19yo M with C3 Glomerulopathy s/p failed DDRT now w/ ESRD on HD since January 2015

- In 2013, presented to OH with acute onset LE edema and weight gain. Per patient and mother had been in his usual state of health until 2d prior to presentation.

- On arrival, hypertensive to 190/120mmHg w/ creatinine of 1.7

- ROS: negative for fevers/chills, gross hematuria, frothy urine, recent infections, rash, joint pain
WORK-UP

- UA: 300+ protein, large blood
- 24hr UPr: 11.8g
- Albumin: 2.0
- Additional Work-up:
  - C3: 40.1  C4: 31.9  CH50: 21
  - ANA: negative
  - Anti-GBM: negative
  - ASO: 115

- Renal Biopsy: Diffuse, proliferative glomerulonephritis with mainly C3 deposits; 6/24 cellular crescents with minimal sclerosis
- Genetic studies negative for mutations in the alternate complement cascade components.
CLINICAL COURSE

- Unclear what treatment regimen he received following diagnosis but was initiated on HD soon after.
- March 2014 underwent DDRT (16yo donor) with delayed graft function:
  - Urine studies negative for protein and serum complement levels normal; creatinine 3.0
  - Renal allograft biopsy for DGF: Diffuse, proliferative glomerulonephritis with C3 deposits, consistent with recurrent C3 GN.
  - No evidence of acute cellular or antibody mediated rejection.
- July 2014: developed nephrotic range proteinuria and started on Eculizumab.
- October 2014 – admitted with elevated BP, creatinine of 4.0, low C3 and 2g proteinuria:
  - Allograft biopsy: recurrent C3 GN with cellular crescents.
- January 2015: progressive deterioration in renal function and restarted on HD.
Multiple admissions at Bellevue Hospital for shortness of breath – found to have PE now on AC, pericardial effusion w/ cardiac arrest, recurrent PNAs and currently undergoing work-up for pulmonary granulomas
Until recently, clinically classified as either Primary or Secondary MPGN based on a pattern of injury seen on LM and EM.

Increased understanding of underlying pathology has led to a reclassification of MPGN based on IF findings.

MPGN accounts for 7-10% of all cases of biopsy confirmed GN.

Presentation is usually slowly progressive disease with hematuria and non-nephrotic range proteinuria.
thy)

IF, immunofluorescence; MPGN, membranoproliferative GN.
The reclassification of MPGN has led to the emergence of a new spectrum of diseases called C3 glomerulopathies.

MPGN or other proliferative GN (e.g. mesangioproliferative GN or crescentic GN) on LM

- C3 + immunoglobulin on IF
  - Immune-complex-mediated GN
    - Mesangial and intramembranous highly electron-dense deposits on EM → DDD

- C3 alone on IF
  - C3 glomerulopathy: complement alternative pathway-mediated GN
    - Mesangial, subendothelial, subepithelial, and/or intramembranous deposits on EM → C3GN
PATHOGENESIS

- Antibodies
- C3 convertase (C3 nephritic factor)
- Complement regulators
  - Factor H
  - Factor I
  - Factor B
- Mutations in complement regulators
  - Factor H
  - Factor I
  - MCP/CD46
  - CFHR 5
  - CFHR 3-1
- Allele variants
  - Factor H
  - C3
  - MCP
- Mutations in complement factors
- Abnormal C3 convertase activity
- Complement-mediated MPGN
Properdin - positive regulator of the AP and acts as a stabilizer of C3 convertase – in its absence C3 convertase rapidly degrades halting additional amplification of the AP.

- Experimental studies of mice deficient in properdin revealed decrease in C3 glomerular deposits and inflammation

- Genetic mutations in Factor H, I, membrane cofactor protein (MCP/CD46) leading to unrestrained alternative pathway activity have all been described

- CFHR5 nephropathy
  - C3 GN endemic to Cyprus based on study of two families with inherited glomerular disease described 2009 (Licht et al)
  - Mutation in gene encoding complement factor H related protein 5 resulting in a novel CFHR5 that is less effective in associating with surface bound C3b to effectively regulate activity of c3 and c5 convertase
ACQUIRED CAUSES OF AP DYSREGULATION

- **C3 Nephritic Factors**
  - Detected in the serum of 40-50% of patients with C3GN
  - C3Nef is an IgG auto-antibody that directly stabilizes C3-convertase and potentiates its cleaving action and prevents the inhibitory actions of factor H
  - Uncontrolled C3 activation and consumption leads to low serum C3 levels and increased generation of C3 convertase and C5 convertase
  - Often associated with an accompanying genetic abnormality – typically in gene encoding Factor H or autoantibodies to Factor H or I
    - May explain why treatments directed solely at targeting C3Nef have been ineffective
INVESTIGATIONS FOR C3 GLOMERULOPATHY

Investigations of the complement cascade
Measurement of serum complement proteins
- Complement C3
- Complement factor H
- Complement factor I
- Complement factor B

Testing for the presence of C3 nephritic factor
Testing for the presence of anti-factor H autoantibodies

Quantifying CD46 expression on peripheral blood mononuclear cells

Screening for mutations
Genes that encode complement regulators
- CFH (encoding complement factor H)
- CFI (encoding complement factor I)
- CD46 (encoding CD46)
- CFHR1, CFHR2, CFHR3, CFHR4 and CFHR5 (encoding members of the complement factor H-related protein family)

Genes that encode complement activators
- CFB (encoding complement factor B)
- C3 (encoding complement C3)
IMMUNOSUPPRESSIVE AGENTS - in setting of acquired antibodies to an inhibitory protein of the alternative pathway

Plasma exchange with replacement of factor H in cases due to genetic mutations in CFH

Eculizumab

Effective in treatment of PNH and aHUS (conditions that are both marked by alternative pathway dysregulation)
ECULIZUMAB

- A recombinant, monoclonal antibody derived from murine antihuman C5 antibody
- Minimize Fc-mediated functions
- Blockage of the complement cascade at the C5 level preserves early components essential for opsonization and clearance

Zuber, et al; Nature 2012
## ECULIZUMAB IN TREATMENT OF C3 GLOMERULOPATHIES

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C3Nef = C3 nephritic factor; Salb = serum albumin; Scr = serum creatinine. ¹ Creatinine and proteinuria levels were unchanged during 1 year of therapy while repeat allograft biopsies at 6 and 12 months showed continuously active GN with increased chronicity.
ECULIZUMAB IN TREATMENT OF C3 GLOMERULOPATHIES

- Open-label study of Eculizumab therapy in 6 subjects with C3 glomerulopathies (3 with DDD and 3 with C3GN, 3 with disease recurrent in allograft kidney)
- All patients had biopsy proven disease within 6 months of enrollment, >1g protein and >50% increase in baseline creatinine
- Treated with Eculizumab at 900mg IV weekly for 4 weeks and then 1200mg IV weekly for total treatment period of 53 weeks
- Primary endpoint: change in proteinuria or creatinine over treatment period
- Secondary endpoint: changes in renal histopathology after 1 year of therapy

Bomback, et al CJASN 2012
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Baseline characteristics: 25yo M, 162mos from Dx, negative for genetic mutations

Began Eculizumab while on prednisone and cellcept w/ recently increased dosages in setting of rising creatinine from baseline of 1.5 to 2.1, increase in proteinuria from 2.1 to 4.6g/g and biopsy revealing diffuse MPGN

Steroids tapered off at week 16 and cellcept off at week 24 – over the next 24weeks creatinine rose to 2.4 and proteinuria rose to 1.8g/g

Repeat biopsy compared to pre-treatment biopsy revealed increased chronicity with 85% globally sclerotic glomeruli (increased from 50%)
C3GN2

- Baseline characteristics: 22yo M, 138mos from Dx, in native kidney and 8mos in allograft, +C3Nef mutation
- s/p LRRT w/ recurrent disease dx by biopsy 4mos after transplant when proteinuria increased from .1g to 1.4g and increase in creat to 1.9
- Following treatment proteinuria improved while remained stable; Levels of sMAC decreased and remained normal
- Repeat biopsy with less mesangial and endocapillary proliferation
- 7 weeks after discontinuing, creatinine was 8.4 and repeat biopsy revealed recurrent C3GN with crescents – treated with pulse steroids, plasmapheresis and Eculizumab with improvement in creat to 3.8
Baseline characteristics: 20yo M, 14mos from Dx in native kidney and 2mos in allograft, +C3Nef and MCP mutation

s/p LRRT recurrent disease diagnosed by biopsy due to increase in creatinine from 1.3 to 2.2.

Started on eculizumab 2mos later with creat of 1.8 and no proteinuria

Creatinine fell from peak of 2.0 to 1.4 and baseline sMAC level fell to normal range by week 4

No significant change in pre and post treatment biopsies
- 3/6 post-treatment biopsies should improvement in histologic activity
- Pre-treatment biopsy for patient C3GN3 demonstrates positivity for C3 and C5b-9 but no staining for IgG or light chains
- Post-treatment biopsy w/ persistence of C3 and C5b-9 as well as new appearance of IgG and K in same distribution
  - Presence of staining for IgG2, and IgG4 and K expected if eculizumab is binding directly to glomerular mesangium
  - ?persistence of C5-9 may reflect ½ prlonged life of Eculizumab when bound to extracellular matrix
ECULIZUMAB

- Only therapy that has been studied in a prospective trial and limited to 6 patients
- Based off of limited data, optimal candidates are most likely patients that have had a relatively short duration of disease and have shown active disease by renal biopsy with limited fibrosis
- Implications of Ig deposition in context of long-term management unknown
Histologic C3GN recurs in approximately 40-60% of transplanted patients at a median of 28mons post-transplant.

Graft loss reported to be about 50% and occurs at a median of 18months after histologic diagnosis.

Limited data suggests that Eculizumab is effective in treating rapidly progressive / crescentic forms of C3GN recurrent in the renal graft.

Utility of starting it early in patients with history of active/recurrent C3GN.
THANK YOU!