Clinical Case Presentation

Dana Assis, MD
Clinical Presentation

• 63 year old male with medical history AIDS (CD4 11, VL 62K), Hep C cirrhosis (never treated), DM II c/b diabetic retinopathy, HTN, CKD III, former IVDU. Presents to clinic with up trending creatinine (previous baseline Cr 1.7-1.9 since 2014), hematuria, and nephrotic range proteinuria.
• ROS negative for weight loss/gain, cough, shortness of breath, chest pain, nausea, vomiting, diarrhea, abdominal pain, joint pains, fevers, chills, rashes.

• ROS positive LE swelling three years, foamy urine 8 months.

• PMHx: AIDS dx 1995, on ARV since 1996, stopped taking for 3 years, then restarted one year ago. Following with hepatology for possible hepatitis C treatment

• Social: IVDU x 20 years, No etoh, Puerto Rico

• FHx: DM, HTN, no Renal/Rheum disease

• Meds: Novolog, epzicom, norvir, prezista, darunavir, losartan, amlodipine, aspirin, mvi
Physical Exam

- BP 162/71 P 61 O2 100% RA
- Gen NAD
- CV s1s2 diastolic murmur rusb
- Pulm cta bl
- Abd soft nd nt
- Ext b/l 2+ pitting edema extending to shins
Laboratory Findings
# Basic Metabolic Panel

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Urine

- 4/2015 Up 471 Ucr 81
- 10/2015 Up 488 Ucr 101
- Umicroalbumin 2598 mg/L Urine cytology negative for malignant cells, positive for red blood cells
- HIV VL 62,500 copies/mL
- Hep BcAb reactive sAg NR
- K/L 3.86 Kappa free 803 Lambda free 208
- IgG lambda band identified
- IgG 2900 IgA 318 IgM 154
- RF Negative
- C3 104 C4 27
- TC 142 TG 148 LDL 76 HDL 36
- Albumin 2.4
- Hb 9.9
- ANCA negative
- ANA negative
- Anti GBM negative
Imaging

- Renal ultrasound normal renal sonogram both kidneys measuring 10-11cm in length. No evidence of renal calculi. No hydronephrosis. No renal mass. Bladder outline normal with splenomegaly
- Cirrhotic morphology of liver portal hypertension with splenomegaly no ascites
Differential Diagnosis

- Diabetic Nephropathy
- HIV associated Nephropathy / ICD
- MPGN Hep C
- Amyloidosis
Renal Pathology Biopsy

- Diffuse nodular glomerulosclerosis, consistent with diabetic nephropathy
- Interstitial inflammatory cell infiltrate diffuse and mild
- Negative congo red stain for amyloid
- Interstitial fibrosis/tubular atrophy (20-30%)
- Global glomerulosclerosis 2/49
- Moderate arteriolar hyalinosis
- Marked thickened glomerular basement membranes
- No evidence of immune complex mediated GN, HIV or Hep C infection associated GN or monoclonal associated disease.
Diabetic Nephropathy

• Targeting Signaling Pathways Nephrotic syndrome
• Angiopoietin like 4
Primary metabolic defect

Hyperglycemia → Cytokines → AGES

Secondary mediators and receptors

Pyridoxamine → CCR2/CCR5 antagonist and others → anti-IL1β (Gevokizumab)

Angiotensin II → Aldosterone → MR

Endothelin → Uric acid

Xanthine oxidase

Vitamin D receptor agonists

Signaling

NFκB → NOX1/4

JAK/STAT → ASK-1

Bindarit → GKT137831

JAKinibs eg. Baricitinib → GS-4997

Pentoxifylline, CTP-499, PF-00489791

Pathogenic processes

Inflammation → Fibrosis → Renal cell injury

Progression of diabetic kidney diseases
Complexity Podocyte Foot Process
Angiopoietin like protein 4
Angiopoietin-like-protein 4

• Podocyte phenotype
  – Loss of glomerular basement membrane (GBM) charge and foot process effacement
  – Two types of Angptl4
    • Hyposialylated form secreted from podocytes
    • Sialylated form secreted from skeletal muscle, heart, and adipose tissue.
Podocyte-secreted angiopoietin-like-4 mediates proteinuria in glucocorticoid-sensitive nephrotic syndrome

Lionel C Clement¹, Carmen Avila-Casado²⁵, Camille Macé¹⁵, Elizabeth Soria², Winston W Bakker³, Sander Kersten⁴ & Sumant S Chugh¹
Article Highlights

• Angptl4 is upregulated in serum and podocytes of patients and mouse/rat models of MCD
• Transgenic NPHS2-angptl4 rats versus aP2
• Sialylation of Angptl4
γ2 Nephrotoxic Serum (NTS)
Phosphate Buffered Saline (PBS)
Lipopolysaccharide (LPS)
• Increased proteinuria = increase mRNA expression Angptl4
• Seen in mouse model MCD
Relationship between Angptl4 overexpression and proteinuria
Summary Slide

• Transgenic expression of Angptl4 from podocyte reproduced key feature of MCD

• Absence of proteinuria in aP2-Angptl4 transgenic rats – localized production of Angptl4 by podocytes in proteinuric disease

• Treatment with sialic acid precursor N-acetyl-D-mannosamine (ManNAc) converts high pI glomerular Angptl4 to neutral Angptl4 \textit{in vivo} and reduces albuminuria and proteinuria
Circulating angiopoietin-like 4 links proteinuria with hypertriglycerideremia in nephrotic syndrome

Lionel C Clement\textsuperscript{1,6}, Camille Macé\textsuperscript{1,6}, Carmen Avila-Casado\textsuperscript{2,3}, Jaap A Joles\textsuperscript{4}, Sander Kersten\textsuperscript{5} & Sumant S Chugh\textsuperscript{1}
Study Highlights

• Mechanism between proteinuria and hyperlipidemia in nephrotic syndrome

• In this study high serum levels of angptl4 (presumably normosialylated based on neutral isoelectric point) in other glomerular diseases as well

• Systemic feedback loop – role of circulating Angptl4
b

Systemic loop

Glomerular disease

Proteinuria

Urinary loss of albumin with lower FFA content

Hypoalbuminemia

Circulating albumin with higher FFA content

Threshold for nephrotic-range proteinuria

Elevated plasma FFA-to-albumin ratio

Increased entry of FFA into tissues

Upregulation of Angptl4 in skeletal muscle, heart, adipose tissue

Increased circulating Angptl4

Angptl4 binds glomerular endothelial α4β5 integrin

Angptl4 inhibits endothelial bound LPL activity

Reduced generation of FFA from triglycerides

Hypertriglyceridemia
Plasma ANGPTL4 Volunteer v Untreated Patients

* P < 0.05 ** P <0.01 *** P <0.001
PAN hyperTG present throughout proteinuria and persisted despite normalization proteinuria
Angplt4 Adipose versus NPHS2 rats
Hypertriglyceridemia was absent in Angptl4 mice despite these mice having significant $P<0.001$ proteinuria.
Origins of circulating Angplt4

Mild upregulation in GM subsided day 9

No glomerular upregulation
Test effect of raising plasma FFA levels on nephrotic syndrome
High circulating Angptl4 levels reduce proteinuria
Angplt4 interaction with αγβ5 integrin

• Recombinant normosialylated rat Angplt4 (mimics circulating Angptl4 in nephrotic state) protect cultured endothelial cells from oxidative stress

• Hyposialylated Angplt4 (key mediator of proteinuria that secreted by podocytes in MCD) increased effects of oxidative stress
b

Systemic loop

Glomerular disease

Proteinuria

Urinary loss of albumin with lower FFA content

Hypoalbuminemia

Circulating albumin with higher FFA content

Threshold for nephrotic-range proteinuria

Elevated plasma FFA-to-albumin ratio

Increased entry of FFA into tissues

Upregulation of Angptl4 in skeletal muscle, heart, adipose tissue

Increased circulating Angptl4

Angptl4 binds glomerular endothelial αvβ5 integrin

Angptl4 inhibits endothelial bound LPL activity

Reduced generation of FFA from triglycerides

Hypertriglyceridemia

Local loop
Upregulation of podocyte-secreted angiopoietin-like-4 in diabetic nephropathy

Jing Ma · Xiao Chen · Jian-Si Li · Lei Peng · Shi-Yao Wei · Shi-Lei Zhao · Tong Li · Dan Zhu · Yi-Xin He · Qiu-Ju Wei · Bing Li

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Study Highlights

• Explore effect of Angptl4 on DN
• Streptozotocin induced diabetic model
• Urinary level of angptl4 and relationship with albuminuria
Summary

• Angplt4 plays a role in nephrotic syndrome
• Connection between albuminuria and hypertriglyceridemia
• Role in DN
The End

• Happy Birthday Apra and Mansi