RENAL PATHOLOGY

RAPID PROGRESSIVE GLOMERULONEPHRITIS
CHRONIC KIDNEY DISEASE

APRIL 2020

REFERENCE: ROBBINS & COTRAN PATHOLOGY AND RUBIN'S PATHOLOGY

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OBJECTIVES FOR PATHOLOGY LECTURES 5 & 6:
NEPHROTIC AND NEPHRITIC SYNDROME
AND
RAPID PROGRESSIVE GLOMERULONEPHRITIS, CHRONIC KIDNEY DISEASE,

At the end of the activity (2 lectures) the students will be able to:

- Recognize the five major renal glomerular syndromes.
- Describe the main differential pathological diagnosis for each syndrome.
- Perform a clinico-pathological correlation.
- Describe the patterns of injury of each syndrome.

Key Outlines:

- The nephrotic syndrome: (Minimal change, FSGS, membranous, diabetes).
- The nephritic syndrome: (Acute post streptococcal Glomerulonephritis GN, Lupus nephritis).
- Asymptomatic Hematuria: IgA Nephropathy.
- Rapidly progressive GN: (Crescentic GN)
- The Chronic Renal Failure.

OUTLINE FOR LECTURE 6

- Clinical manifestation of kidney disease
- Rapidly progressive GN: (Crescentic GN)
  - Introduction
  - Light microscopy
  - Type I
  - Type II
  - Type III
- The Chronic Renal Failure.
  - Introduction
  - Common causes
  - Clinical features
  - Light microscopy

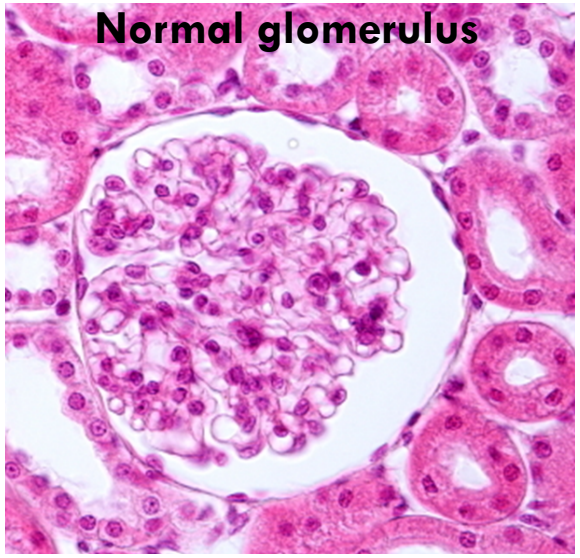
CLINICAL MANIFESTATION OF KIDNEY DISEASE

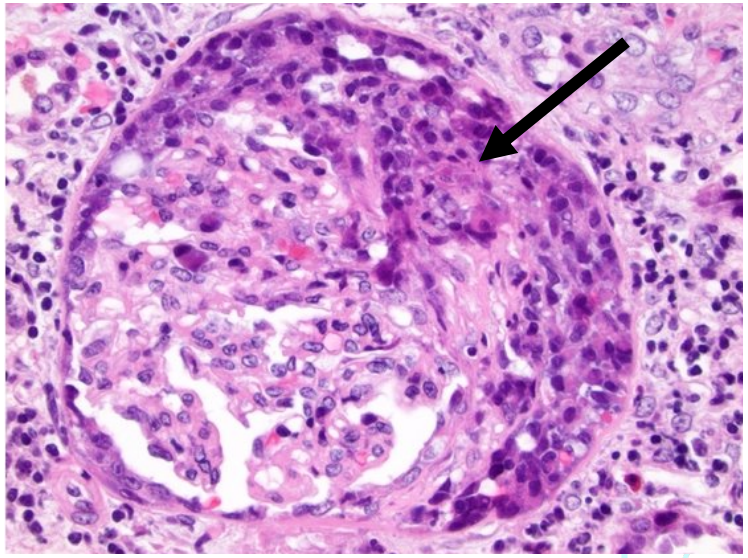
▪ **Nephritic syndrome**	Results from glomerular injury → acute onset of hematuria (rbcs in urine), mild to moderate proteinuria, azotemia, edema & hypertension.
▪ **Nephrotic syndrome**	heavy proteinuria (excretion of more than 3.5 g of protein/day in urine), hypoalbuminemia, severe edema, hyperlipidemia, and lipiduria.
▪ **Asymptomatic hematuria &/or non-nephrotic proteinuria**	a sign of mild glomerular abnormalities e.g. IgA nephropathy.
▪ **Rapidly progressive glomerulonephritis**	Results from severe glomerular injury → loss of renal function within days or weeks → hematuria, dysmorphic rbcs, rbc casts in urine, mild to moderate proteinuria.
▪ **Acute kidney injury**	oliguria or anuria with recent onset of azotemia; can result from glomerular injury (e.g. crescentic glomerulonephritis), interstitial injury, vascular injury (e.g. TMA) or acute tubular injury/necrosis.
▪ **Chronic kidney disease**	any chronic renal diseases that progresses to end stage kidney requiring dialysis and transplantation.
▪ **Urinary tract infection**	affect the kidney (pyelonephritis) or the bladder (cystitis) → bacteriuria and pyuria (bacteria and leukocytes in urine).
▪ **Nephrolithiasis (renal stones)**	renal colic, hematuria (without rbc casts).

RAPID PROGRESSIVE GLOMERULONEPHRITIS (RPGN)
ALSO CALLED AS
CRESCENTIC GLOMERULONEPHRITIS (CRGN)

RPGN/CRGN

- **Also known as Crescentic glomerulonephritis**
- **Rapidly progressive glomerulonephritis (RPGN)** is a clinical syndrome, characterized by
  - » rapid & progressive loss/decline of renal function within weeks to months
  - » Extensive glomerular **crescent formation**.
- Patients present with nephritic syndrome and progress to acute renal failure. The prognosis is poor if untreated, even death.
- Histologically there is severe glomerular injury → in the form of crescent formation, glomerular necrosis and rupture of the glomerular basement membrane. Glomerular crescent formation is a characteristic finding in RPGN. Crescents are also called as glomerular extracapillary proliferations (i.e. proliferation outside the glomerular capillaries).
- Crescents are formed
  - by proliferation of parietal epithelial cells that line the Bowman's capsule
  - and by migration of monocytes/macrophages into Bowman's space

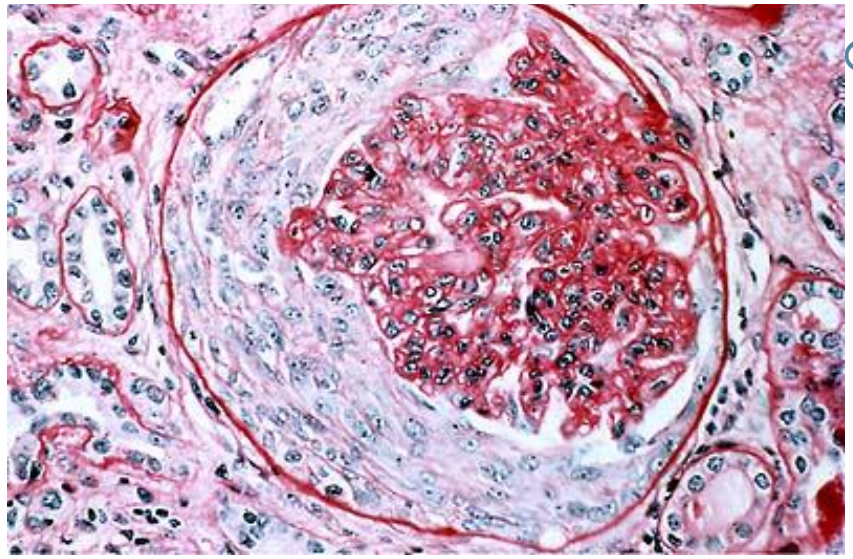


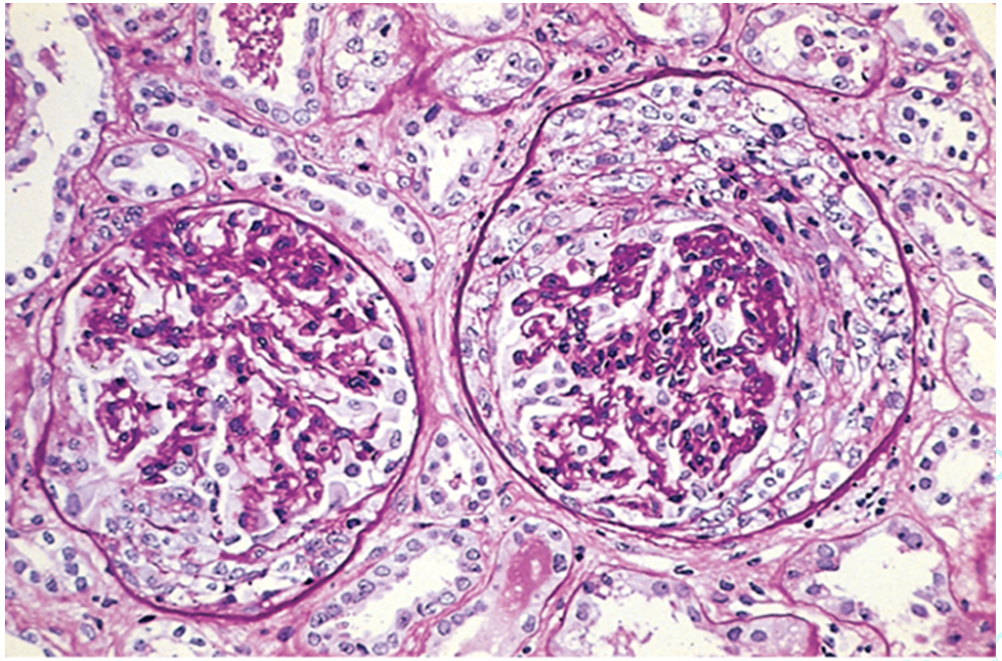


Adnan MM et al. Case Rep Nephrol. 2014

RPGN: LIGHT MICROSCOPY

- Epithelial/cellular crescents are seen in majority (>50%) of the sampled glomeruli in a kidney biopsy.
- It is called crescent because it has a crescent shape.
- The crescents fill the Bowman's space and compress the glomerular capillary loops and can even rupture the GBM.
- The glomeruli may also show necrosis.
- Upon healing the crescents undergo fibrosis/scarring and are called fibrous crescents.





Based on cause (etiology) RPGN is divided into three types:

Types of RPGN/ CrGN

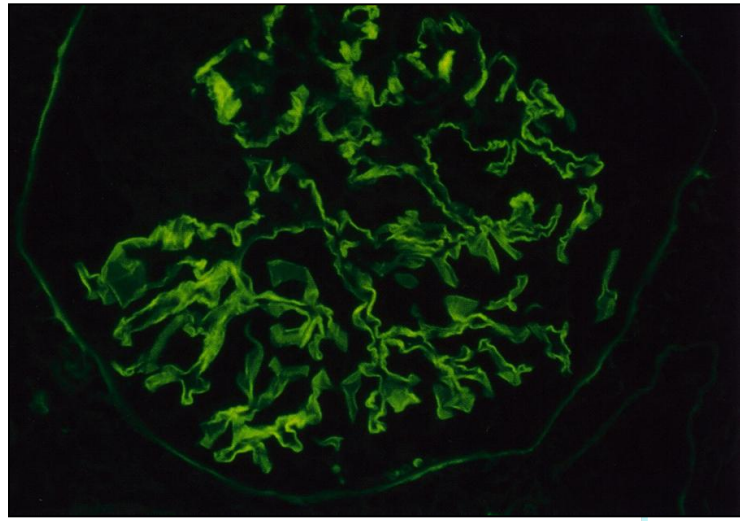
Type I RPGN = anti-glomerular basement membrane antibody–mediated Crescentic GN (about 12%): is characterized by the presence of auto antibodies directed against the glomerular basement membrane

Type II RPGN = immune complex mediated Crescentric GN (about 44%): here the crescents are seen in renal disease in which there is deposition of antigen antibody immune complexes e.g. SLE, IgA nephropathy, post-infectious GN etc.

Type III RPGN (Pauci-immune) ANCA-Associated Crescentric GN (about 44%): characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) e.g. granulomatosis with polyangitis (Wegener's) and Microscopic polyangiitis.

TYPE I RPGN = ANTI-GLOMERULAR BASEMENT MEMBRANE ANTI-BODY DISEASE (ANTI-GBM DISEASE)

- Anti-GBM antibody disease is a rare autoimmune disorder. In it there are auto-antibodies directed against an antigen that is normally present in the glomerular basement membrane (GBM).
- On IF → characteristic linear staining/positivity with IgG immunoglobulin along the GBM (pic).
- Patient's serum is positive for anti-GBM antibodies.
- When anti-GBM disease is associated with pulmonary hemorrhage (hemorrhagic pneumonitis) this combination is called as Goodpasture's syndrome (in these patients, the anti-GBM antibodies also bind to pulmonary alveolar capillary basement membranes).

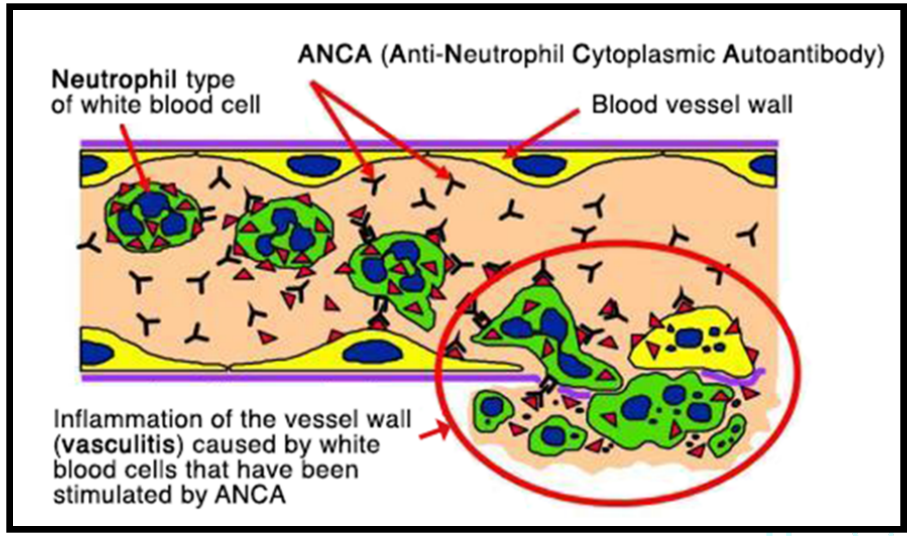


TYPE II RPGN = IMMUNE COMPLEX MEDIATED CRESCENTRIC GLOMERULONEPHRITIS

- It results from any immune complex mediated renal diseases in which there is deposition of antigen antibody immune complexes in the glomeruli. The crescents represent a more aggressive form of various immune complex mediated GNs, e.g.:
  - poststreptococcal GN,
  - Lupus nephritis (in systemic lupus erythematosus)
  - IgA nephropathy and Henoch-Schönlein purpura.
  - Etc.
- A consistent finding in this form of GN is that:
  - on IF study there is positivity with various immunoglobulins and/or complements
  - and on EM study there are electron dense immune deposits.

TYPE III RPGN = PAUCI-IMMUNE ANCA-ASSOCIATED GN

- It is called in pauci-immune GN because there is
  - ✓ no anti-GBM antibody
  - ✓ & no immune complex deposition (so IF is negative/almost negative and there are no deposits on EM).
- Most patients have circulating antineutrophil cytoplasmic autoantibodies (ANCAs) in the blood. ANCA are autoantibodies that target antigens present in neutrophil cytoplasm.
- ANCA causes abnormal activation of neutrophil. As a result:
  - there is adhesion of the neutrophils to endothelial cells lining the capillaries (esp. glomerular capillaries)
  - Neutrophils release injurious products → that promote endothelial injury, vascular inflammation (vasculitis and fibrinoid necrosis of arteries and arterioles) and crescentic GN.
- Note: RPGN type I and II are ANCA negative.
- Pauci-immune cresentric GN is associated with systemic diseases like
  - granulomatosis with polyangitis (formerly called Wegener's Granulomatosis)→ cANCA positive
  - microscopic polyangiitis → pANCA positive.



https://unckidneycenter.org/files/2017/10/anca-vasculitis-vessel-wall.png

RPGN/ CRGN: CLINICAL FEATURES

- Present as rapid & progressive loss/decline of renal function within weeks to months, usually as nephritic syndrome that progresses to acute renal failure (marked oliguria and azotemia).
- Proteinuria sometimes approaching nephrotic range may occur.
- Timely diagnosis is important.
- Treatment: Type I and Type III RPGN respond well to plasmapheresis (it removes pathogenic antibodies from the circulation), steroids and cytotoxic agents. Type II RPGN does not respond well to plasmapheresis, the original underlying disease needs to be treated.
- Some patients require long-term dialysis or transplantation.

CHRONIC RENAL FAILURE (CRF)
OR
CHRONIC KIDNEY DISEASE (CKD)

CHRONIC RENAL FAILURE (CRF)/ CHRONIC KIDNEY DISEASE (CKD)

- Chronic kidney disease describes the slow or gradual loss of kidney function.
- CKD can be the consequence of irreversible acute disease or progressive slow scarring in any type of chronic renal disease.
- The end result is end stage kidney disease.
- In end-stage kidney there is scarring of all 4 renal compartments: glomerular sclerosis, tubular atrophy, interstitial fibrosis and arteriosclerosis, regardless of the primary/original site of injury.
- The prognosis is poor. Patients need with dialysis or transplantation otherwise death from uremia will results.
- Dialysis and kidney transplantation allow long-term survival.

CRF/CKD: COMMON CAUSES

- Chronic glomerulonephritis like RPGN, membranous GN, membranoproliferative GN, FSGS, IgA nephropathy, etc.
- Diabetic Nephropathy
- Hypertension
- Reflux nephropathy in children
- Polycystic kidney disease
- Kidney infections & obstructions
- Others

CRF/CKD: CLINICAL FEATURES

In the early stages of chronic kidney failure → few signs or symptoms. Chronic kidney failure may not become apparent until your kidney function is significantly impaired.

Some patients are oliguric and some patients are not oliguric.

Gradual rise in BUN and serum creatinine.

High levels of urea in the blood can result in:

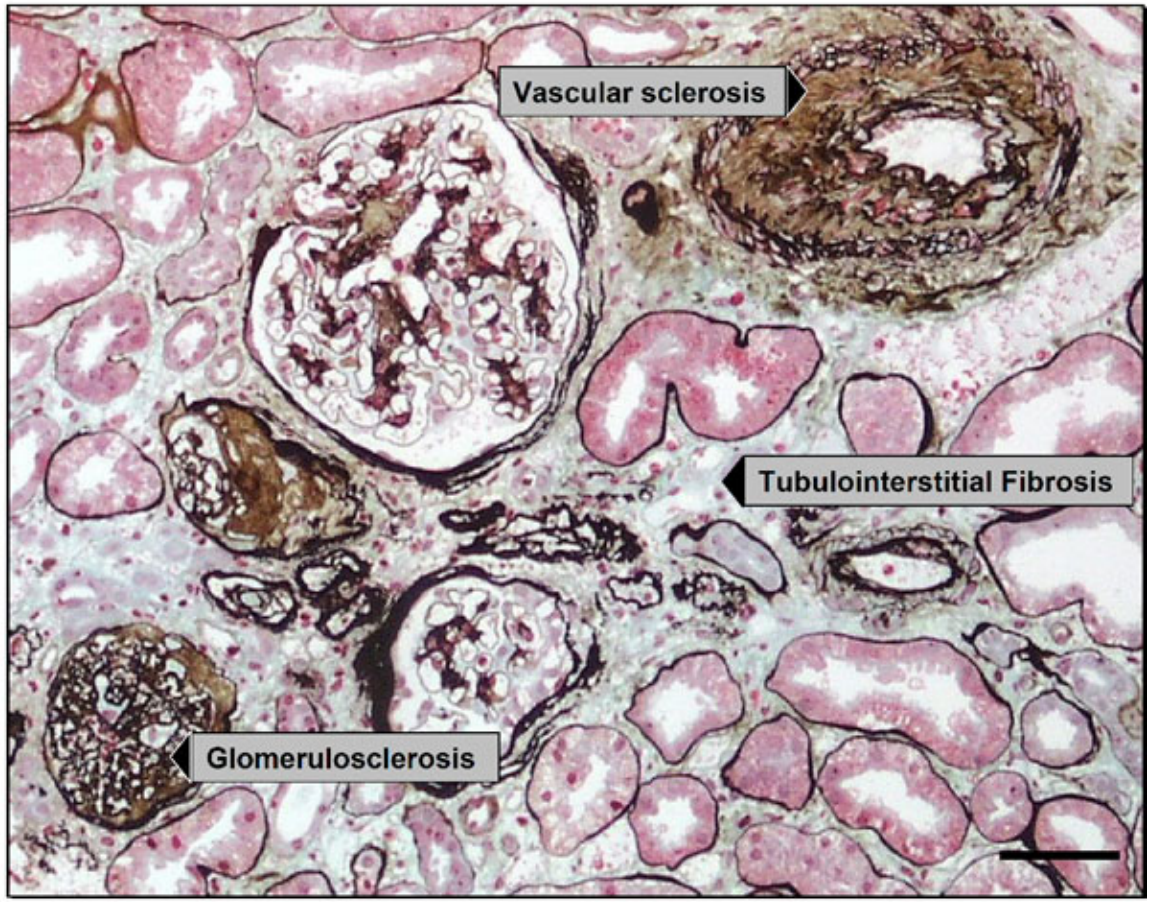
- **Azotemia** (increased urea and creatinine)
- **Acidosis, hyperkalemia, Hypokalemia** (due to failure of kidney to activate Vit D).
- **Abnormal fluid volume → c**hanges in urine output e.g. initially increased urine output and later decreased urine output. The sodium and water retention can lead to volume overload and congestive cardiac failure.
- Low levels of calcium → renal osteodystrophy
- **Anemia** due to decreased erythropoietin.
- **Hypertension** due to excess renin production.
- Etc.

CKD: MORPHOLOGY

Grossly the kidneys are small and contracted with granular surface. Markedly damaged kidneys are designated "end-stage kidneys".

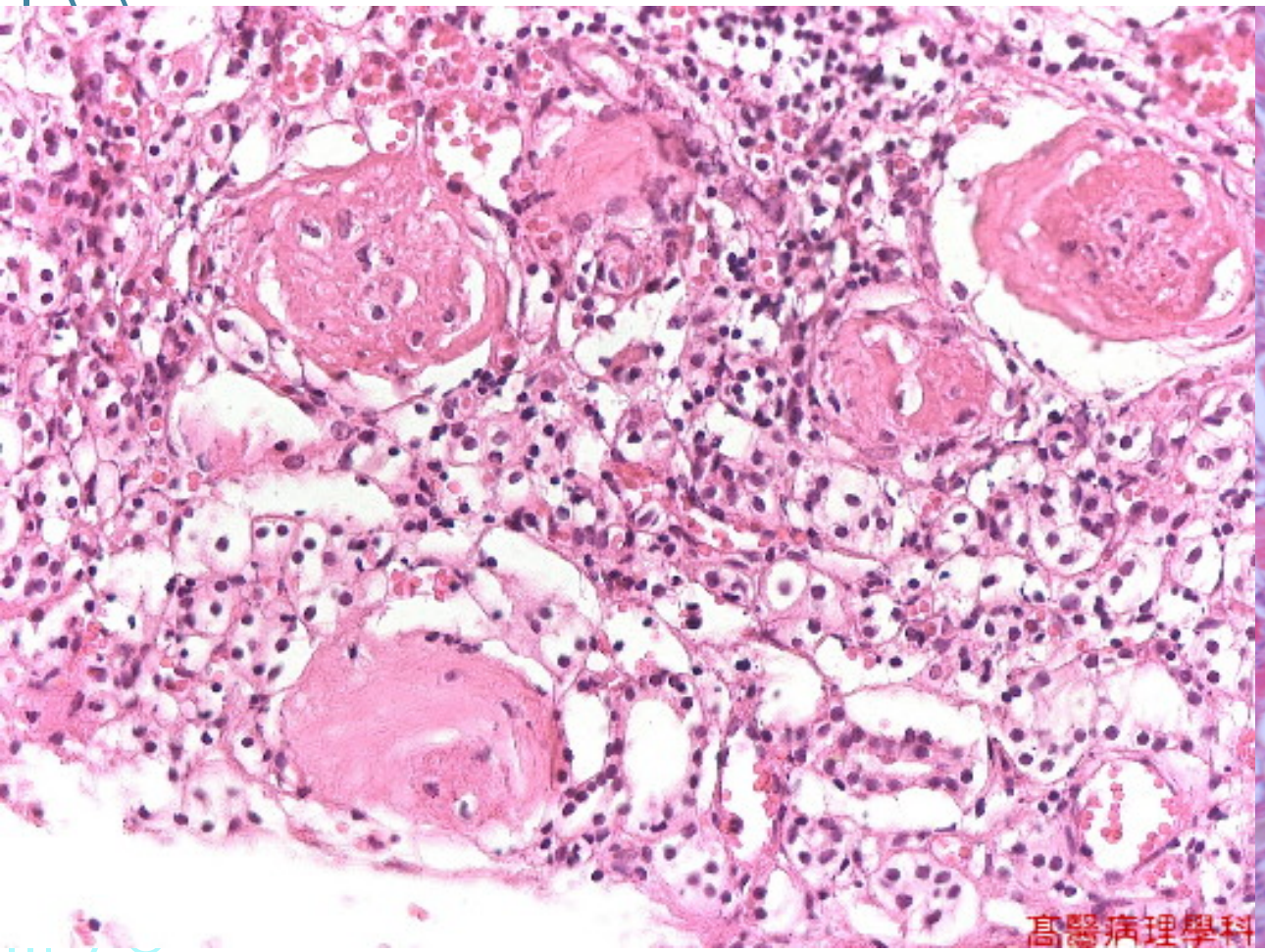
Light microscopy:

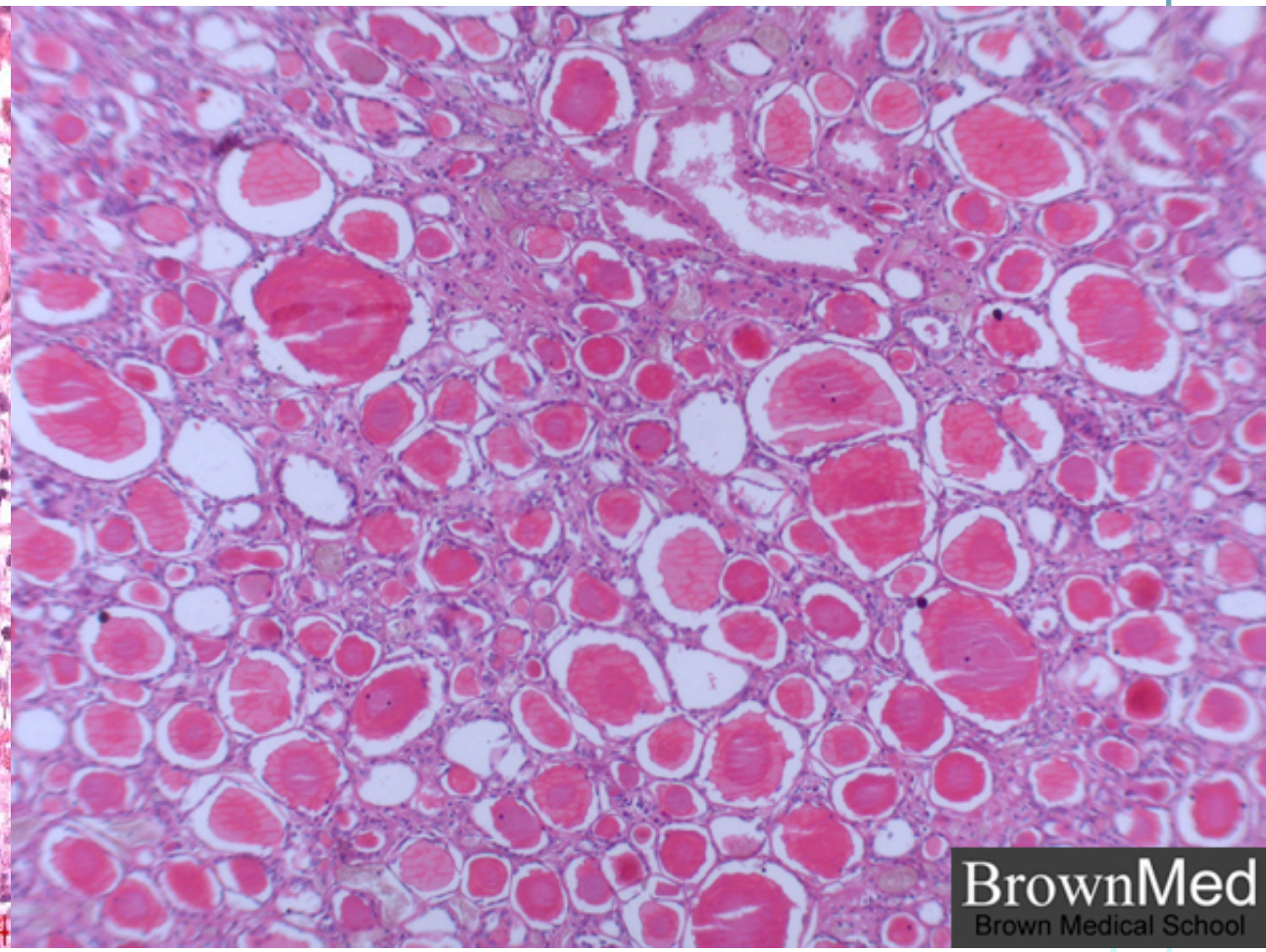
- Glomeruli → most of the glomerular are sclerosed (fibrosed/scarred) called glomerulosclerosis.
- Tubules → show prominent atrophy with thyroidization of tubules (tubules are filled with eosinophilic hyaline casts resembling colloid of thyroid gland).
- Interstitium → prominent interstitial fibrosis with lymphocytic infiltrate
- Blood vessels→ show thick walled arteries and arterioles with narrowed lumen.



Hewitson, 2012 Fibrogenesis Tissue Repair. 5(Suppl 1):S14. doi: 10.1186/1755-1536-5-S1-S14

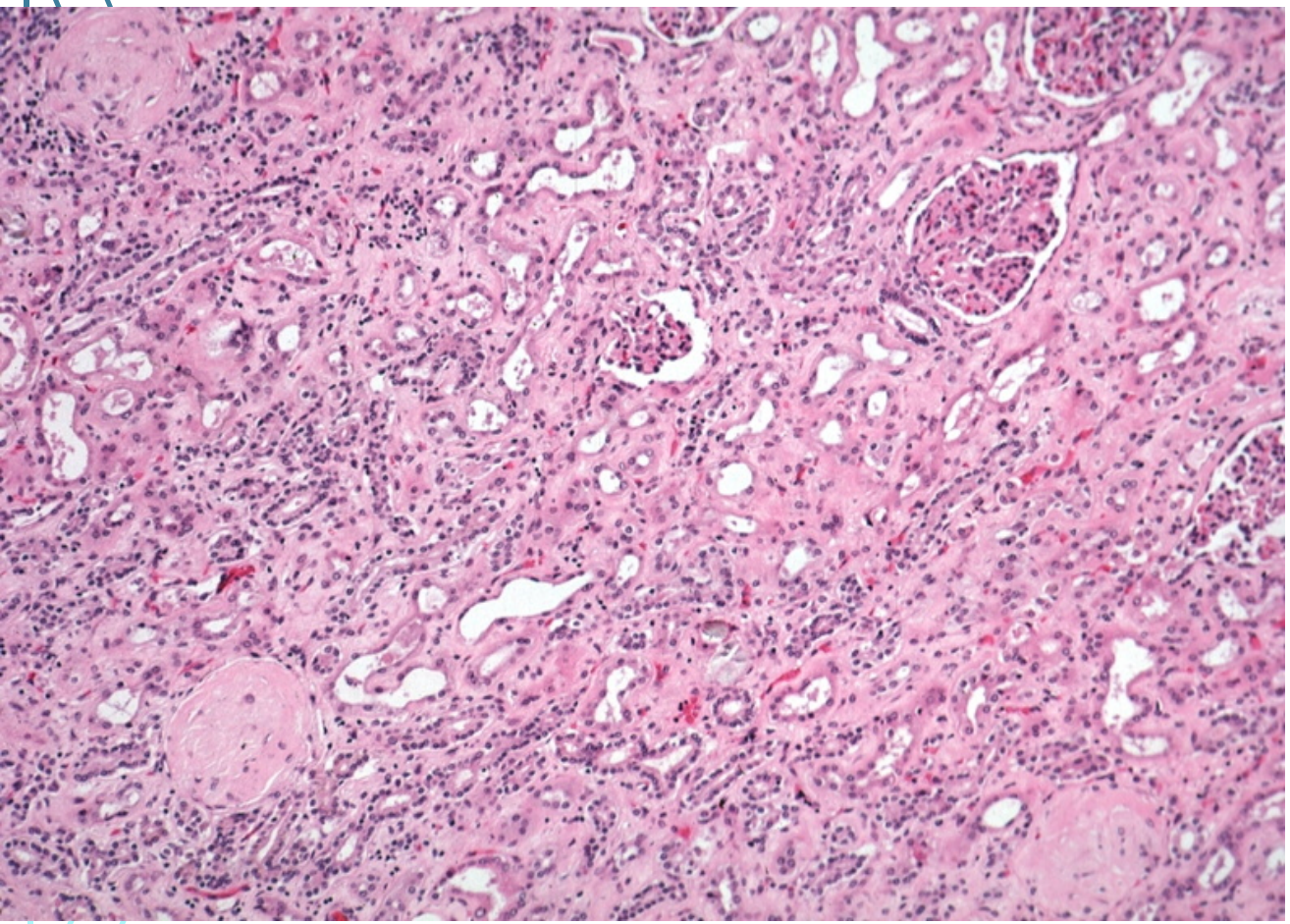
END STAGE KIDNEY





http://pathology.class.kmu.edu.tw/ch13/129-2.jpg

END STAGE KIDNEY



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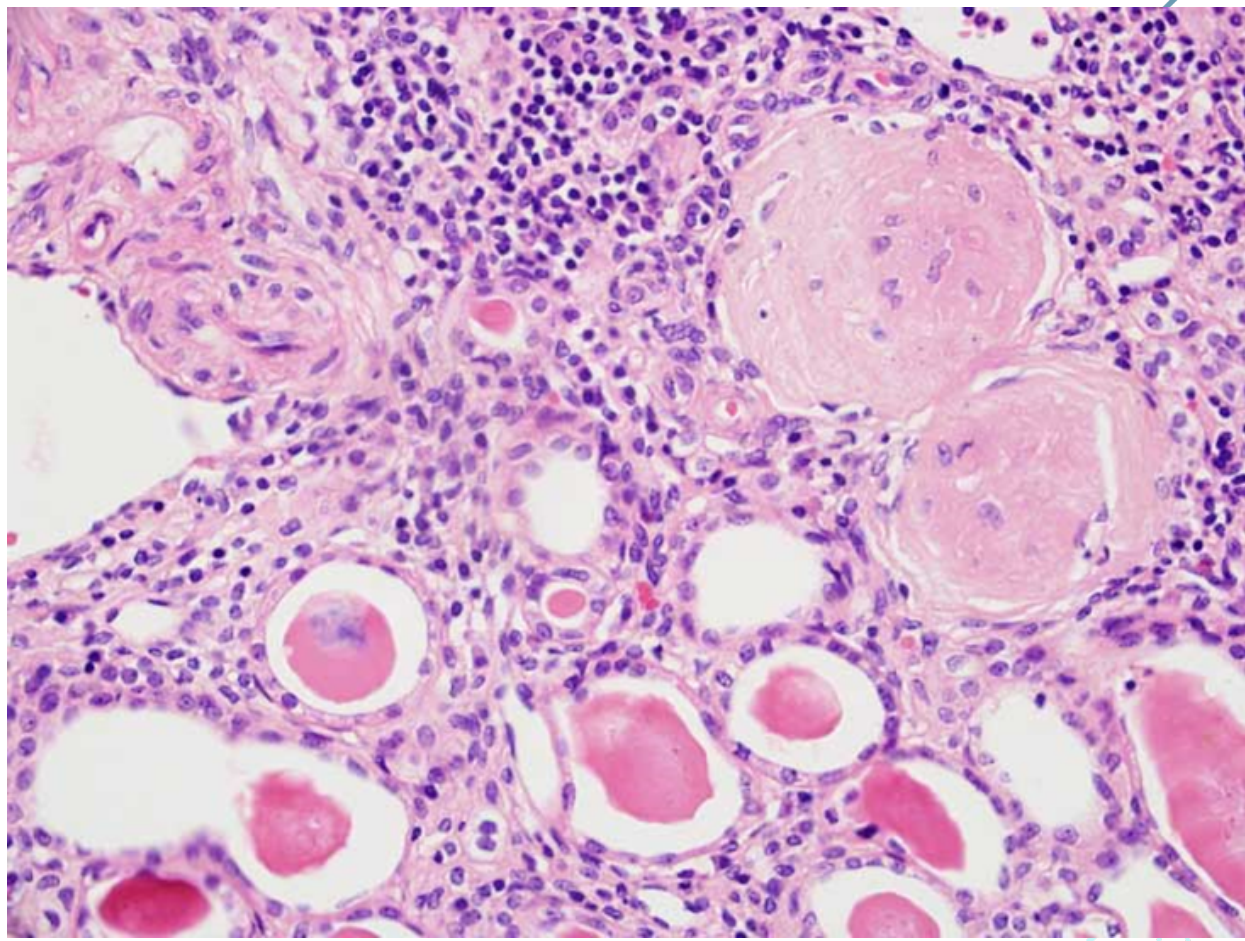

http://www.iupui.edu/~pathol/c604_Systemic/labs/lab10/images/l-87.jpg

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