FSGS AND Transplant

Sushma Bhusal

11.17.15
48 yo AA female with h/o ESRD from FSGS, s/p DDRT in 2010, presented with dysuria, suprapubic and RLQ pain x 3 days on 11/8/15

Had C diff 3 months prior, treated with 2 courses of Flagyl

Also UTI around the same time (multiple)
HPI

- DDRT in Feb 2010, course complicated by ureteral reimplantation, AMR, ATN. Cr around eventually stabilized around 1.3

- Cr increased to 1.6 in 10/2010, increased proteinuria, tx biopsy with 1/23 glomeruli FSGS

- Treated with plasmapheresis and high dose Pred, stopped in 2013

- Cr stabilized around mid 2s until 3/2015, slow rise to 3s since then
PMH/PSH
- DDRT for ESRD secondary to FSGS
- Recurrent FSGS
- RIJ DVT
- Hyperthyroidism
- Recurrent UTIs
- C diff

FH: Mother and sister with Ca breast

SH: Non smoker, social drinker, no illicits
Prograf 5 mg bid
Prednisone 5 mg po d
Sodium bicarbonate 650 mg bid
Ferrous sulfate 1 tid
Omeprazole 20 mg po d
Septra SS q other day
Vasotec 5 mg bid
Physical Exam

- **Vitals**: Temp 98.8, HR 89, RR 18, BP 122/70, O2 Sat 99%
- **General appearance**: alert, NAD
- **HEENT**: sclera anicteric, mmm
- **Lungs**: clear to auscultation bilaterally
- **Heart**: regular rate and rhythm, S1, S2 normal, no m/r/g
- **Abdomen**: soft, RLQ tenderness; bowel sounds normal
- **Extremities**: no edema
<table>
<thead>
<tr>
<th></th>
<th>CBC</th>
<th>CMP</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>12.3</td>
<td>139</td>
</tr>
<tr>
<td></td>
<td>7.6</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td>226</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>38.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
<td>88</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liver test</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Bilirubin: 0.5</td>
<td>Alk Phos: 69</td>
</tr>
<tr>
<td>Direct Bilirubin: 0</td>
<td>Albumin: 3.1</td>
</tr>
<tr>
<td>AST: 11</td>
<td>Total protein: 6.1</td>
</tr>
<tr>
<td>ALT: 18</td>
<td></td>
</tr>
</tbody>
</table>

- **Ca⁺**: 9.2
- **Phos**: 5.3

**UA**: Small blood
- Protein Large
- RBC – 7
- WBC – 10
- No bacteria
- LE / Nit - Neg
Renal US

Interval development of hydroureteronephrosis of the right lower quadrant renal allograft, with area transplant and periureteral stranding c/f infection vs. recent obstruction
Hospital Course

- Treated with Ceftriaxone, unasyn
- Urine culture negative
- Diarrhea resolved, C diff negative
- Renal biopsy undertaken
- Cr stabilized 2.4-2.6
- No Urology intervention for mild hydro
Differential Diagnosis

- Pre-renal AKI in the setting of diarrhea
- ATN
- Acute Rejection
- Chronic progressive disease
- Recurrent FSGS
Biopsy
Biopsy
KIDNEY, TRANSPLANT: PERCUTANEOUS NEEDLE CORE BIOPSY

- ACUTE TUBULAR INJURY, DIFFUSE AND MODERATE
- CHRONIC INTERSTITIAL INFLAMMATORY CELL INFILTRATE, DIFFUSE AND MODERATE
- NEGATIVE C4D STAIN IN PERITUBULAR CAPILLARY
- NEGATIVE SV40 STAIN FOR POLYOMA VIRUS
- INTERSTITIAL FIBROSIS/TUBULAR ATROPHY, 50-60 %
- GLOBAL GLOMERULOSCLEROSIS, 14/45
FSGS and Transplant

- Introduction
- Pathophysiology
- Treatment options
Introduction

- Accounts for 20% of NS in children and 40% in adults

- Global incidence of FSGS estimated at 8 cases/million/yr

- In US, prevalence 4%, lifetime risk for FSGS estimated at 0.2% for European Americans and 0.7% for AA

- Progression to ESRD occurs in 40–60% of FSGS pts within 10–20 years from diagnosis, making FSGS mc primary glomerular disease in dialysis patients

Fogo, A. B. Nat. Rev. Nephrol. 2015
Cravedi et al. Am J Transplant. 2013 Feb
Currently recognized forms

1. Genetic
2. Adaptive (post-adaptive)
3. Virus associated
4. Drug-induced
5. Primary (idiopathic)
<table>
<thead>
<tr>
<th>Forms</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| Genetic        | • a/w mutations > 20 genes,  
• encoded in the nuclear or mitochondrial genome  
• encoding a range of molecules, viz slit diaphragm and actin cytokeleton |
| Post adaptive  | • mismatch b/w physiological load (partly body size and other determinants of glomerular BF) and glomerular filtration surface (partly nephron number),  
• leads to podocyte stress, podocyte detachment and loss |
| Virus associated| • Parvovirus B19 and HIV  
• Via direct viral infection of the podocyte, circulating viral proteins or inflammatory cytokines released by other infected cells that interact with podocyte receptors |
| Drug induced   | • act on podocyte (pamidronate, interferon-alpha)  
• damage the tubulointerstitium (e.g. lithium, cyclosporine, tenofovir |
| Idiopathic     |                                                                                 |
Pathological variants

NOS

Perihilar

Tip

Collapse

Cellular
Pathophysiology of Recurrence

- 27 yo patient with ESRD caused by primary FSGS, developed severe nephrotic syndrome shortly after receiving a kidney tx from 24 yo sister

- Graft biopsy D6: FSGS recurrence, podocyte foot-process effacement and loss of the interdigitating arrangements.

- Severe hypoalbuminemia, rapidly deteriorating graft function + an intra-abdominal hematoma, renal allograft removal on D14

- Kidney transplanted to 66 yo with ESRD from DM2 nephropathy

- Immediately post re-transplantation, the graft regained function, proteinuria decreased, and glomerular lesions regressed, shown by allograft bx on D8 and D25 after re-transplantation

Gallon et al NEJM 2012
Risk factors for Recurrence

- Younger age (especially in children <6 at FSGS onset)
- Nonblack race
- Rapid progression to ESRD in the native kidney (<3 years)
- Heavy proteinuria pre-transplantation period
- Loss of previous allografts to recurrence

Cravedi et al. Am J Transplant. 2013 Feb
Pathophysiology of Recurrence

Insights from Buffalo Rats

- Buffalo/Mna rats develop spontaneous proteinuria a/w renal histology of FSGS

- Transplanted kidney from a healthy MHC-compatible LEW.1W, FSGS recurs

- Buffalo/Mna kidneys transplanted into normal LEW.1W rats, proteinuria and renal lesions regress

Cravedi et al. Am J Transplant. 2013 Feb
Insights from Buffalo Rats

Role of T cells?
- Studies in these rats: cells in kidney infiltrate were macrophages, monocytes and Th2 cells
- Rx with deoxyspergualin derivative LF15-0195 a/w the formation of Treg, reduction in proteinuria in the initial kidney disease and prevention of recurrence

Inherited podocyte defects: recurrence in NPHS2 gene mutation
- ? Inherited defects elicit immune response to accelerate glomerulosclerosis

Cravedi et al. Am J Transplant. 2013 Feb
Circulating Factors

- suPAR

- Cardiotrophin-like cytokine 1 (CLC-1)
  - a member of the interleukin-6 family,
  - Decreases nephrin expression in cultured podocytes and its blockade reverses the permeability effect of sera from FSGS patient

- Protein tyrosine phosphatase receptor-O (PTPro)
  - transmembrane protein expressed on the apical surface of podocyte foot processes
  - activity is required to maintain glomerular permeability
  - Mechanism of PTPro phosphatase activity in glomerular filtration and the identities of the PTPro ligand and substrate unclear

Reiser et al. Advances in CKD 2014
Circulating urokinase receptor as a cause of FSGS


- uPAR is a (GPI)-anchored three-domain (DI, DII and DIII) protein, identified as a cellular receptor for urokinase, also as a versatile signaling orchestrator through association with other transmembrane receptors, including integrins.

- uPAR can be released from the plasma membrane as a soluble molecule (suPAR) by cleavage of the GPI anchor.

- Can be further cleaved in the linker region between DI and DII, releasing fragmentS.

- Circulating protein ranging from 20 to 50 kDa.

- Enhanced circulating suPAR deposits into the glomeruli, allowing activation of podocyte β3 integrin, which drives podocyte foot process effacement, proteinuria and initiation of FSGS.
suPAR measurement in the serum of subjects with glomerular disease
Pre-transplantation suPAR serum concentration may be a predictor of heightened risk of recurrent FSGS after transplantation.
suPAR serum concentrations and podocyte β3 integrin activity determine Rx response to plasmapheresis in recurrent FSGS
suPAR activates β3 integrin and causes foot process effacement in Plaur−/− mouse kidneys and albuminuria in Plaur−/− mice
Sustained overexpression of suPAR in the blood of wild-type mice leads to an FSGS-like glomerulopathy. (Reiser et al. Nature Medicine 2011)
Administration of blocking antibody to uPAR ameliorates suPAR-caused kidney damage

Pitfalls

- Serum levels of suPAR above the suggested threshold of 3000 pg/mL were found in patients without recurrent FSGS.

- Plasma suPAR levels elevated in several inflammatory conditions viz chronic infections (including tuberculosis and malaria), bacterial pneumonia, bacterial and viral CNS infections, sepsis and various cancers.

- Single center cohort of 23 patients
  - serum suPAR levels were similar amongst idiopathic FSGS secondary FSGS and MCD
  - Did not predict responsiveness to steroid therapy in patients with idiopathic FSGS or MCD

- Uninterpretable with low GFR
Progression of FSGS injury

- Various insults directed to or inherent within the podocyte → nephrotic proteinuria

- Wharram et al. induced precise levels of podocyte depletion by titrating dose of diphtheria toxin in transgenic mice
  - Podocyte depletion <20%: transient proteinuria and mesangial expansion
  - Loss of 20% to 40% of podocytes: persistent proteinuria and focal glomerulosclerosis, no progressive renal function decline
  - >40% podocyte loss: progressive glomerular failure
Progression of FSGS injury

- Chimeric model: subpopulation of podocytes express toxin receptor, podocyte injury and dedifferentiation shown to spread to neighboring toxin-resistant podocytes

- Podocytes shed into the urine for months after a brief toxin exposure

- Local propagation of injury: podocyte loss requires that neighboring podocytes must undergo hypertrophy to cover a larger area of the capillary loop can place stress on the podocyte

Cravedi et al. Am J Transplant. 2013 Feb
Possible pathways for regeneration of podocytes from PEC migration to the glomerular tuft and for the development of sclerosis

Fogo, A. B. Nat. Rev. Nephrol. 2015
Proposed Mechanism of FSGS Recurrence

Figure 1.
Proposed pathogenic mechanism(s) of FSGS recurrence after transplant.
Treatment algorithm for FSGS

Treatment of FSGS recurrence

Challenging, with none of the multiple approaches providing consistent efficacy

1. Plasmapheresis
2. Calcineurin inhibitors
3. Rituximab
4. Renin angiotensin system inhibitors
5. CTLA4 Inhibition
6. Galactose and adalimumab
Treatment of FSGS recurrence: Plasmapheresis

- Rationale: potential existence of circulating factor
- Mostly retrospective studies
- Prospective study: Gohh et al
  - 10 pts with high risk for recurrence
  - 8 PP in perioperative period
  - Recurrence: proteinuria > 3 gm/24 hr/biopsy findings
  - 3 patients had recurrence

Gohh et al. Am J Transplant. 2005
Treatment of FSGS recurrence: CNI

Rationale:

- T cell inhibition (small studies)
- Antiproteinuric effect by inhibition of calcineurin-mediated dephosphorylation of synaptopodin, critical for stabilizing the actin cytoskeleton in podocyte

Higher trough levels to overcome hypercholesterolemia

Prospective cohort study in children by Salomon et al (n=17), 14 with CR of proteinuria maintained for several years, trough 250-350 ng/ml (IV converted to PO in 3-4 weeks)
## CsA studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Treatments</th>
<th>Incidence of FSGS recurrence/Remission Rate</th>
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</thead>
<tbody>
<tr>
<td><strong>Prevention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banfi G, et al. (52)</td>
<td>Retrospective</td>
<td>- Steroids + AZA (n=6)</td>
<td>2 (33%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Steroids + CsA (n=19)</td>
<td>10 (55%)</td>
</tr>
<tr>
<td>Schwarz A, et al. (43)</td>
<td>Retrospective</td>
<td>- Steroids + AZA (n=7)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Steroids + CsA (n=8)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Inguilli E Tejani A (53)</td>
<td>Retrospective</td>
<td>- Steroids + AZA (n=22)</td>
<td>4 (18%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Steroids + CsA (n=18)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inguilli E, et al. (42)</td>
<td>Case report</td>
<td>Progressive up titration of oral CsA doses</td>
<td>1 Complete and 1 partial remission</td>
</tr>
<tr>
<td>Salomon R, et al. (40)</td>
<td>Retrospective</td>
<td>I.v. CsA (n=16), trough levels: 250–350ng/mL</td>
<td>Complete remission: 13 (81%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Partial remission: 2 (13%)</td>
</tr>
<tr>
<td>Raafat RH, et al. (41)</td>
<td>Retrospective</td>
<td>Oral CsA doses were up titrated until proteinuria reduction or serum creatinine elevation (n=16)</td>
<td>Complete remission: 11 (65%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Partial remission: 2 (12%)</td>
</tr>
<tr>
<td>Canaud G, et al. (72)</td>
<td>Prospective cohort</td>
<td>I.v. CsA, combined with high-dose steroids and intensive plasmapheresis (n=10)</td>
<td>Complete remission: 9 (90%) [Incidence of complete remission in a control historical cohort: 5/19 (27%)</td>
</tr>
</tbody>
</table>
Treatment of FSGS recurrence: Rituximab

Rationale:

- Depletion of a circulating autoAb or interference with the presentation of B-cell Ag
- rituximab binds directly to SMPDL-3b protein (implicated in actin remodeling), prevents its down regulation in podocyte
## Rituximab Cases in recurrent FSGS

<table>
<thead>
<tr>
<th>Author Year</th>
<th>N</th>
<th>P/IM</th>
<th>Age Yr</th>
<th>Dose</th>
<th>Other Rx</th>
<th>CR/PR/NR</th>
<th>REL</th>
<th>SAE</th>
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<tbody>
<tr>
<td>Benz 2004 [62]</td>
<td>1</td>
<td>P</td>
<td>16</td>
<td>375 mg/m² X4</td>
<td>S,C,CsA,T</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nozu 2005 [63]</td>
<td>1</td>
<td>P</td>
<td>12</td>
<td>375 mg/m² X4</td>
<td>NA</td>
<td>NA</td>
<td></td>
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<tr>
<td>Pescovitz 2006 [64]</td>
<td>1</td>
<td>P</td>
<td>7</td>
<td>375 mg/m² X6</td>
<td>S</td>
<td>NA</td>
<td></td>
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<tr>
<td>Hristea 2007 [65]</td>
<td>1</td>
<td>IM</td>
<td>22</td>
<td>375 mg/m² X2</td>
<td>PT,C</td>
<td>NA</td>
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<td>Kamar 2007 [66]</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>375 mg/m² X2</td>
<td>PT,C</td>
<td>NA</td>
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<tr>
<td>Grossman 2007 [67]</td>
<td>1</td>
<td>IM</td>
<td>48</td>
<td>375 mg/m² X2</td>
<td>PT,S,MMF,T</td>
<td>PR</td>
<td>0</td>
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<td>Meyer 2007 [68]</td>
<td>1</td>
<td>IM</td>
<td>29</td>
<td>375 mg/m² X3</td>
<td>PT,S,MMF,T</td>
<td>PR</td>
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<tr>
<td>El-Firjani 2008 [69]</td>
<td>1</td>
<td>IM</td>
<td>46</td>
<td>375 mg/m² X6</td>
<td>PT</td>
<td>NA</td>
<td></td>
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<tr>
<td>Yabu 2008 [70]</td>
<td>4</td>
<td>IM</td>
<td>41–47</td>
<td>375 mg/m² X6</td>
<td>PT,MMF</td>
<td>0/0/4</td>
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<tr>
<td>Hickson 2009 [5]</td>
<td>4</td>
<td>P</td>
<td>5–19</td>
<td>375 mg/m² X2–4</td>
<td>PT,S,C,CSA,T, MMF,B</td>
<td>4</td>
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<td>Shimizu 2010 [71]</td>
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<td>20</td>
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<td>LCAP</td>
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<td>Grenda 2011 [72]</td>
<td>1</td>
<td>P</td>
<td>5</td>
<td>375 mg/m² X4</td>
<td>PT,S,CSA</td>
<td>CR</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Sethna 2011 [73]</td>
<td>4</td>
<td>P</td>
<td>13–18</td>
<td>375 mg/m² X4</td>
<td>PT,S,C,CSA,MMF</td>
<td>3/1/0</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Tsagalis 2011 [74]</td>
<td>4</td>
<td>IM</td>
<td>21–48</td>
<td>1000 mg X2</td>
<td>C,PT,S,C,CSA,MMF</td>
<td>2/2/0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Okamoto 2011 [75]</td>
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<td>P</td>
<td>15</td>
<td>200 mg X2</td>
<td>PT,S,T,M</td>
<td>PR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stewart 2011 [76]</td>
<td>1</td>
<td>P</td>
<td>16</td>
<td>375 mg/m² X4</td>
<td>PT,S,MMF,T,CSA</td>
<td>CR</td>
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<td>Audard 2012 [77]</td>
<td>4</td>
<td>IM</td>
<td>28–43</td>
<td>375 mg/m² X1-2</td>
<td>S,MMF,T</td>
<td>4/0/0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kumasi 2013 [78]</td>
<td>8</td>
<td>NA</td>
<td>Amount NA X1-4</td>
<td>PT,MMF,T</td>
<td>2/4/2</td>
<td>0</td>
<td>Yes</td>
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</table>
Renin angiotensin system inhibitors

Few cases reported on the use of RAS inhibitors in patients with FSGS recurrence

Freiberger et al: Case with FSGS recurrence after transplant that safely achieved proteinuria remission with intensified RAS inhibition via triple RAS therapy: ACE-I, ARB and a renin inhibitor

Watch for hyperk, elevated Cr
CTLA4 Inhibition

Mundel et al. NEJM 2013
- described 5 pts with FSGS and proteinuria with B7-1 immunostaining of podocytes in kidney-biopsy specimens.
- Abatacept (CTLA 4 Ig) induced partial or complete remissions of proteinuria in these patients

Johnson et al. Ped Nephrol 2015
- 1 patient with MCD, 1 patient with primary FSGS and 3 patients with recurrent FSGS after tx received CD80 blocking Abs (abatacept or belatacept)
- Urinary CD80 and CTLA-4 levels were measured by ELISA. Glomeruli were stained for CD80.
- Results: CD 80 undetectable, resolution of proteinuria in MCD, no response in FSGS patients
- Conclusion: role of podocyte CD80 in dev of proteinuria in MCD, not so in FSGS
Thank You