Glomerular Diseases

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Classification of Glomerular Diseases

- Podocyte
  - Focal Segmental Glomerulosclerosis
  - Membranous Nephropathy
  - Minimal Change Disease
  - Poststreptococcal GN
  - HIV-Associated Nephropathy
  - Diabetic Nephropathy

- Glomerular Basement Membrane
  - Alport Syndrome
  - Goodpasture Syndrome

- Glomerular Endothelial Cell
  - Poststreptococcal GN
  - Preeclampsia
  - Thrombotic Microangiopathy
  - Vasculitis

- Glomerular Endothelial and Mesangial Cells
  - Membranoproliferative GN
  - Systemic Lupus Erythematosus

- Mesangial Cell
  - Diabetes Mellitus
  - Fibrillary Glomerulopathy
  - Henoch-Schönlein Purpura
  - IgA Nephropathy
  - IgM Nephropathy
  - C1q Nephropathy
  - Systemic Lupus Erythematosus

*Classically presents with the nephrotic syndrome.
†Often presents with the nephrotic syndrome.
Classification of pathologic and clinical manifestations of glomerular injury

**Histopathologic name**
- Minimal Change Disease
- Focal Segmental Glomerulosclerosis
- Nodular Glomerulosclerosis
- Membranous Nephropathy
- Membranoproliferative GN
- Mesangioproliferative GN
- Proliferative GN
- Crescentic GN

**Clinical name**
- Minimal Change Disease
- FSGS, HIV nephropathy
- Diabetic Nephropathy, Amyloidosis
- Membranous Nephropathy
- MPGN
- IgA Nephropathy
- Post-infections (Post-Strep) GN
- Rapidly Progressive GN (RPGN)
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- Proliferative Glomerulonephritis (PGN)
- Crescentic Glomerulonephritis (CGN)

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Minimal Change Disease
Case presentation

• Bella is a 19 year old high school student referred for proteinuria. She developed edema to thighs 3 wks ago. She has been previously healthy. She takes no medications.
Minimal Change Disease
Case presentation

- **Exam:** BP 101/63, exam normal except for 2+ pitting lower extremity edema bilaterally
- **Labs:** urine prot 4+, alb 2.2, cholesterol 498, creat 0.6
- **Diagnosis:** Nephrotic syndrome
Minimal Change Disease
Case presentation

• Patient started on prednisone 60 mg daily. Returns 1 wk later – edema resolved and urine protein is down to trace.

• **Diagnosis**: Minimal Change Disease
Minimal change disease

- **Definition**: Histopathologic lesion with normal glomeruli on light microscopy and diffuse foot process fusion on electron microscopy, associated with nephrotic syndrome.
Minimal Change Disease

• **Pathogenesis:**
  – leading hypothesis: immune dysfunction/T cell activation leads to release of a cytokine
  – the cytokine (“permeability factor”) targets podocytes disrupting GBM charge barrier and causing proteinuria
Minimal Change Disease, LM

Appears normal
Minimal Change Disease, LM

Proximal tubular epithelial cells filled with lipid and protein ("lipoid nephrosis")
Minimal Change Disease, EM

A) Normal

B) MCD

P - Podocyte
CL - Cell Layer
GBM - Glomerular Basement Membrane
US - Ultrastructure
Minimal Change Disease

• Epidemiology:
  – Most common cause of nephrotic syndrome in children
  – Less common in adults

• Ethiology:
  – Primary - idiopathic
  – Secondary:
    • Drugs: NSAIDs
    • Tumors: lymphomas
    • Immune modulation: vaccinations
Minimal Change Disease

- **Clinical characteristics and treatment:**
  - Abrupt onset of florid nephrotic syndrome
  - Normal blood pressure
  - Renal function usually remains good
  - 90% respond rapidly to corticosteroids, adults are slower to respond than children
  - Relapses are characteristic and respond to re-treatment
Minimal Change Disease

- **Clinical characteristics and treatment:**
  - Frequently relapsing or steroid-resistant cases respond to other immunosuppressive agents (mycophenolate, cyclosporine, cyclophosphamide)
  - Some become steroid dependent until puberty, when most cases finally remit
  - Long term prognosis is **excellent**
Minimal Change Disease
Case follow-up

- Patient was treated with a 4 months prednisone taper with complete resolution of proteinuria. However, 1 mo after stopping prednisone, her proteinuria increased to 3+, which indicated a relapse. Started on CellCept (Mycophenolate), again with resolution of proteinuria after 1 wk. Pt then treated with CellCept x 1 year. She remains in complete remission.
Classification of pathologic and clinical manifestations of glomerular injury

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Focal Segmental Glomerulosclerosis Case presentation

• Laurent is a laboratory technician who has diagnosed himself with nephrotic syndrome.
Focal Segmental Glomerulosclerosis
Case presentation

• He is a 45 year old African American male w h/o HTN, who developed progressively increasing lower extremity edema for the past 6 mo
Focal Segmental Glomerulosclerosis

Case presentation

• He was seen by his PCP several times, and his medications were adjusted. However, in spite of proteinuria on UA, no diagnosis was made.

• **Medications**: verapamil and lasix

• **On exam**, his BP is 145/91, remainder unremarkable except for tight 4+ LE edema
Focal Segmental Glomerulosclerosis
Case presentation

• **Labs** 9 mo prior:
  – 2+ protein on UA
  – serum albumin 4
  – cholesterol 300, LDL 180

• **Current labs:**
  – serum albumin 2.8
  – cholesterol 396, LDL 270 and
  – creatinine 1.2
  – Urinalysis 4+ protein and a few granular casts
  – Urine protein/creatinine ratio 12
Focal Segmental Glomerulosclerosis
Case presentation

• **Diagnosis**: Nephrotic syndrome

• Kidney biopsy was performed, demonstrating focal segmental glomerulosclerosis
Focal Segmental Glomerulosclerosis

- **Definition**: Histopathologic lesion with sclerosis of some but not all (hence focal) glomeruli that involves a portion (segment) of the glomerular tuft.

![Diagram: Normal vs. FSGS](image-url)
Focal Segmental Glomerulosclerosis

• Ethiology and pathogenesis:
  – Primary:
    • presumed due to a circulating factor (?cytokine) that damages VEC
  – Secondary (associated with other conditions):
    • HIV, heroin abuse, sickle cell disease, massive obesity.
    • maladaptive response to nephron loss
  – Inherited
    • linked to mutations of the VEC proteins nephrin, podocin etc, causing “podocytopathy”.
Secondary Focal Segmental Glomerulosclerosis
Focal Segmental Glomerulosclerosis

- **Morphology:**
  - Sclerotic segments show basement membrane collapse, increased matrix, trapping of plasma proteins in glomerular capillary walls by light microscopy
  - Pronounced tubular atrophy and interstitial fibrosis
Focal Segmental Glomerulosclerosis

segmentally collapsed

unaffected
Focal Segmental Glomerulosclerosis

Effacement of VEC in sclerotic and non-sclerotic segments by EM; no deposits.

GBM collapse and foot process fusion

less affected segment
Focal Segmental Glomerulosclerosis

- **Epidemiology:** most common cause of primary nephrotic syndrome in African-American adults

- **Clinical characteristics:**
  - Nephrotic syndrome (primary disease or HIV nephropathy) or nephrotic range proteinuria (most secondary forms)
  - **Proteinuria is non-selective** in contrast with minimal change disease
  - Hypertension, reduced GFR
  - **Slow and variable** response to steroids
  - Progression to chronic glomerulosclerosis; 50-80% to ESRD within several years
  - Children have better prognosis than adults
  - Recurrence post transplant is common in idiopathic FSGS leading to graft failure
Focal Segmental Glomerulosclerosis

- **Treatment:**
  - Only idiopathic FGSG has a chance to respond to immunosuppressive treatment. Therefore, it is imperative to determine whether the disease is primary or secondary.
  - Primary disease:
    - Steroids
    - Immunosuppressive cytotoxic agents - Cyclosporine, Tacrolimus, Mycophenolate
  - Primary and secondary disease:
    - ACE/ARB and anti-lipid agents
  - HIV-associated FSGS
    - Antiretroviral medications
Focal Segmental Glomerulosclerosis
Case follow-up

- Patient was started on prednisone. Two weeks later he was admitted with bacteremia. His prednisone was tapered and he was started on cyclosporine. Patient was unable to tolerate medication, switched to CellCept. This medication was stopped after several months due to lack of efficacy.
Focal Segmental Glomerulosclerosis
Case follow-up

- His proteinuria increased to 40 g/24 hrs, and serum creatinine progressively increased to 3. Patient failed other immunosuppressive medications, and had multiple infectious complications. He also had severe complications of nephrotic syndrome – resistant anasarca, deep venous thrombosis from hypercoagulable state, pericardial effusion, and chronic hypotension due to low plasma oncotic pressure.
Focal Segmental Glomerulosclerosis
Case presentation

• He was started on dialysis to control edema, but could not tolerate fluid removal due to hypotension. After hospitalization that lasted 4 months, patient finally agreed to have bilateral renal artery embolization, a procedure called “chemical nephrectomy”. He is now hemodialysis-dependent, and has much improved clinically.
Now let’s see if you’ve been paying attention...
Patient has nephrotic syndrome, biopsy below. Which statement about this disease is INCORRECT:

A. It is the most common cause of nephrotic syndrome in children
B. It is characterized by sudden onset of florid nephrotic syndrome
C. It is poorly responsive to steroids
D. It can be caused by NSAIDs
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Membranous Glomerulonephropathy
Case presentation

• Jacob is a 25 yo previously healthy hospital security guard, who was referred for evaluation of proteinuria.
Membranous Glomerulonephropathy
Case presentation

- He noticed LE edema several weeks prior. He was hypertensive at 155/90. His serum creatinine was 0.9, alb 2.2, cholesterol 311 w LDL 173, Urine - 5g protein/24 hrs.
Membranous Glomerulonephropathy  

Case presentation

• **Kidney biopsy** showed Membranous Glomerulopathy.

• **Clinical course**: patient was treated with an immunosuppressive regimen consisting of prednisone and cyclophosphamide for 6 months, and responded with markedly decreased proteinuria (0.5 g/24 hrs). He was seen in follow-up several years later and had trace proteinuria and normal creatinine.
Membranous Glomerulonephropathy

• **Definition:** Histopathologic lesion characterized by glomerular basement membrane thickening due to immune complex entrapment, associated with nephrotic syndrome
Membranous Glomerulonephropathy

**Pathogenesis:** A chronic immune-complex nephritis caused by:

- Ab directed against intrinsic GBM Ag (primary)
- Circulating immune complex entrapment in the GBM (secondary)

Both activate complement, which damages podocytes and makes them leaky
Pathogenesis of primary membranous GN

[Diagram showing the process of antibody-antigen interaction and immune complex formation leading to membranous glomerulopathy]
Membranous Glomerulonephropathy

- **Pathology:** *light microscopy:* diffuse, uniform thickening of basement membrane with small subepithelial projections ("spikes") of basement membrane in capillary loops.
Membranous Glomerulonephropathy, LM
Membranous Glomerulonephropathy, LM

“Spike” formation on subepithelial (urinary) side of GBM, (silver stain)
Membranous Glomerulonephropathy, LM

normal
Membranous Glomerulonephropathy, IF

- *Immunofluorescence microscopy*: diffuse, coarsely granular pattern to IgG along capillary loops.

![Immunofluorescence images](image-url)
Membranous Glomerulonephropathy, EM

Subepithelial electron-dense immune deposits
Membranous Glomerulonephropathy, EM
Membranous Glomerulonephropathy

• **Epidemiology:**
  – most common cause of primary nephrotic syndrome in **Caucasian** adults

• **Ethiology:**
  – Primary
  – Secondary:
    • Drugs: penicillamine, captopril, gold
    • Malignancy (solid tumors)
    • Infection: hepatitis B, syphilis
    • Autoimmune disease: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA)
Membranous Glomerulonephropathy

• **Clinical features:**
  – insidious onset of nephrotic syndrome, usually without identifiable preceding illness;
  – variable, but often indolent course

• **Prognosis:** “Rule of thirds” (without treatment):
  – 1/3 – Spontaneous remission
  – 1/3 – Partial remission / slow deterioration
  – 1/3 – Progress to ESRD
Membranous Glomerulonephropathy

• Predictors of poorer outcome are:
  – tubulointerstitial fibrosis
  – elevated cr at diagnosis
  – male sex
  – hypertension
  – older age
  – and heavy proteinuria.

• Treatment:
  – Steroids alone are not very effective
  – Prednisone alternating with Cyclophosphamide
  – Cyclosporin
Now let’s see if you’ve been paying attention...
Patient has nephrotic syndrome and biopsy is depicted below. Which statement is INCORRECT:

A. It is the most common cause of idiopathic nephrotic syndrome in African American adults
B. It is characterized by slow and variable response to steroids
C. It can be associated with HIV
D. This disease does not affect podocytes
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### Classification of pathologic and clinical manifestations of glomerular injury

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Histopathologic name: Membranoproliferative Glomerulonephritis

Clinical name: Membranoproliferative Glomerulonephritis
Membranoproliferative Glomerulonephritis (Type I)
Case presentation

• Jasper is a 48 year old Caucasian male with h/o polysubstance abuse.
Membranoproliferative Glomerulonephritis (Type I)
Case presentation

• He was admitted to the hospital with generalized swelling, hypertensive urgency and pulmonary edema. He was homeless, but is currently living at Rubicon drug treatment center.
Membranoproliferative Glomerulonephritis (Type I)
Case presentation

• His serum cr in 2, serum albumin is 2.5, urine protein to creatinine ratio is 10, UA showed proteinuria and hematuria. Further workup revealed that patient is positive for hepatitis C and cryoglobulins.
Membranoproliferative Glomerulonephritis (Type I)
Case presentation

• Kidney biopsy revealed membranoproliferative glomerulonephritis (MPGN), type I.
• Patient was not a candidate for treatment due to poor social situation and history of non-compliance. His renal function has deteriorated and he became dialysis-dependent within 6 months.
Membranoproliferative Glomerulonephritis (Type I)

- **Definition:** histopathologic lesion characterized by mesangial proliferation and interposition into the glomerular capillary wall with double contours ("tram tracking") of GBM on light microscopy
Membranoproliferative Glomerulonephritis (Type I)

- **Pathogenesis**: deposition of subendothelial immune complexes in glomerulus with abnormal activation of complement, production of “nephritic factors” and glomerular injury
Mesangial interposition into GBM in MPGN
Membranoproliferative Glomerulonephritis (Type I)

Light microscopy: glomerular hypercellularity and lobular simplification
Membranoproliferative Glomerulonephritis (Type I)

Light microscopy: splitting of GBM ("tram-track") is characteristic
Membranoproliferative Glomerulonephritis (Type I)

Immunofluorescence: coarse granular staining of IgG and C3 along capillary loops
Membranoproliferative Glomerulonephritis (Type I), EM

Electron Microscopy: subendothelial deposits with new formation of GBM (splitting)
Membranoproliferative Glomerulonephritis (Type I), EM, LM
Membranoproliferative Glomerulonephritis (Type I)

• **Epidemiology:**
  – Primary – children and young adults, rare
  – Secondary – adults, more common

• **Ethiology:**
  – Primary (idiopathic)
  – Secondary (seen in association with other disorders)
    • SLE, hepatitis C (often with cryoglobulinemia), endocarditis
    • Malignancy (lymphoma, leukemia)
Membranoproliferative Glomerulonephritis (Type I)

• **Clinical characteristics**
  – Nephrotic/nephritic
  – Depressed serum complement levels
  – Few remissions, usually unrelenting course
  – 50% with renal failure in 10 years
Membranoproliferative Glomerulonephritis (Type I)

• **Treatment:**
  – Primary in children – immunosuppression
  – Secondary – treat the original disease (antiviral or antibacterial agents), antiplatelet agents, immunomodulation in some cases
Now let’s see if you’ve been paying attention...
Which statement regarding the disease with LM/IF below is INCORRECT:

A. This is the most common cause of primary nephrotic syndrome in Caucasian adults
B. 2/3 of patients will develop spontaneous or partial remission without treatment
C. Can be associated with solid tumors
D. EM would show reduplication of GBM with “tram tracking”
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IgA Nephropathy (Berger’s Disease)
Case presentation

• Alice is a 24 year old white female with history of hypertension, who is 16 wks pregnant. She is referred by her OB for proteinuria, hematuria and hypertension. Patient has a history of gross hematuria following upper respiratory infections.
IgA Nephropathy
Case presentation

• Her BP is 155/90, she has trace LE edema, and her UA shows 3+ protein and 20 rbc. Her renal function is normal. She is managed conservatively with labetalol for BP control and bed rest. Her proteinuria is monitored and remains stable throughout the pregnancy. She is delivered via C-section at 37 weeks gestation.
IgA Nephropathy
Case presentation

• 6 weeks post-partum her proteinuria remains unchanged at 3g/24 hrs. Kidney biopsy is performed and shows IgA nephropathy with 50% glomerulosclerosis and moderate interstitial fibrosis. She is started on ACE-I, fish oil and prednisone, but then lost to follow-up.
IgA Nephropathy

• **Definition:** Histopathologic lesion of a glomerulonephritis characterized by prominent IgA–containing immune deposits in the mesangium.
IgA Nephropathy

• **Pathogenesis:**
  – Error of IgA production and clearance
    • abnormally high production of mucosal and marrow IgA in response to an environmental Ag
    • abnormal glycosylation reduces plasma clearance of IgA by the liver
    • IgA deposition as immune complexes in the mesangium; there it activates complement.
IgA Nephropathy
IgA Nephropathy

LM: Mesangial hypercellularity and matrix expansion
IgA Nephropathy

- IF: mesangial IgA, diffuse and granular, in “pruned bush” pattern
IgA Nephropathy, LM, IF
IgA Nephropathy

EM: mesangial immune deposits
IgA Nephropathy

• **Epidemiology:** the most common primary GN worldwide

• **Clinical features:**
  
  • The classic presentation is **gross hematuria**, occurring **coincidentally** with a **upper respiratory infections**. Hematuria subsides and recurs every few months.

  • In the background, there is indolent development of mild nephritic or nephrotic features

  • Very rarely develops crescentic RPGN
IgA Nephropathy

• May be associated with Henoch-Schoenlein purpura, a systemic disorder of children that includes purpuric skin lesions, abdominal pain and arthralgia.

• Prognosis: variable, with many patients maintaining normal renal function for many years; but slow progression to chronic renal failure in 40%. Recurrence post-transplant is frequent.
Now let’s see if you’ve been paying attention...
Which diagnosis can you suspect from the light microscopy below:

A. Membranous nephropathy
B. Minimal change disease
C. FSGS
D. Membranoproliferative Glomerulonephritis (MPGN)
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Acute Post-Streptococcal Glomerulonephritis
Case presentation

• Edward is transferred to VCU from outside hospital for acute glomerulonephritis. He is an 18 year old Caucasian male with h/o tonsillectomy at age 5.
Acute Post-Streptococcal Glomerulonephritis
Case presentation

• Ten days prior to admission he had strep throat with positive rapid strep test, and was started on augmentin by his PCP.
Acute Post-Streptococcal Glomerulonephritis
Case presentation

• He was referred for admission after he developed tea colored urine, and was found to have hematuria, proteinuria and HTN. Pt reports 20 lbs wt gain in 3 days w periorbital and upper body edema, and abdominal pain. He now denies any sore throat.
Acute Post-Streptococcal Glomerulonephritis
Case presentation

• **SH** is significant for tobacco, alcohol and marijuana use

• **Exam**: BP 175/77, ps 49. Young athletic wm in no acute distress. Lungs were clear and heart was regular, with 2/6 systolic murmur at base. Abdomen was soft, diffusely tender, with liver and spleen edges palpable. Trace LE edema. No rash.
Acute Post-Streptococcal Glomerulonephritis

Case presentation

• **Labs** showed cr 1.3, albumin 2.7, urinalysis 178 rbc and 25 wbc, 3+ protein and several red blood cell casts. ASO titer and streptozyme were positive. C3 complement level was low.

• **Diagnosis**: Acute post-streptococcal GN.
• Due to worsening renal function, we performed renal biopsy, which confirmed the above diagnosis. Patient was treated with diuretic and ace inhibitor. Patient’s condition improved and he was discharged with follow-up in renal clinic.
Acute Post-Streptococcal Glomerulonephritis

Case presentation

• His creatinine normalized after 1 mo. After 4 months, he was off antihypertensives, however his UA still showed 3+ blood and 2+ protein. He was lost to follow-up since that visit.
Acute Proliferative (Poststreptococcal, Postinfectious) GN

• **Definition**: acute nephritic syndrome that develops following infection by nephritogenic strains of strep or other organisms
Acute Proliferative (Poststreptococcal, Postinfectious) GN

• Epidemiology and ethiology:
  – Most common GN in children
  – Incidence declines with age
  – Usually 1 – 4 weeks post infection caused by nephritogenic strains of strep (usually group A strep)
  – Also reported with pneumococcal and staphylococcal infections, some viral diseases (mumps, measles, chickenpox, and hepatitis B and C).
Acute Proliferative (Poststreptococcal, Postinfectious) GN

• **Clinical features:**
  – history of infection 1-4 wks prior
  – abrupt onset of nephritic syndrome
  – oliguria
  – hematuria (*tea-colored urine*)
  – edema
  – hypertension
  – azotemia
Acute Proliferative (Poststreptococcal, Postinfectious) GN

- urinalysis usually reveals proteinuria, red cells, white cells, and casts
- High antistreptolysin O (ASO) titers in post-streptococcal cases
Acute Proliferative (Poststreptococcal, Postinfectious) Glomerulonephritis

- **Pathogenesis**: Deposition of immune complexes in capillary loops, with complement (C3) activation. Implicated are “planted” antigens, like endostreptosin and nephritis-associated plasmin receptor.
Postinfectious Glomerulonephritis Capillary Viewed by Electron Microscopy (top right) and High Magnification Light Microscopy (bottom)

Normal glomerular capillary

- Neutrophils
- Hump-like Subepithelial Immune Complex Deposits
Acute Proliferative (Poststreptococcal, Postinfectious) GN

- **Pathology:** *light microscopy:* enlarged, hypercellular glomeruli with endothelial and mesangial cell proliferation. Neutrophils may be present. Crescents may be seen.
Acute Proliferative (Poststreptococcal, Postinfectious) GN
Acute Proliferative (Poststreptococcal, Postinfectious) GN

- *Immunofluorescence microscopy*: coarsely granular ("lumpy-bumpy") pattern along capillary loops.
Acute Proliferative (Poststreptococcal, Postinfectious) GN

- *Electron microscopy*: subepithelial "hump-like" deposits.
Acute Proliferative (Poststreptococcal, Postinfectious) GN
Acute Proliferative (Poststreptococcal, Postinfectious) GN

- **Treatment**: supportive
  - Diuretics
  - Antihypertensives
  - Antibiotics do not change course in post-strep GN

- **Prognosis**:
  - majority (especially children) become clinically asymptomatic
  - some may develop rapidly progressive GN
  - adults can progress to chronic GN
Now let’s see if you’ve been paying attention...
This IF staining pattern is most likely to be seen in:

A. RPGN
B. Membranous nephropathy
C. IgA nephropathy
D. FSGS
This IF staining pattern is most likely to be seen in:

A. RPGN
B. Membranous nephropathy
C. IgA nephropathy
D. FSGS
Classification of pathologic and clinical manifestations of glomerular injury

**Histopathologic name**
- Minimal Change Disease
- Focal Segmental Glomerulosclerosis
- Nodular Glomerulosclerosis
- Membranous Nephropathy
- Membranoproliferative GN
- Membranoproliferative GN
- Mesangio proliferative GN
- Proliferative GN
- Crescentic GN

**Clinical name**
- Minimal Change Disease
- FSGS, HIV nephropathy
- Diabetic Nephropathy, Amyloidosis
- Membranous Nephropathy
- MPGN
- IgA Nephropathy
- Post-infections (Post-Strep) GN
- Rapidly Progressive GN (RPGN)

**Nephritic**

**Nephrotic**
Classification of pathologic and clinical manifestations of glomerular injury

**Histopathologic name**

- Minimal Change Disease
- Focal Segmental Glomerulosclerosis
- Nodular Glomerulosclerosis
- Membranous Nephropathy
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- Proliferative GN
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**Clinical name**

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- Rapidly Progressive GN

**Nephrotic**

**Nephritic**
Rapidly Progressive Glomerulonephritis
Case presentation

• Carlisle is a 50 year old Caucasian male who is transferred from outside hospital for rapidly progressive renal failure with hematuria and proteinuria.
Rapidly Progressive Glomerulonephritis
Case presentation

• He was very fit and healthy until several weeks prior to admission, when he developed a protracted upper respiratory illness requiring several visits to PCP and emergency rooms and several courses of antibiotics.
Rapidly Progressive Glomerulonephritis
Case presentation

• He was finally admitted after he was found to have bilateral pulmonary infiltrates, gross hematuria and elevated creatinine. His condition deteriorated and he required mechanical ventilation for acute respiratory failure.

• Bronchoscopy was consistent with pulmonary hemorrhage.
Rapidly Progressive Glomerulonephritis
Case presentation

- His renal function deteriorated and he was started on hemodialysis.
- His C-ANCA were positive at high titer.
- Kidney biopsy was performed and showed crescentic pauci-immune glomerulonephritis.
- **Diagnosis:** Granulomatosis with polyangiitis, with alveolar hemorrhage and rapidly progressive glomerulonephritis.
Rapidly Progressive Glomerulonephritis
Case presentation

• Clinical course: He was treated with intravenous steroids, cyclophosphamide and plasmapheresis with gradual improvement in respiratory and renal function. He recovered completely.
Rapidly Progressive Glomerulonephritis

• **Definition:** acute nephritic syndrome associated with rapidly deteriorating renal function (over weeks). Histopathologically this is crescentic GN.

• **Ethiology:**
  1. Anti-GBM disease
  2. Immune complex-mediated crescentic GN (any GN that has gone severe - lupus nephritis, post-infectious GN, IgA nephropathy)
  3. Pauci-immune GN (vasculitic diseases –Granulomatosis with Polyangiitis, Microscopic Polyangiitis)
Rapidly Progressive (Crescentic) Glomerulonephritis

- **Clinical features**: Rapid and progressive loss of renal function with severe oliguria and death within weeks to months in untreated cases.

- **Treatment**: heavy immunosuppression with steroids and cytotoxic agents (cyclophosphamide, mycophenolate), many times plasmapheresis is used to remove anti-GBM antibodies quickly.

- **Prognosis**: May be related to the number of crescents; those with >80% crescents do more poorly. Recurrence post-transplant is unusual.
Rapidly Progressive (Crescentic) Glomerulonephritis
Rapidly Progressive (Crescentic) Glomerulonephritis, LM
Crescentic GN is a histopathologic equivalent for RPGN

- Type I – Anti-GBM disease
- Type II – Immune-complex GN
- Type III – Pauci-immune GN
Anti-GBM Disease, pathogenesis

Anti-GBM disease is caused when anti-GBM antibodies bind to capillary basement membranes and attract and activate white blood cells (such as neutrophils). This causes the white blood cells to attack vessel walls resulting in vessel wall inflammation (glomerulonephritis and alveolar capillaritis).

Blood vessel (capillary) wall  Neutrophil type of white blood cell

Inflammation of the vessel wall caused by white blood cells that have been stimulated by anti-GBM bound to capillary basement membranes (GBM)
Anti-GBM Disease
Anti-GBM Disease

- IF reveals linear (not granular) deposition of IgG and C3 along the GBM
- EM shows no deposits
Anti-GBM Disease
Anti-GBM Disease

- In some cases IgG and C3 may also bind the pulmonary alveolar capillary basement membranes, producing a syndrome (Goodpasture’s syndrome) of pulmonary hemorrhage and renal failure.
Crescentic GN type II, Immune-Complex-Mediated GN

- May be associated with any immune-complex type GN including SLE, IgA nephropathy, or postinfectious GN.
Immune-Complex-Mediated Crescentic GN

- IF will reveal a coarse, granular or “lumpy-bumpy” staining pattern. Treatment is directed at the underlying disease.
Immune-Complex-Mediated Crescentic GN

- EM usually shows deposits
Crescentic GN type III, Pauci-Immune GN

• **Pauci-immune GN** shows no antibodies or immune-type complexes in the kidney either by IF or EM. Diagnostic antibodies are in the plasma, and are called Anti-Neutrophil Cytoplasmic Antibodies (ANCA)

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C-ANCA  P-ANCA
Pauci-Immune GN

- Feature of Granulomatosis with Polyangiitis (GPA), Microscopic Polyangiitis (MPA), or other vasculitic diseases.
Pauci-immune GN

Inflammation of the vessel wall (vasculitis) caused by white blood cells that have been stimulated by ANCA.
# Crescentic GN (RPGN)

<table>
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<th>Pathogenesis</th>
<th>Anti-GBM GN (I)</th>
<th>Immune-complex GN (II)</th>
<th>Pauci-immune GN (III)</th>
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<tr>
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<td>Anti-GBM Ab to type IV collagen</td>
<td>Circulating immune complexes</td>
<td>Ab against neutrophils (ANCA)</td>
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<td>Clinical examples</td>
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<td>Severe Lupus Nephritis, severe Post-Strep GN</td>
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<td>Crescents</td>
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<td>IF</td>
<td>Linear IgG</td>
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<tr>
<td>EM</td>
<td>No deposits</td>
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Now let’s see if you’ve been paying attention...
Which statement regarding the disease depicted on electron micrograph below is INCORRECT:

A. This disease has poor prognosis
B. This disease is treated in supportive fashion with diuretics and antihypertensives
C. Light microscopy would show proliferative GN
Which statement regarding the disease depicted on electron micrograph below is INCORRECT:

A. This disease has poor prognosis
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C. Light microscopy would show proliferative GN
Chronic Glomerulonephritis (CRGN)

- Poststreptococcal GN
- Crescentic GN
- Membranous nephropathy
- Focal segmental glomerulosclerosis
- Membranoproliferative GN
- IgAN
- Others
Chronic Glomerulonephritis (CRGN) Case presentation

• Emmett is a 25 year old student with history of HTN self-referred to renal clinic to have his “kidneys checked”.
Case presentation

• He reports that he was seen by a private nephrologist in town 2 years prior and had a kidney biopsy, which showed “chronic changes”. He did not have insurance and could not afford to pay medical bills, therefore he has not followed up. He is not taking any medications.
Chronic Glomerulonephritis (CRGN)
Case presentation

- Patient is asymptomatic
- PE: BP170/110, trace LE edema.
- Labs BUN 55, creatinine 6.2
- UA 3+ protein, 5 rbc per hpf, and some broad granular casts.
- Renal ultrasound: 8.5 cm kidneys bilaterally with thin echogenic cortex.
- **Diagnosis**: chronic glomerulonephritis
Chronic Glomerulonephritis (CRGN)

- **Pathology**: kidneys are grossly shrunken, and microscopically show significant and widespread global glomerular sclerosis, with interstitial fibrosis and tubular atrophy, “end-stage kidney”.
Chronic Glomerulonephritis (CRGN)

- **Epidemiology**: an important cause of end-stage renal disease. It is usually first noted in young to middle-age adults.
- **Pathogenesis**: usually at time of diagnosis, glomerular changes of CRGN are so far advanced that determination of exactly how they became sclerotic is impossible to work out. It may therefore be the end-stage of such processes as FSGS, MGN, RPGN, or MPGN.
Chronic Glomerulonephritis (CRGN)

• **Clinical features**: usually insidious onset, and discovered late in its course with renal insufficiency. Patients usually have edema, HTN and heavy proteinuria.
Chronic Glomerulonephritis (CRGN)

• **Treatment**
  – Control of BP
  – Use of ACE inhibitor
  – Control of hyperlipidemia
  – Avoidance of other nephrotoxic substances
  – Cessation of smoking
Chronic Glomerulonephritis (CRGN)

- **Prognosis**: poor renal prognosis and patient needs to be prepared for dialysis or kidney transplantation
Now let’s see if you’ve been paying attention...
Look at biopsy slides below. Which statement about this disease is INCORRECT:

A. Plasmapheresis should be started to remove circulating antibodies
B. This disease can be associated with pulmonary hemorrhage
C. This disease is associated with Antinuclear Cytoplasmic antibodies (ANCA)
D. This disease clinically presents as RPGN
Look at biopsy slides below. Which statement about this disease is INCORRECT:

A. Plasmapheresis should be started to remove circulating antibodies
B. This disease can be associated with pulmonary hemorrhage
C. **This disease is associated with Antinuclear Cytoplasmic antibodies (ANCA)**
D. This disease clinically presents as RPGN
THE END

YOU MADE IT!