REVISE
NEPHROLOGY

Glomerulonephritis

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Learning points

- Difference between nephrotic syndrome and glomerulonephritis (GN)
- What is dysmorphic RBC and RBC cast
- Classification of GN and work-up
- Infection related GN (staph versus strep GN), IgA nephropathy, Goodpasture disease and Alport's syndrome
- Rapidly progressive GN
- *ANCA positive GN covered in the vasculitis talk*

Nephrotic and nephritic syndromes are glomerular pathologies……what is the difference?

- Nephrotic syndrome: increased glomerular permeability to proteins causing >3.5 g proteinuria/24 hours, hypoalbuminemia and edema
- Nephritis/GN : **glomerular inflammation** causing hematuria with dysmorphic RBCs/RBC casts, reduced GFR, non-nephrotic proteinuria, edema, hypertension
- GN may be smouldering and slowly progressive or rapidly progressive (days, weeks or months) and associated with extensive crescent formation i.e. rapidly progressive glomerulonephritis (RPGN)

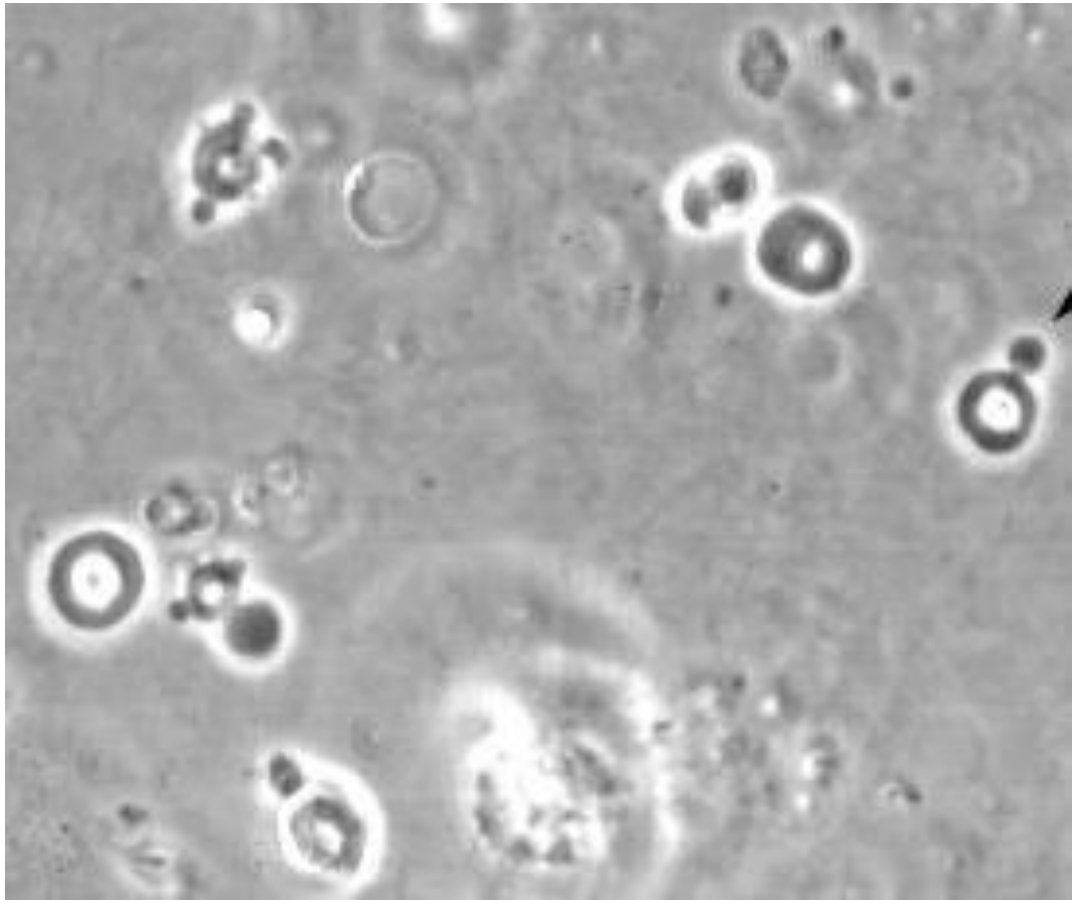
NOTE: Microscopic hematuria is >2 RBCs per high power field in spun urine

Dysmorphic RBCs >5% of total urinary RBCs to diagnose nephritis/GN

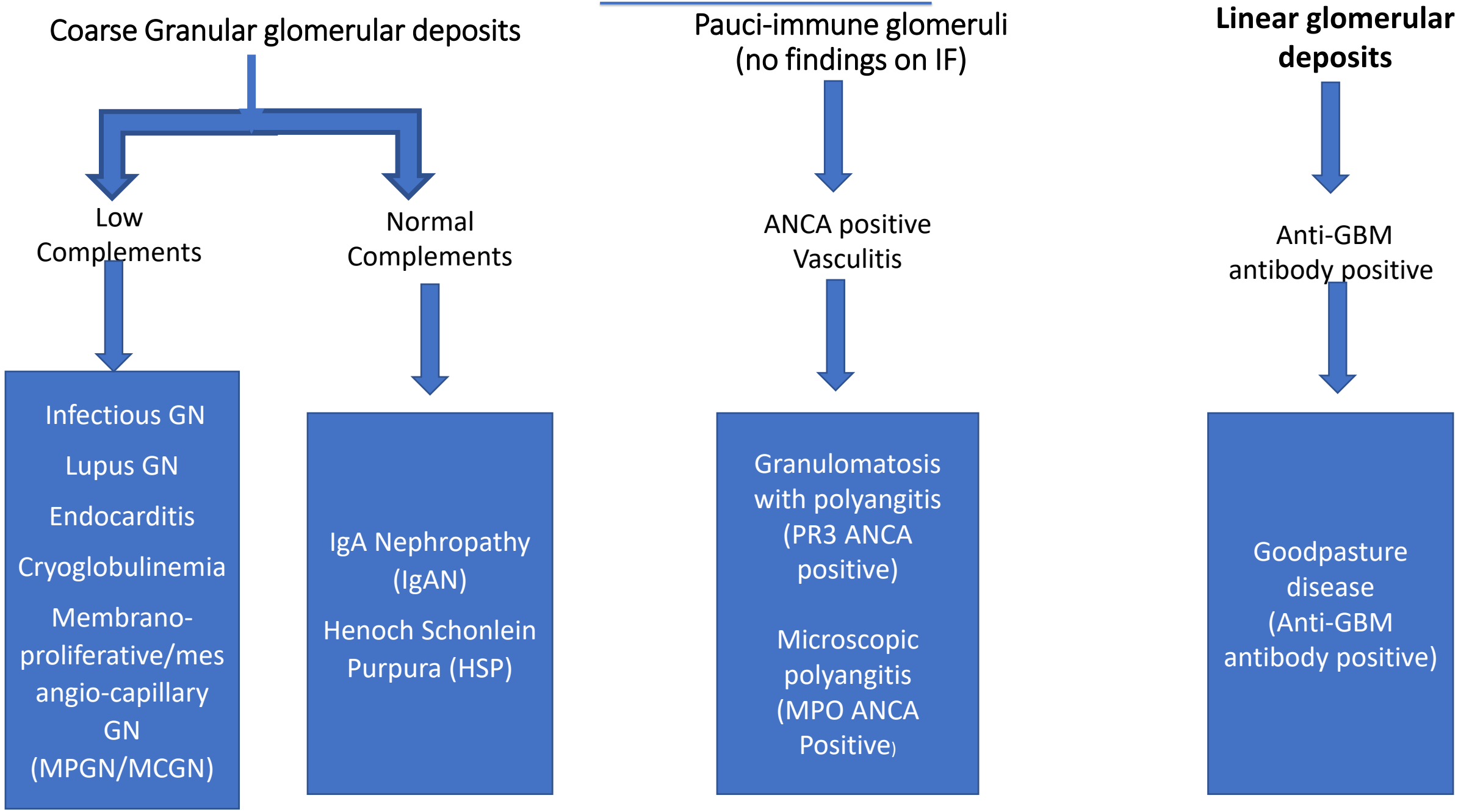
What is dysmorphic RBC and RBC cast?

- Mechanical damage caused by passage of RBC through the GBM followed by osmotic injury sustained by RBCs during passage through the hypotonic tubular segment cause ***dysmorphic RBC***
- RBC casts are RBCs embedded in Tamm-Horsfall protein (THP) which is secreted by the TAL cells and is the most abundant protein in urine

Picture of dysmorphic RBC



GN CLASSIFICATION



GN workup

–**Serum complements** (low in post-infectious nephritis, lupus nephritis, nephritis associated with endocarditis and cryoglobulinemia)

-**Blood cultures and antistreptococcal antibodies** in case of suspicion of post infectious GN when there is history of preceding pharyngitis or impetigo

– **ANA, ENA, Ds-DNA** to exclude lupus nephritis

– **Hepatitis and myeloma screen** (to exclude cryoglobulinemic nephritis and mesangio-capillary glomerulonephritis)

– **ANCA** (rule out vasculitis e.g.PR3 ANCA positive granulomatosis with polyangitis and MPO ANCA positive microscopic polyangitis)

-**Anti-GBM antibody** to rule out Goodpasture syndrome

Infection Related GN rather than Post Infectious GN

- Often refers to post-streptococcal (common in children) **but** in adults Staphylococcus associated GN as common
- Although PSGN continues to be the most common cause of acute nephritis in children globally, it primarily occurs in resource-limited countries
- Post-streptococcal GN occurs 2 weeks after skin or pharyngeal infection while staphylococcus associated GN occurs simultaneously with infection (so...infection related GN and NOT post-infectious GN)
- **Group A** beta-hemolytic **streptococcus or streptococcus viridans (27.9%), staphylococcus (24.4%)** and others- salmonella, E.coli, leptospira, trepanoma , HIV, EBV, CMV, mumps, influenza, Histoplasma, candida, plasmodium etc.
- Staph GN commoner in elderly, diabetics and alcoholics and >half develop CKD or ESRD (unlike excellent prognosis in post-step GN)

Infection Related GN

- Hypocomplementemia (usually low C3 with normal C4 suggest activation of alternate pathway)
- Biopsy:

- LM : glomerulus LOOKS full of cells with paucity of open capillaries

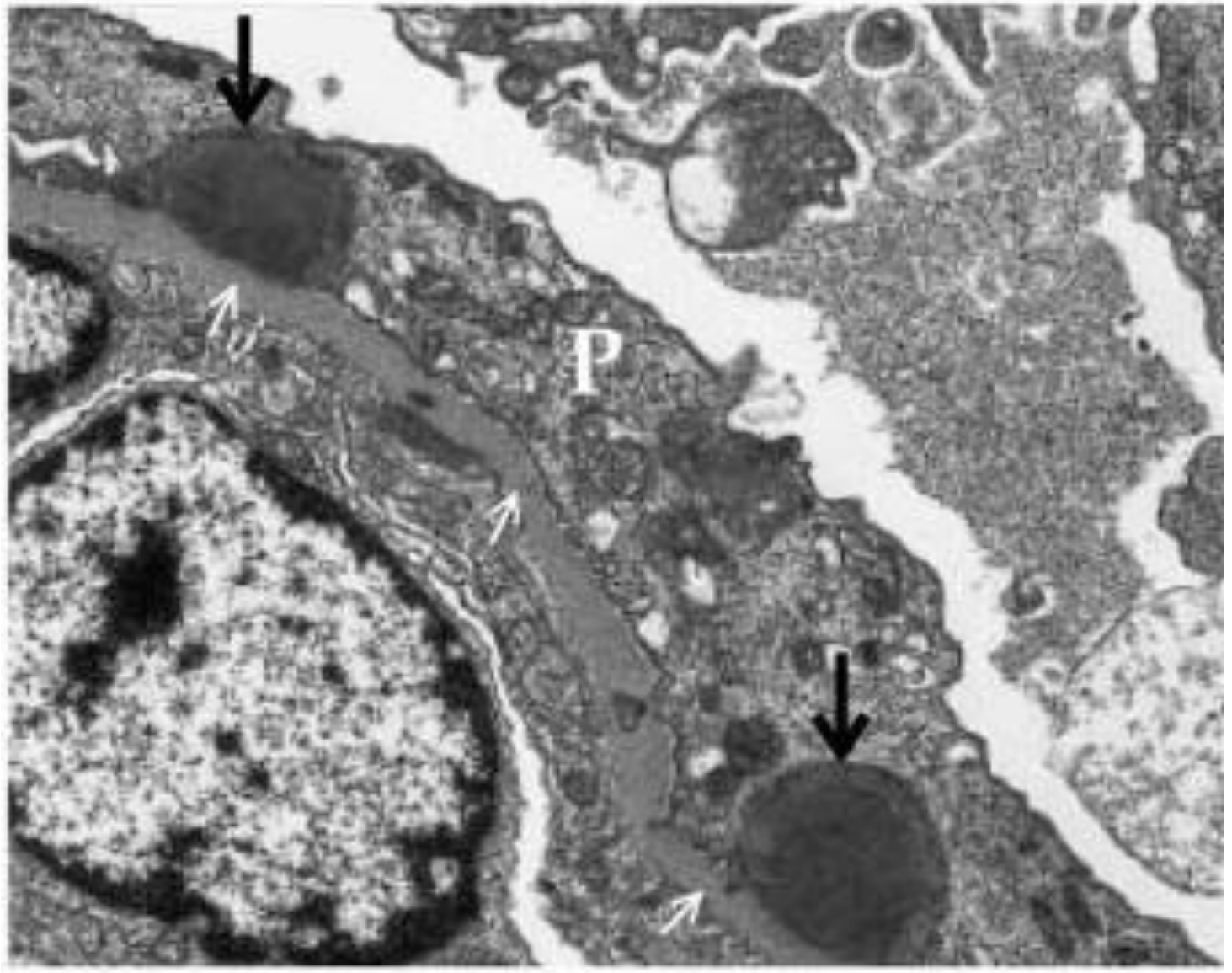
(diffuse endocapillary GN i.e. capillaries full of neutrophils and proliferation of endothelial and mesangial cells)

- EM shows **hump shaped sub-epithelial deposits** (NOT the spike and dome feature of subepithelial deposits in membranous nephropathy)

- IF shows **C3 dominant staining**(100%) with/without IgG, IgM and often heavy **IgA staining in staph GN**

EM showing subepithelial hump in post-streptococcal GN

- No spike and dome phenomenon of GBM as seen with subepithelial deposits in membranous GN



Staph vs post-strep GN

Staphylococcal GN

- GN simultaneously with infection
- In elderly and specially diabetics/alcohlics/malignancy
- Associated infections: skin(38%), lung(22%),endocarditis(10%),deep abscess(3%) and UTI(3%)
- On IF often IgA dominance or co-dominance
- Upto half develop CKD or ESRD

Post streptococcal GN

- GN upto two weeks after infection
- Common in children
- Follows throat(ASO, anti-DNase B, anti-NAD, and AHase titres high) or skin infections(anti-DNase B and AHase high)
- On IF C3 dominant
- Renal recovery in >90% specially children

Treatment of Infection related GN

- Supportive in general : Antihypertensive drugs, diuretics, and dietary salt restriction to control hypertension and fluid overload
- Antibiotic course in recurrent streptococcal infection
- For staphylococcal GN: appropriate antibiotics and if needed, surgery (e.g. deep seated abscess)
- No role for immunosuppressive therapy

IgA Nephropathy (IgAN)

- Commonest cause of GN worldwide specially in developed nations
- Also called synpharyngitic GN: haematuria within 24-48 hours of URTI unlike 2-3 weeks gap in post-streptococcal GN
- Characterised by mesangial proliferation and deposition of IgA in glomeruli
- Regular recurrence after transplant implies a defect in the host IgA immune system rather than predominantly local renal pathology
- Peak incidence in 2^{nd} and 3^{rd} decades with 2:1 M to F preponderance
- Direct association with infections unproved

Pathogenesis

- IgA is the predominant immunoglobulin found on mucosal surfaces
- Synpharyngitic presentation + biopsy evidence of IgA in the mesangium led to the conclusion that excess mucosal IgA production (due to infection)leads to mucosal IgA entering the body and travel to the kidney causing IgAN……BUT…..
- Bone marrow produces IgA1 while mucosal surfaces make both

(IgA2>IgA1)

- Bone marrow derived IgA1 found in plasma is monomeric while mucosal surfaces have polymeric IgA (pIgA)
- **While predominant IgA deposit in kidney in IgAN is pIgA1, the mucosal surface production of pIgA1 is actually reduced**

While predominant deposit in kidney in IgAN is pIgA1, the mucosal surface production of pIgA1 is actually reduced….

1. Impaired mucosal defences allows antigens to enter body and cause excess systemic IgA formation

2. Possibility of mucosal IgA producing cells translocating to bone marrow

3. The **IgA1 is defectively glycosylated** in IgAN which leads to:

- Reduced clearance of the defective IgA1 by liver
- Increased mesangial deposition of the defective IgA1
- IgG and IgA autoantibodies against the defective IgA1 and the resulting complexes deposited in the mesangium

Note- Some evidence of tonsillar overproduction of pIgA1 along with bone marrow BUT effects of tonsillectomy on IgAN unclear

Diseases associated with IgAN

- Celiac disease
- Rheumatic disorders: RA, ankylosing spondylitis, Reiter syndrome
- Cirrhosis: Alcoholic liver disease, NASH, Hepatitis B and C
- Lung: Sarcoidosis
- Infection: HIV

Clinical Features

- Peak incidence in 2nd and 3rd decades
- Commoner in Caucasians
- Episodic macroscopic hematuria in **40-50%** (often within 24-48 hours of URTI)
- Microscopic hematuria in **30- 40%** (with usually subnephrotic proteinuria)
- Nephrotic syndrome in 5%
- Rapidly progressive GN in 5%
- Rarely as AKI
- Rarely as malignant hypertension

Diagnosis and prognosis

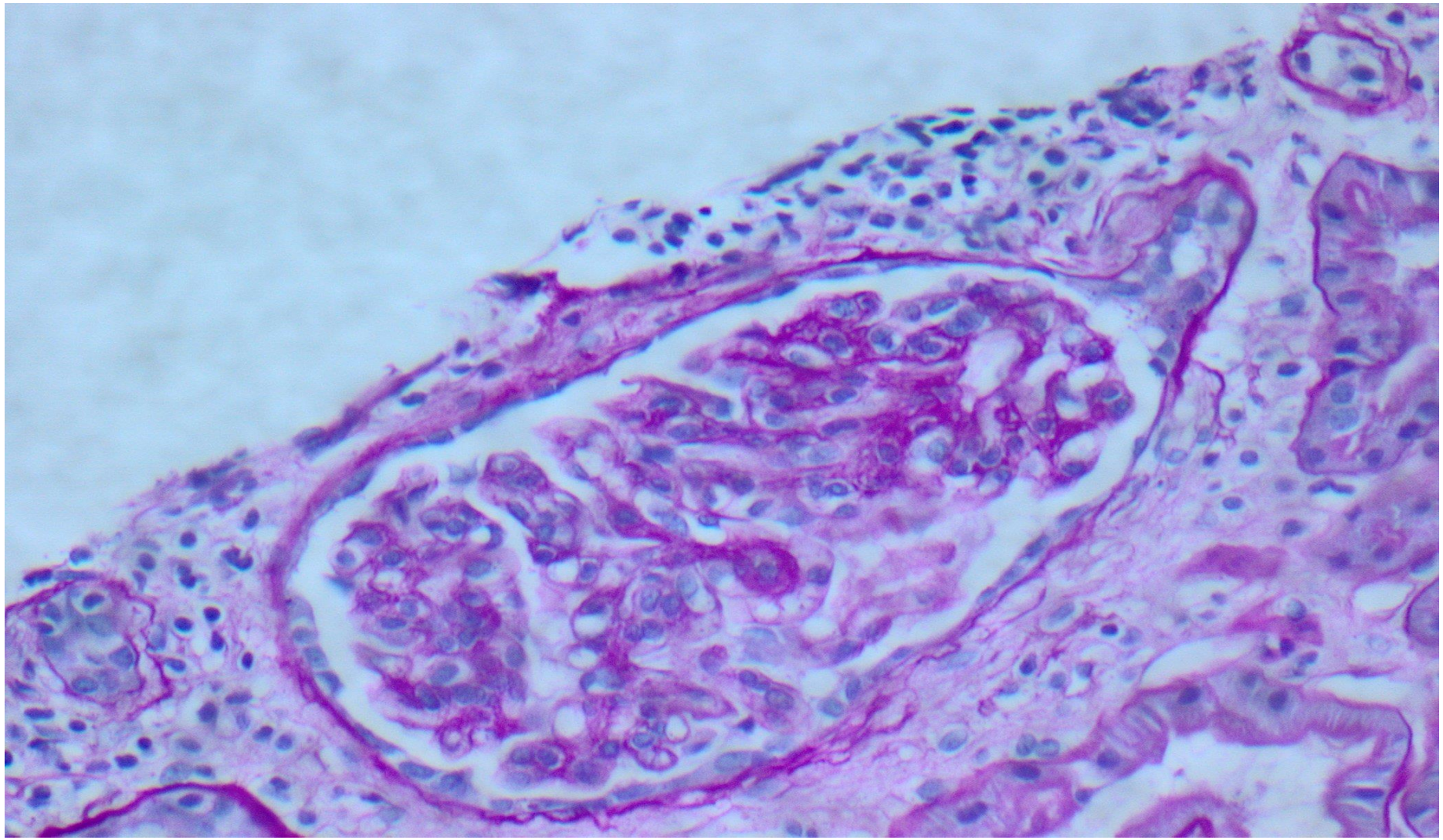
- Biopsy findings:

  -LM usually shows diffuse mesangial proliferation and hypercellularity

  -EM shows electron dense deposits in the mesangium

  - IF show diffuse mesangial IgA deposits
- Serum IgA levels raised in up to 50% (but not diagnostic)
- *ESRF can occur in up to 50% patients with maximum risk in those with* ***persistent proteinuria> 1g/day, HTN and CKD***
- *Although transplant outcome is same as in non IGAN recipient, biopsy reveals IgA deposits in > 50% transplanted kidneys*

LM of IgAN showing proliferating mesangium



Prognosis in IgAN

- Markers of poor prognosis
  - Elevated serum creatinine concentration
  - Hypertension (>140/90 mmHg)
  - Persistent (> six months) protein excretion >1g /day
- Oxford-MEST histological classification
  - Mesangial hypercellularity
  - Endocapillary hypercellularity (*better response to therapy*)
  - Segmental glomerulosclerosis
  - Tubular atrophy/interstitial fibrosis
- Presence of crescents are marker of poorer prognosis

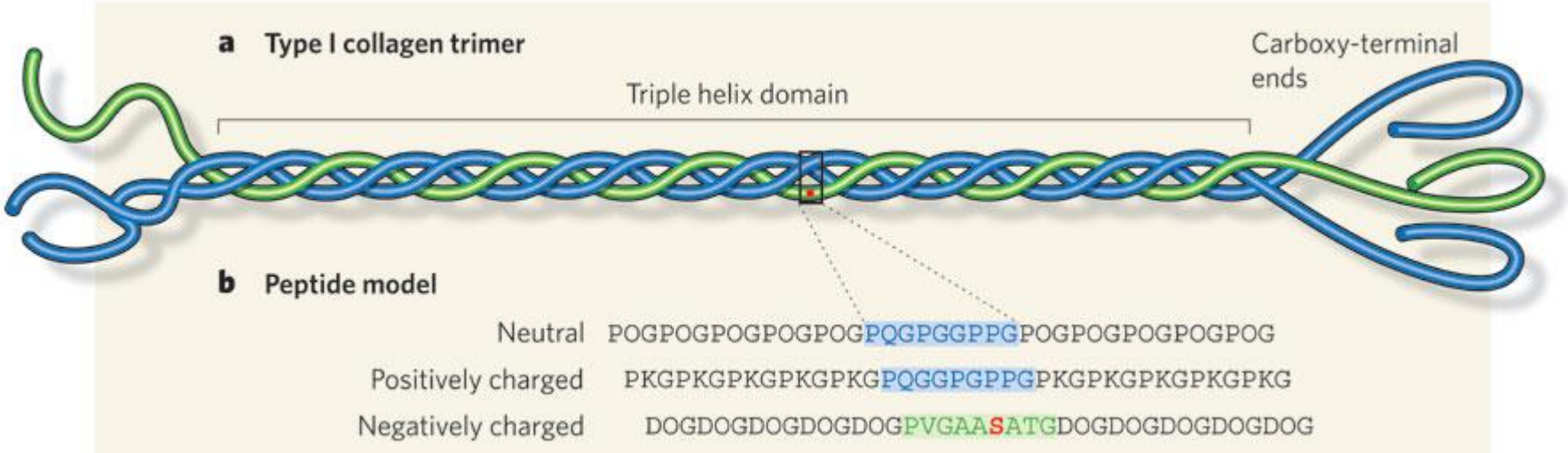
Treatment

- Absence of proteinuria/HTN/low GFR :6-monthly follow-up and no treatment
- Proteinuria and/or HTN: ACEI or ARB AND SGLT2 inhibitors
- Proteinuria> 1g/day and GFR> 50 ml/min despite 3-6 months ACEI/ARB: 6-month course of prednisolone
- Chronically low GFR or glomerulosclerosis and tubulointerstitial atrophy /fibrosis on renal biopsy: no benefit from steroid therapy
- Some studies in Japan support tonsillectomy but not widely practiced worldwide

Goodpasture Disease : Revise collagen first

- Collagen consists of three polypeptides called alpha-chains (1400 amino acids long) wrapped around each other in a triple helix -rope like structure
- Collagen has a C terminal noncollagenous domain (NC1) of 230 amino acids and a smaller N terminal noncollagenous domain of 20 amino acids
- Type I: found in skin, bone, tendon and cornea
- Type II: found in cartilage, intervertebral disc and vitreous body
- Type III: found in blood vessels and foetal skin
- **Type IV: found in basement membrane (involved in pathogenesis of Alport syndrome and anti-GBM disease)**

Collagen Structure



Type IV collagen

- Collagen type IV is found exclusively in basement membranes
- Tissue distribution of three different forms of type IV collagen:

- Alpha1-alpha1-alpha2: found in all basement membranes

- Alpha3-alpha4-alpha5: **exclusively in GBM**, tubular basement membrane, eye, lungs, cochlea

- Alpha5-alpha5-alpha6: Skin, distal tubular basement membrane **(but not GBM)**

NOTE: Anti-GBM antibody in Goodpasture disease is against alpha 3 chain

Anti- GBM antibody (Goodpasture) disease

- Circulating antibodies against NC1 domain of the alpha-3 chain of type IV collagen found in GBM and alveolar membranes
- Present with RPGN as well as pulmonary haemorrhage in 40 to 60% Additional insult needed for lung manifestation -smoking, infection, cocaine inhalation, fluid overload or hydrocarbon exposure

Goodpasture syndrome is RPGN + lung haemorrhage from any cause *(pauci-immune small vessel vasculitis, lupus, cryoglobulinemia, HSP, etc.)*

Goodpasture disease is RPGN+ lung haemorrhage + anti-GBM antibody

NOTE: Only 20-40% of hemoptysis with RPGN is due to Goodpasture disease

Anti- GBM antibody (Goodpasture) disease

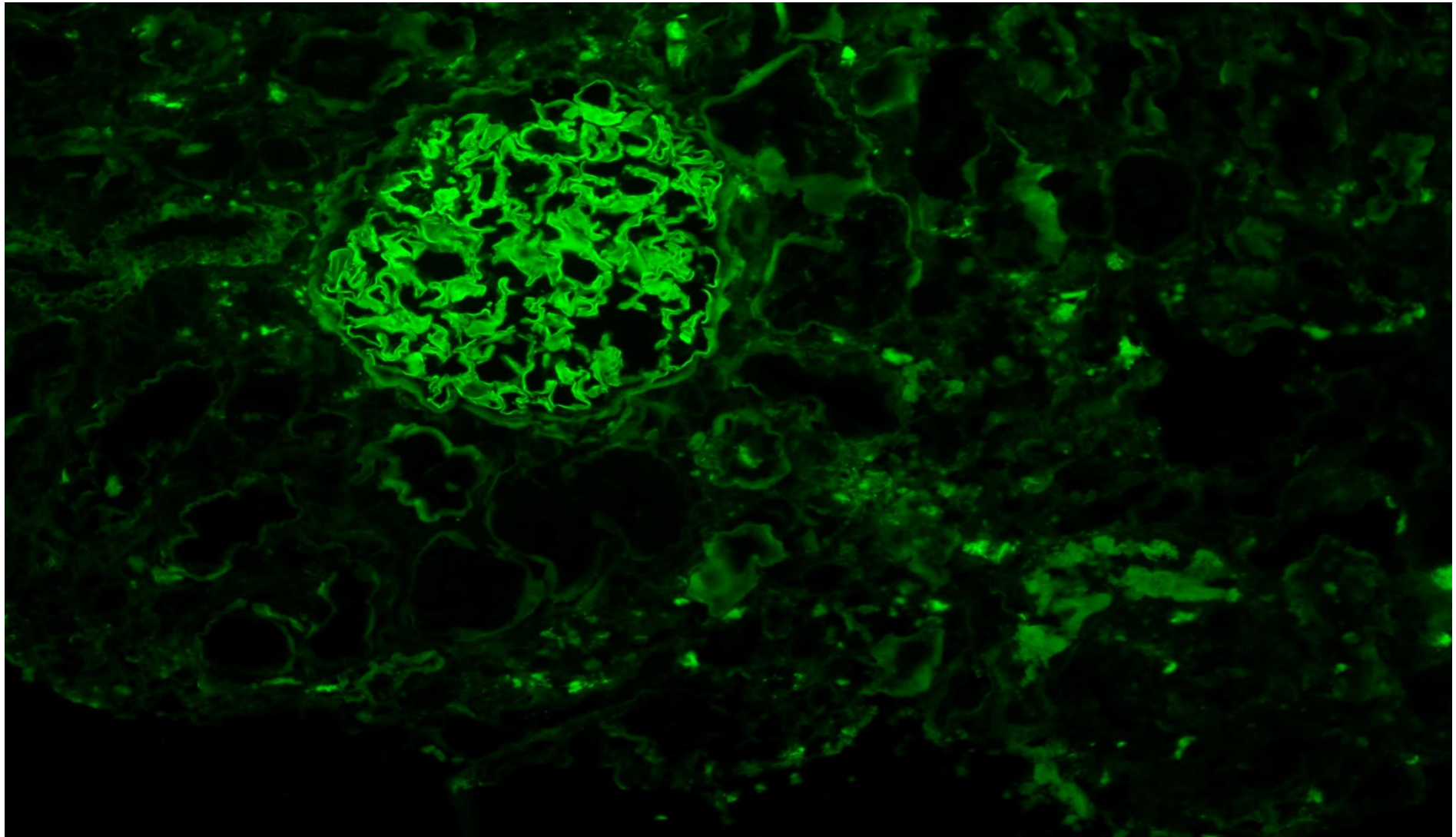
- Sometimes clinically and radiologically lung haemorrhage not obvious and increased CO uptake (DLCO) helpful
- Usually acute but sometimes isolated lung disease for months before renal involvement obvious
- **Systemic complaints typically absent (presence suggests vasculitis)**
- Diagnosis

  Anti-GBM antibody in plasma

  Biopsy: diffuse proliferative GN often with crescents on LM/EM and characteristic linear deposition of IgG along the GBM on IF

NOTE: 10 to 40% may also be MPO ANCA +

IF image of anti-GBM disease- linear IgG deposition



Treatment of anti-GBM antibody disease

- **Early diagnosis vital for response to therapy and prognosis**
- Untreated more than 90% result in death or dialysis
- Plasma exchange upto two weeks + prednisolone and cyclophosphamide upto three months
- Rituximab if refusal/contraindication to cyclophosphamide
- Plasma exchange is absolute indication in pulmonary haemorrhage independent of severity of renal disease

TREATMENT CONTINUE…

- Maintenance therapy usually not adviced
- Immunosuppression/plasma exchange not indicated in ESRF with no lung haemorrhage

EXCEPTION: Double ANCA/anti-GBM positive even if in ESRF at presentation, the young and those with acute presentation

- Prognosis correlates with renal disease at presentation
- Those needing dialysis at presentation usually need maintenance dialysis
- Relapse **generally uncommon(<2%)**;more likely in ANCA positive ,smokers or occupational exposure to hydrocarbon

Transplantation in anti-GBM disease

- Transplant delayed till anti-GBM antibody negative for > 12 months
- Clinical recurrence uncommon
- Anti-GBM disease may seen in 3 to 10 % of renal transplants in Alport’s syndrome

Alport Syndrome

- Commonest cause of hereditary nephritis (1 in 50000 live births)
- Defect in one of the three chains of type IV collagen
- Often associated with sensorineural hearing loss and ocular abnormalities
- Usual presentation in childhood or young adulthood with asymptomatic haematuria or progressive GN
- More than 80% X linked so usually males have worse prognosis

Alport's Syndrome

- Genes encoding the six alpha chains of type IV collagen:
  -*COL4A1* and *COL4A2* at 13q34
  -*COL4A3* and *COL4A4* at 2q35-37
  -*COL4A5* and *COL4A6* on chromosome X
- <u>X linked Alport syndrome</u>: 80% of all patients (mutated A5)
- 90% males and 12% females develop ESRD by 40 years
- Deafness in 80% males and 25% females
- Ocular defects (anterior lenticonus) in 40% males and 15% females
- Rarely leiomyomatosis (multiple benign smooth muscle tumours)

Alport's Syndrome

- Autosomal recessive:15% of cases-mutation effecting both alleles of A3 or A4

-Females as severely effected as males

-Clinically similar to X linked disease in males

-Usually both parents are carriers

- Autosomal dominant: Heterozygous mutation of A3 or A4

-Generally slow progression to ESRD

-Ocular manifestations unusual

Diagnosis

- **Renal biopsy** (No characteristic LM findings)

- Characteristic EM findings include splitting/thinning and thickening/basket weaving of GBM

-Immunostaining for type IV collagen in GBM will show absence of 3/4/5 alpha chains

- **Skin biopsy**: (remember skin collagen is alpha 5-5-6) can show absence of alpha 5 chain in children with X-linked disease
- **Molecular genetic testing**: non-invasive/extremely accurate/prognostic information/ confirm in unequivocal biopsy

Treatment

- No specific treatment
- Usual ACE-I or ARB for proteinuria
- Usual supportive therapy for complications of CKD
- Transplantation gives excellent result
- HOWEVER…..upto 3% of transplants can lead to de novo anti-GBM disease

Rapidly Progressive Glomerulonephritis (RPGN)/Crescentic GN

- Nephritis with rapid progression of renal failure (days to weeks to months)
- Histologically defined by extensive crescents in the glomeruli
  - Normally Bowman’s space has a single layer of parietal and visceral epithelial cells each
  - Cellular glomerular crescents are defined as two or more layers of proliferating parietal epithelial cells in Bowman's space
- Crescent formation is a nonspecific inflammatory response to severe glomerular injury
- Usually RPGN results when >50% of the glomeruli exhibit crescents

RPGN associations

- Pauciimmune RPGN: Negative staining on IF; causing more than 50% of all RPGN, this group is due to ANCA-associated vasculitis
- Anti-GBM antibody associated RPGN: Positive anti-GBM antibodies and linear staining of the GBM on IF, this leads to 20% of all RPGN
- Immune complex mediated RPGN: IF characteristically shows presence of coarse immune deposits in the glomeruli; about 25% of all RPGN and may be due to lupus(commonest) IgAN, infectious GN, or MCGN

RPGN pathogenesis

- Rents in the glomerular capillary wall lead to leakage of plasma products including fibrinogen into bowman's space with subsequent fibrin formation
- This is followed by the influx of macrophages and T cells and the release of proinflammatory cytokines
- The proliferating cells/macrophages/fibrin crowds up the bowman space and chokes the glomerular capillaries (reduced filtration)
- Untreated in later stages, crescent becomes fibrotic

Treatment of RPGN

- Circumferential crescents in > 80 % glomeruli respond very poorly
- Better response in non-circumferential crescents in <50% glomeruli
- Untreated: ESRD invariable
- IV methylprednisolone for 3 days followed by daily oral prednisone, oral or IV cyclophosphamide or rituximab, and plasmapheresis in some settings e.g. anti GBM positive with hemoptysis
- Treat the underlying disease

Thank you

‘A person who never made a mistake never tried anything new’

By Albert Einstein