (6)</td>
<td>24 (28)</td>
<td>43 (49)</td>
</tr>
<tr>
<td>151–1500</td>
<td>21 (24)</td>
<td>55 (63)</td>
<td>36 (41)</td>
</tr>
<tr>
<td>1501–3000</td>
<td>23 (26)</td>
<td>7 (8)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>&gt;3000</td>
<td>38 (44)</td>
<td>1 (1)</td>
<td>4 (5)</td>
</tr>
</tbody>
</table>

Patients were classified at each time point according to ranges of urine protein excretion. Only those patients with urine protein determinations at all time points (N = 87) are included in this analysis.
Proteinuria at pre-Txpl vs 3wks

Myslak et al, AMJ of Transplantation 2006
Beyond 3 wks post-transplantation, proteinuria decreases or does not change significantly in the majority (94%).

Myslak et al, AMJ of Transplantation 2006
Etiology of Post-Transplant Proteinuria

Table 5: Pathologic diagnoses in surveillance biopsies done 1 year after transplantation

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients (%)</th>
<th>Urine protein excretion (mg/day) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>38 (36%)</td>
<td>186 ± 336 (4–1979)</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>8 (7%)</td>
<td>373 ± 364 (72–1080)</td>
</tr>
<tr>
<td>CAN(^1)</td>
<td>42 (39%)</td>
<td>265 ± 292 (19–1344)</td>
</tr>
<tr>
<td>Glomerular disease</td>
<td>9 (8%)</td>
<td>2873 ± 2711 (33–7199)(^2)</td>
</tr>
<tr>
<td>Other pathologies(^3)</td>
<td>10 (9%)</td>
<td>221 ± 240 (78–800)</td>
</tr>
</tbody>
</table>

\(^1\)CAN = Chronic allograft nephropathy.
\(^2\)Proteinuria in the glomerular disease group is significantly different from the other 4 groups (p = 0.009, Kruskal-Wallis).
\(^3\)Includes: BK nephropathy (N = 6); acute tubular necrosis (N = 1); atherosclerotic vascular disease (N = 2); sickle cell nephropathy (N = 1).

Myslak et al, AMJ of Transplantation 2006
Mechanism for Decline in Proteinuria

Decrease in Renal blood flow to Native Kidneys
## Renal Radiopharmaceuticals

<table>
<thead>
<tr>
<th>Renal handling</th>
<th>Radiopharmaceutical</th>
<th>Imaging</th>
<th>Clinical use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular filtration</td>
<td>(^{51})Cr-EDTA</td>
<td>No</td>
<td>GFR</td>
</tr>
<tr>
<td></td>
<td>(^{99m})Tc-DTPA</td>
<td>Yes</td>
<td>GFR</td>
</tr>
<tr>
<td>Tubular secretion</td>
<td>(^{123})I/(^{131})I-OIH</td>
<td>Yes</td>
<td>ERPF</td>
</tr>
<tr>
<td></td>
<td>(^{99m})Tc-MAG3</td>
<td>Yes</td>
<td>ERPF</td>
</tr>
<tr>
<td></td>
<td>(^{99m})Tc-EC</td>
<td>Yes</td>
<td>ERPF</td>
</tr>
<tr>
<td>Tubular retention</td>
<td>(^{99m})Tc-DMSA</td>
<td>Yes</td>
<td>Cortical imaging</td>
</tr>
<tr>
<td></td>
<td>(^{99m})Tc-GH</td>
<td>Yes</td>
<td>Cortical imaging</td>
</tr>
</tbody>
</table>
Glomerular Filtration and Imaging

- Gold standard is inulin clearance
- Radionuclide of choice – 51 Cr-EDTA clearance - closest to inulin
- **99m Tc-DTPA** – technetium-99m-diethlenetriamin pentacetic acid
  - Correlates well with Cr-EDTA and inulin
  - Taken up by glomerular filtration, not secrete/reabsorbed by tubules
  - Can be used for gamma camera imaging
  - Low radiation dose
  - Once reaches kidney- 20% is accumulated and remainder flows away.
Marked reduction in Renal Blood flow to the Native Kidneys

Figure 5: (A) DTPA renogram 1 week before transplant when the random urine protein to creatinine ratio (UPr:Cr) = 4.26. (B) Three weeks post-transplant, UPr:Cr ≤ 0.2.

2 pts had DTPA isotopic renograms

D’Cunha et al, AMJ of Transplantation 2005
A 48 y/o M with DMII (Cr 2mg/dl and proteinuria of 5.9 g/day) - 1 month after: Cr is 1.1 & proteinuria 0.7 g/day.

- (A) 99mTc-MAG3 scintirenography:

- 1 month post-transplantation the renographic curve of the native kidney shows prolonged excretion.

- 2 months after, the parenchymal phase of the native kidney is poor, with a complete flattening of the renal curve. Conversely, the curve of the grafted kidney appears normal.

Piccoli et al, Transplantation 2004
The curve of the grafted kidney shows nl peaked time. The native kidney has a delayed peaked time, with a significantly prolonged parenchymal phase (accounting for ~ 10% of overall function).
Unlikely mechanisms for resolution of proteinuria

- The rapid increase in urinary Cr excretion with immediate graft fxn is an unlikely explanation for the post-transplant decrease in proteinuria.

- Not diluting effect – concentration use in Upr:Cr correct for it.

- CNI-induced renal vasoconstriction causing cessation of proteinuria unlikely – resolution of proteinuria within 12-120 days was observed in the pre-cyclosporine era.
Propose mechanism for resolution of proteinuria of native kidneys.

- Factors in the blood of bilaterally nephrectomized rats can induce renal hypertrophy/hyperfiltration in non-nephrectomized animals cross circulated with nephrectomized animals.

- Extract of normal renal cortical tissue have inhibitory effect on compensatory renal hypertrophy when injected to uni-nephrectomized rats.

- Introduction of a structurally normal allograft might abolish hypertrophy, hyperfiltration, and urine output in the remnant nephrons of the native kidney.

- Cause cessation in native kidney urine output.
Proteinuria

Independent predictors of graft survival, cardiovascular events, and survival.
Death-censored Graft Survivor decreases with increase proteinuria

<table>
<thead>
<tr>
<th>Group</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;0.15</td>
</tr>
<tr>
<td>2</td>
<td>0.15 - 0.5</td>
</tr>
<tr>
<td>3</td>
<td>0.5 - 1.0</td>
</tr>
<tr>
<td>4</td>
<td>&gt;1.0</td>
</tr>
</tbody>
</table>

Cherukuri et al, Transplantation 2010
Death-censored Graft Survivor decreases with increase proteinuria

Cherukuri et al, Transplantation 2010
TABLE 3. Independent effect of proteinuria on the primary outcome measures

<table>
<thead>
<tr>
<th>PCR group</th>
<th>Death-censored graft loss</th>
<th>Death with a functioning graft</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI) $^a$</td>
<td>$P$</td>
</tr>
<tr>
<td>PCR group 1</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>PCR group 2</td>
<td>7.1 (1.7–29.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>PCR group 3</td>
<td>10.5 (2.4–45.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>PCR group 4</td>
<td>16.0 (3.5–72)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cardiovascular events

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (95% CI) $^c$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>1.1 (0.6–2.1)</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>1.3 (0.7–2.7)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>2.2 (1.04–4.9)</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

Cherukuri et al, Transplantation 2010
eGFR changes across PCR groups

Cherukuri et al, Transplantation 2010
Allograft Lost proportional to degree of Proteinuria

Figure 1. Relationship between increasing levels of proteinuria at 1yr posttransplant and subsequent graft survival. In absolute terms, 3.9%, 9.9%, 20%, 33.3%, and 41.2% of kidney allografts were lost during a period of 46 ± 20 mo of follow up in patients who at 1 yr had proteinuria <150 (n = 337), 151 to 500 (n = 182), 501 to 1500 (n = 50), 1500 to 3000 (n = 27), and >3000 (n = 17) mg/d, respectively.

Amer H et al, JASN 2009
Low-grade Proteinuria and Graft Survival

Halimi et al, AMJ of Transplantation 2005
Low-grade Proteinuria and Graft Survival

Halimi et al, AMJ of Transplantation 2005
Take Home Points

- In conclusion, pre-transplant proteinuria, even when high grade, declines rapidly after transplantation (3 - 4.5wks).

- Failure to decline or persistence of proteinuria greater than 1500 mg/day is indicative of allograft pathology.

- Proteinuria an independent predictor of graft loss, cardiovascular events and graft loss.

- Biopsy of Transplanted Kidney is usually indicated for proteinuria beyond 1 month post transplant.
References

- **Rapid resolution of proteinuria of native kidney origin following live donor renal transplantation.**
  D'Cunha PT, Parasuraman R, Venkat KK.

- **Interpreting post-transplant proteinuria in patients with proteinuria pre-transplant.**
  Myslak M, Amer H, Morales P, Fidler ME, Gloor JM, Larson TS, Stegall MD, Cosio FG.

- **Proteinuria after renal transplantation affects not only graft survival but also patient survival.**

- **The clinical significance of early proteinuria after renal transplantation.**
References
