



RENAL PATHOLOGY
RAPID PROGRESSIVE GLOMERULONEPHRITIS
CHRONIC KIDNEY DISEASE

Reference: Robbins & Cotran Pathology and Rubin's Pathology



**Objectives for pathology lectures 5 & 6:
Rapid Progressive Glomerulonephritis, Chronic kidney Disease,
AND
Nephrotic and Nephritic Syndrome:**

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, Membrano-proliferative GN, Systemic Lupus Erythematosus).
- Rapidly progressive GN: (Crescentic GN)
- Asymptomatic Hematuria / Proteinuria: IgA Nephropathy.
- The Chronic Renal Failure.

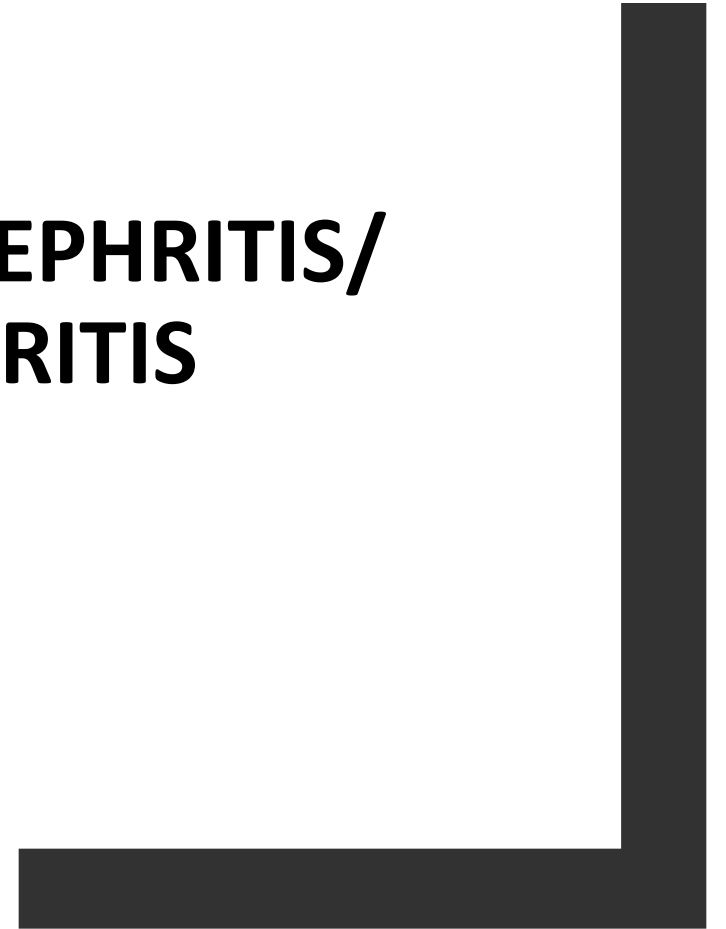
Clinical manifestation of kidney disease

Nephritic syndrome	Results from glomerular injury → acute onset of prominent hematuria (red blood cells in urine), mild to moderate proteinuria, azotemia, edema and hypertension (e.g. acute poststreptococcal glomerulonephritis).
Nephrotic syndrome	characterized by heavy proteinuria (excretion of more than 3.5 g of protein/day in urine), hypoalbuminemia, severe edema, hyperlipidemia, and lipiduria (lipid in the urine).
Asymptomatic hematuria &/or non-nephrotic proteinuria	a sign of mild glomerular abnormalities.
Rapidly progressive glomerulonephritis	Results from severe glomerular injury → loss of renal function within days or weeks → hematuria, dysmorphic red blood cells, red blood cell casts in urine sediments, mild to moderate proteinuria.

Clinical manifestation of kidney disease

Acute kidney injury	oliguria or anuria with recent onset of azotemia. It can result from glomerular injury (e.g. crescentic glomerulonephritis), interstitial injury, vascular injury (e.g. TMA) or acute tubular injury/necrosis.
Chronic kidney disease	result of any chronic renal diseases that progresses to end stage kidney requiring dialysis and transplantation → characterized by prolonged symptoms and signs of uremia.
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/
CRESENTRIC GLOMERULONEPHRITIS
(RPGN/CRGN)**

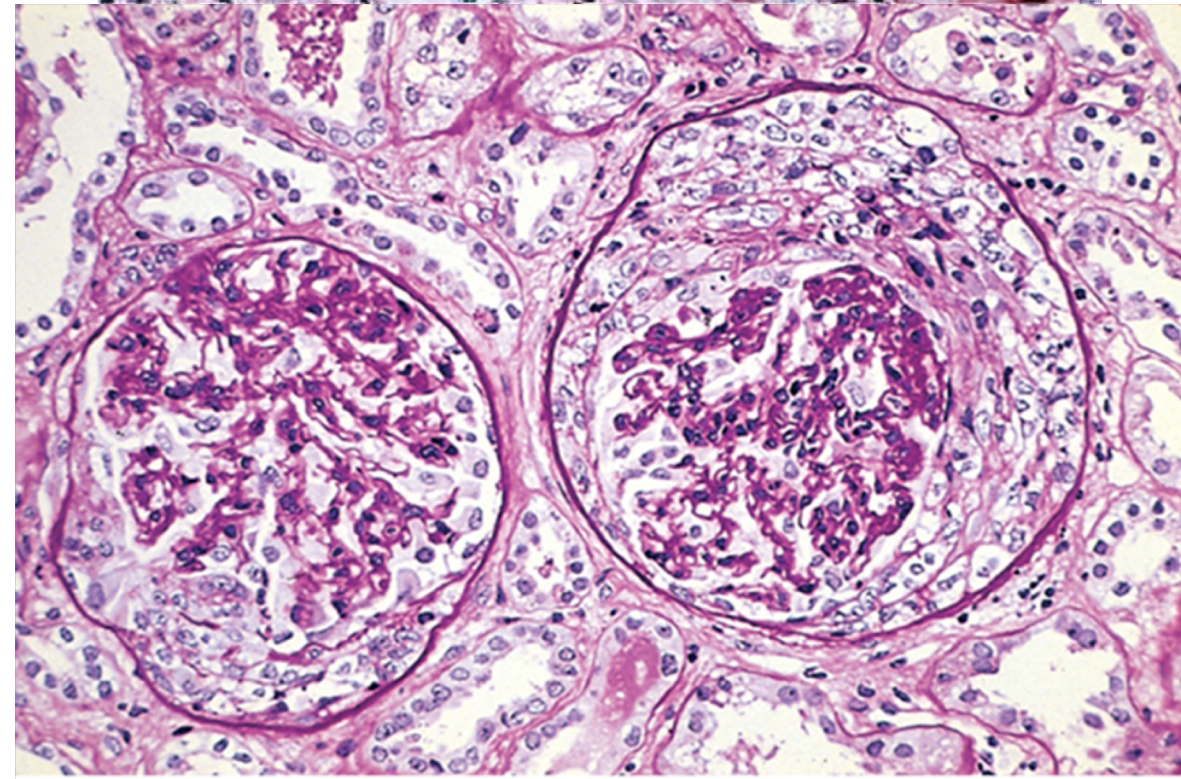
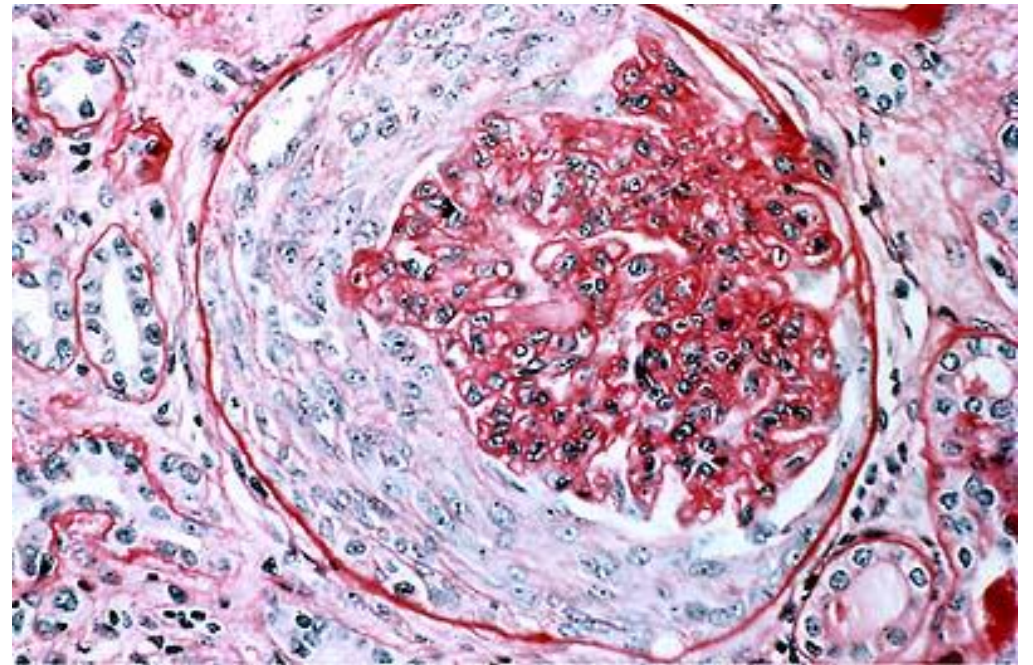


Rapid progressive glomerulonephritis/ crescentic glomerulonephritis (RPGN/CrGN)

- Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome, characterized by rapid and progressive loss of renal function within weeks to months. Patients present with acute renal failure with features of nephritic syndrome and severe oliguria. Has poor prognosis if untreated even death.
- RPGN is commonly associated with severe glomerular injury with necrosis and GBM breaks and subsequent proliferation of parietal epithelium (crescents).
- Histologically there is severe glomerular injury. The characteristic finding in RPGN is the presence of glomerular extracapillary proliferations (i.e. proliferation outside the glomerular capillaries) called as crescents.
- 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

RPGN: Light Microscopy

- Formation of many crescents.
- The crescents eventually fill the Bowman's space, compress the glomeruli and can even rupture the GBM.
- Segments of glomeruli may show necrosis.
- In time with healing the crescents undergo fibrosis/scarring.



Pathogenesis: glomerular injury in RPGN may be immune mediated (e.g. antiGBM autoantibodies or antigen antibody immune complexes) or it may be pauci-immune (associated with antineutrophil cytoplasmic antibodies). And therefore based on etiology RPGN is divided into three types:

Types of RPGN/ CrGN

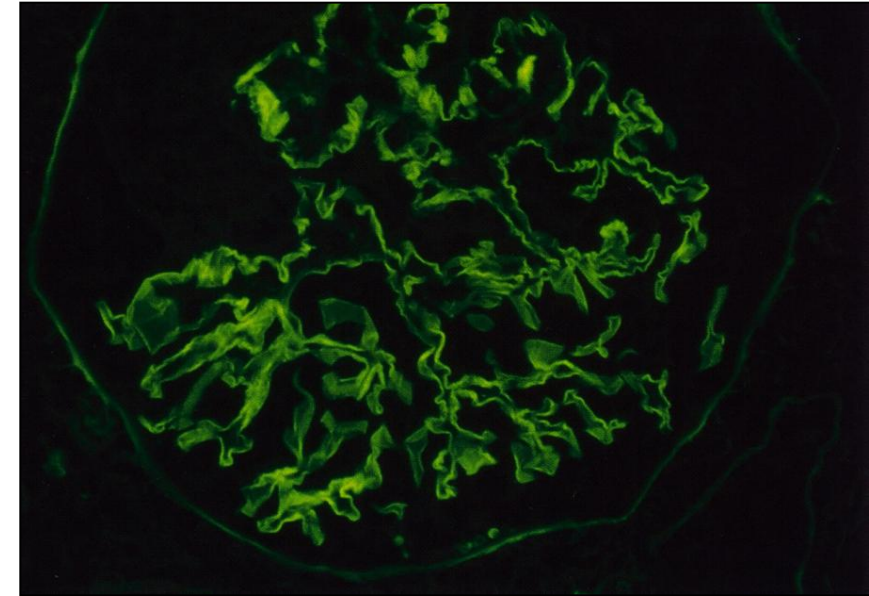
Type I RPGN = anti-glomerular basement membrane antibody-mediated crescentic GN: (12%) is characterized by the presence of auto antibodies directed against the GBM

Type II RPGN = immune complex mediated Crescentic GN: (44%) is caused by the formation and deposition of antigen antibody immune complexes e.g. SLE, IgA nephropathy, post-infectious GN etc.

Type III RPGN (Pauci-immune) ANCA-Associated Crescentic GN: (44%) the glomeruli are damaged by Activation of anti-neutrophil cytoplasmic antibodies e.g. Wegener granulomatosis and microscopic polyangitis

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 normally present in the glomerular basement membrane (GBM).
- On IF → characteristic intense linear staining/positivity with IgG along the GBM.
- Patients have nephritic syndrome picture
- patient's serum will have anti-GBM antibodies → helpful in diagnosis.
- If anti-GBM disease is associated with pulmonary hemorrhage (hemorrhagic pneumonitis) the condition is classified as Goodpasture's syndrome (in these patients, the anti-GBM antibodies also bind to pulmonary alveolar capillary basement membranes).
- Timely diagnosis of anti-GBM disease is important.
- Treatment: plasmapheresis, which removes pathogenic antibodies from the circulation.

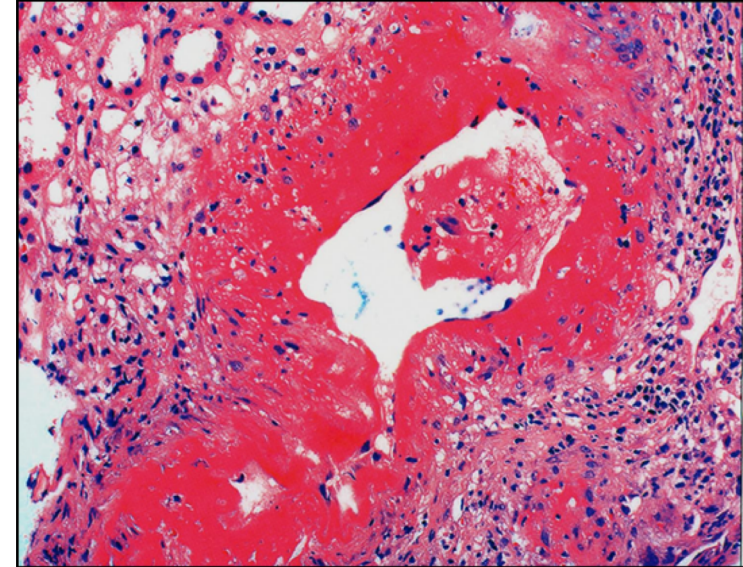


Type II RPGN = Immune complex mediated crescentic glomerulonephritis

- Crescents can be a complication of any of the immune complex mediated GN e.g.
 - poststreptococcal GN,
 - systemic lupus erythematosus,
 - IgA nephropathy and Henoch-Schönlein purpura.
- A consistent finding in this form of GN is that:
 - on IF there is presence of immune complexes (immunoglobulin and/or complement)
 - and on EM there are electron dense immune deposits.
- This disorder usually does not respond well to plasmapheresis.

Type III RPGN = Pauci-immune ANCA-associated GN (Wegener's granulomatosis with polyangitis)

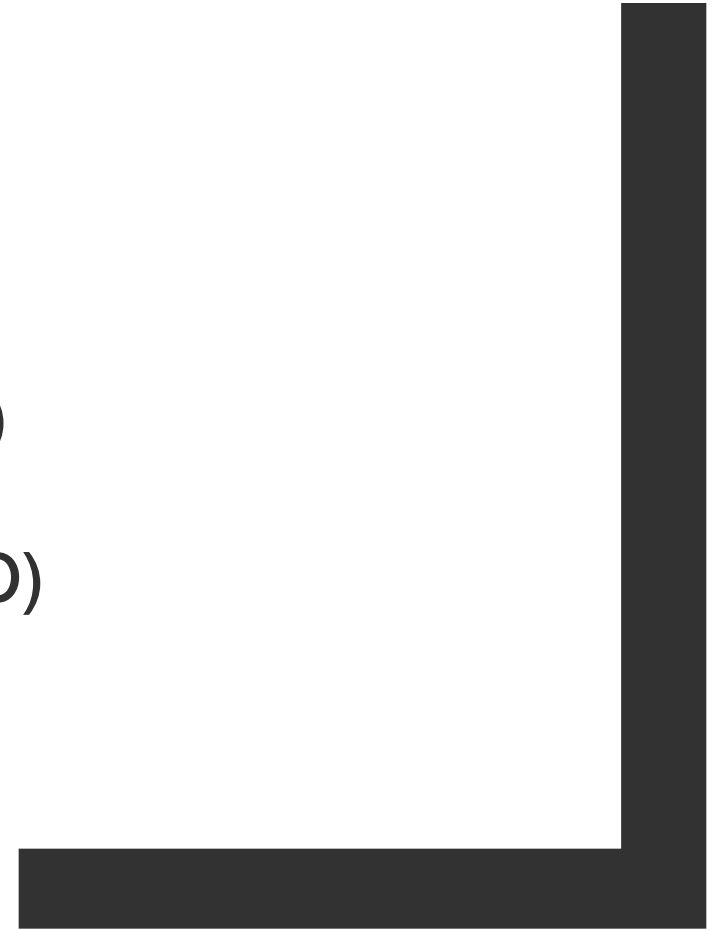
- Patients have autoantibodies directed against antigens present in the cytoplasm of neutrophils called antineutrophil cytoplasmic autoantibodies (ANCA).
- ANCA causes abnormal activation of neutrophil → adhesion of the neutrophils to endothelial cells lining the capillaries (esp. glomerular capillaries) → neutrophils promote vascular inflammation which leads to
 - glomerular injury with crescent formation.
 - necrosis (fibrinoid type) in the glomeruli and other blood vessels (arteries and arterioles). Some blood vessels can show transmural full thickness inflammation and necrosis (photo).
- Pauci-immune crescentic GN can be idiopathic or associated with systemic vasculitis like microscopic polyangiitis or Wegener granulomatosis.
- Note: in pauci-immune GN there is
 - ✓ no anti-GBM antibody
 - ✓ & no immune complex deposition so the IF is negative/almost negative and there are no deposits on EM (and that is why the name “pauci-immune” GN).
- Note: RPGN type I and II are ANCA negative.



RPGN/ CrGN: clinical features

- Present as nephritic syndrome that can progress to acute renal failure (marked oliguria and azotemia).
- Proteinuria sometimes approaching nephrotic range may occur.
- Some patients require long-term dialysis or transplantation.
- The prognosis can be roughly related to the fraction of involved glomeruli.

**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 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 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.

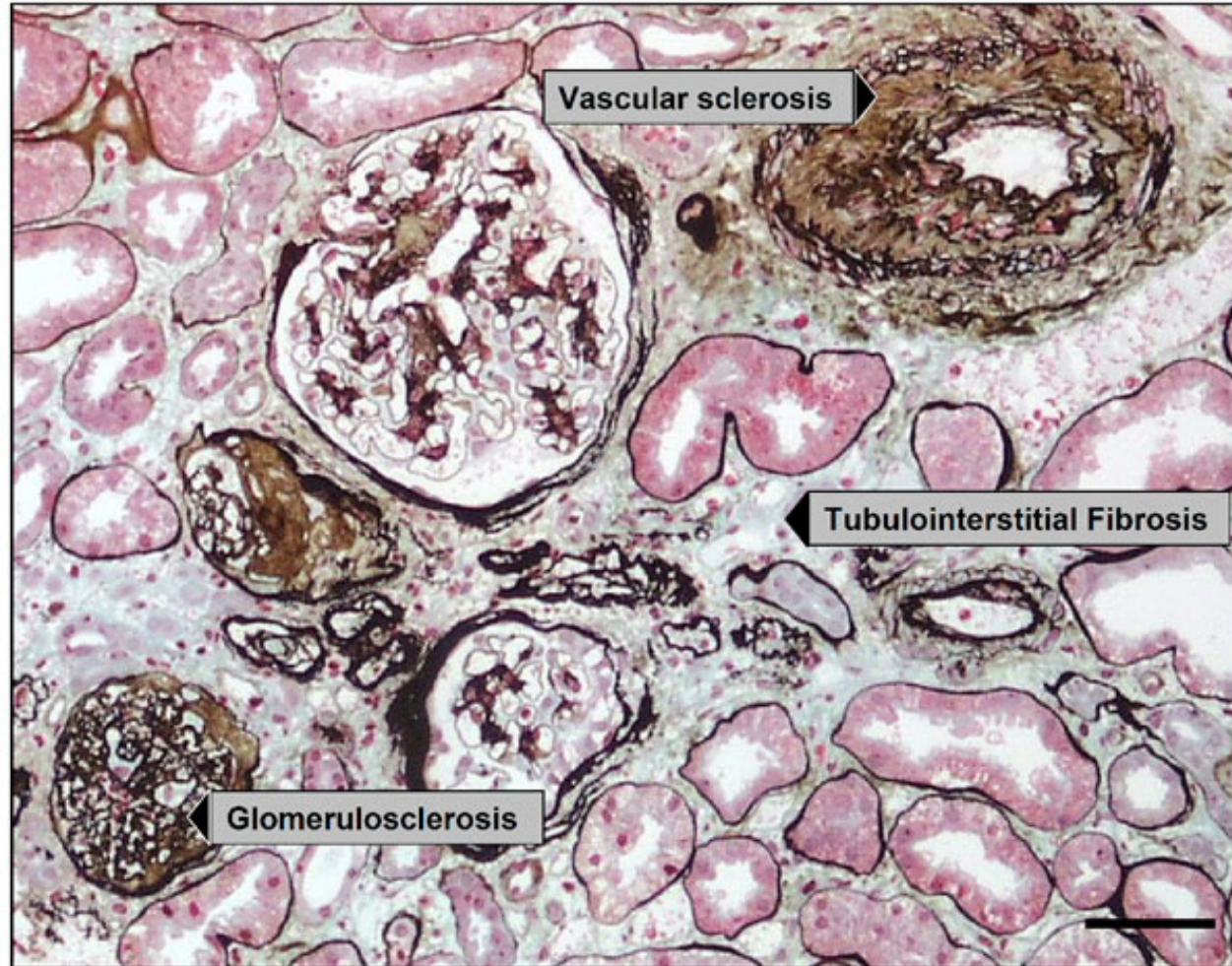
Gradual rise in BUN and serum creatinine.

High levels of urea in the blood can result in:

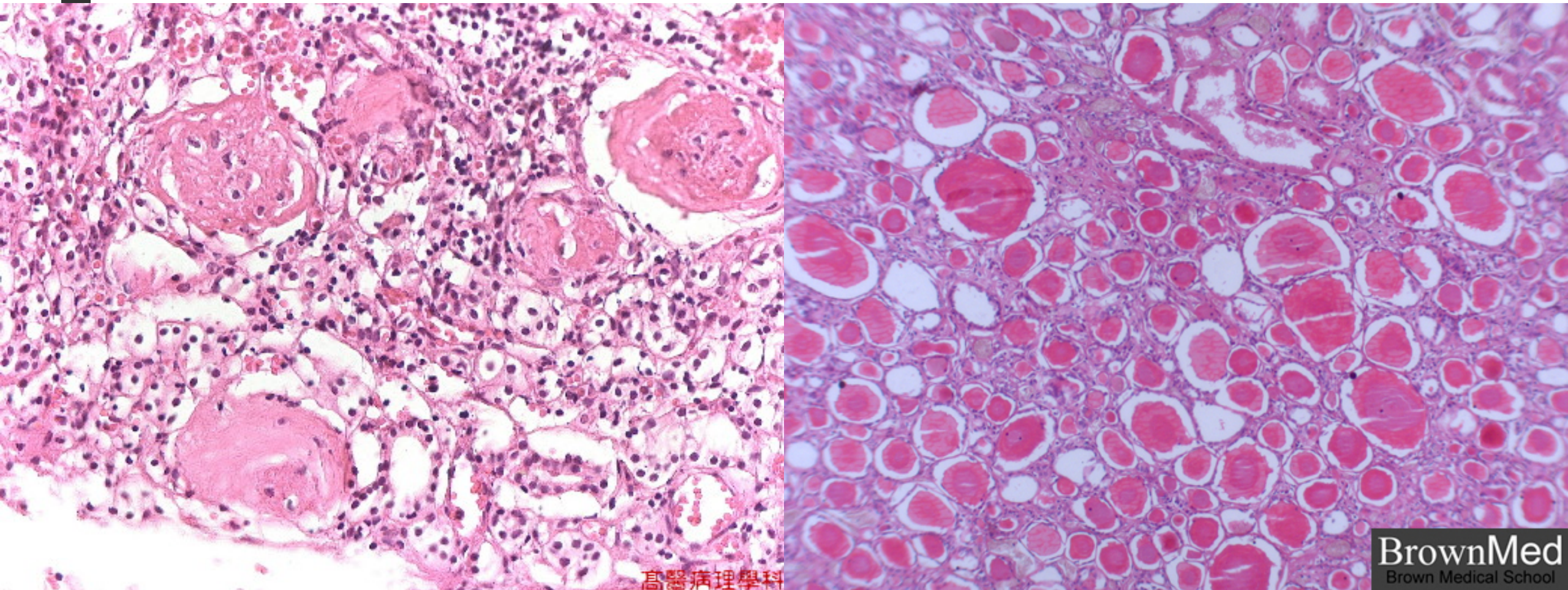
- **Azotemia** (increased urea and creatinine)
- **Acidosis, hyperkalemia, Hypokalemia** (due to failure of kidney to activate Vit D).
- **Abnormal fluid volume** → changes in urine output e.g. initially increased urine output and later decreased urine output. The sodium and water retention can lead 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 symmetrically contracted with red-brown and diffusely granular surface.
- Light microscopy usually shows:
 - ✓ Glomerular sclerosis and scarring of majority of the renal glomeruli
 - ✓ marked interstitial fibrosis with lymphocytic infiltrate
 - ✓ atrophy of the tubules in the cortex
 - ✓ loss of portions of the peritubular capillary network
 - ✓ Thick walled arteries and arterioles with narrowed lumina
- Such markedly damaged kidneys are designated "end-stage kidneys"

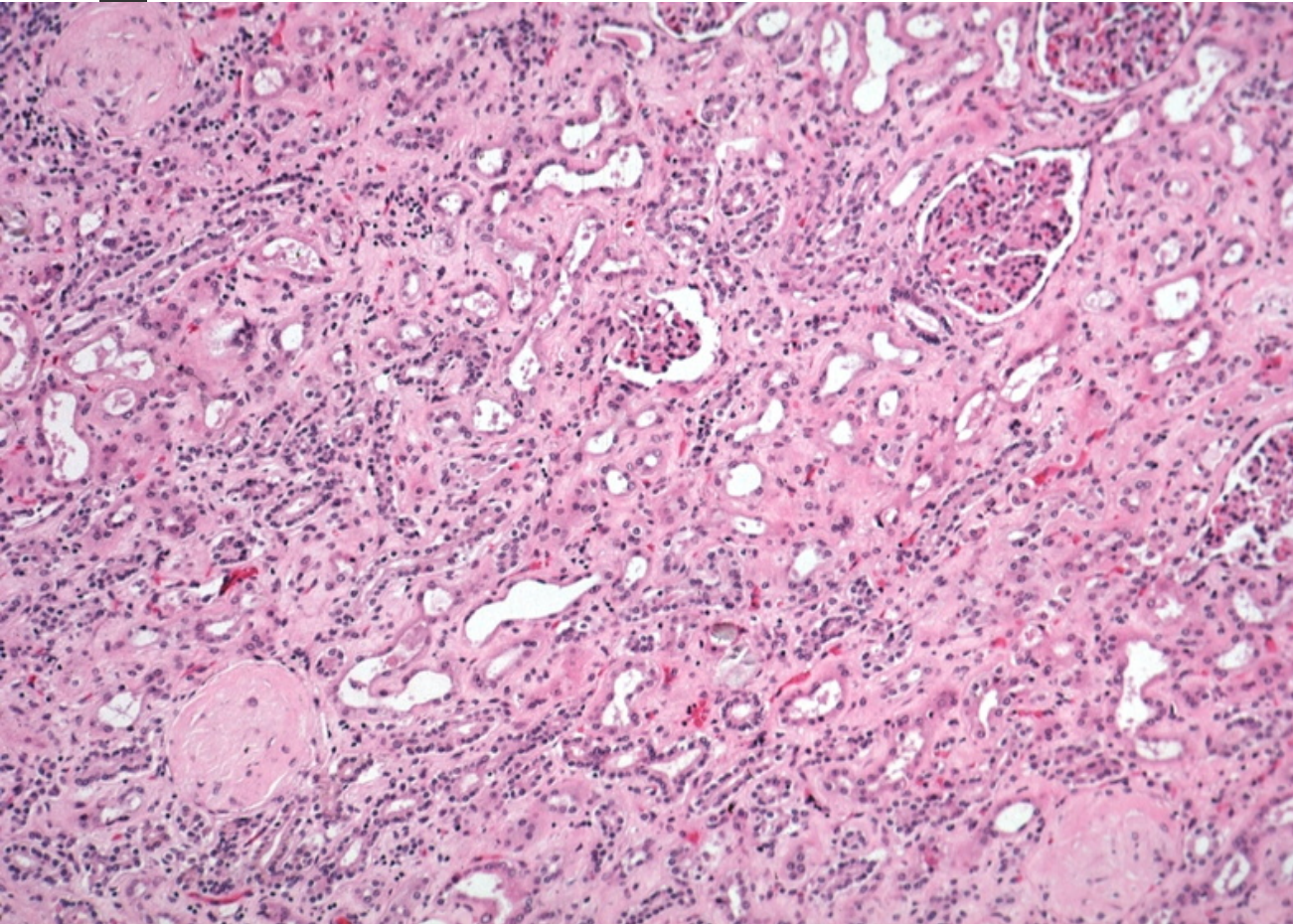


End stage kidney

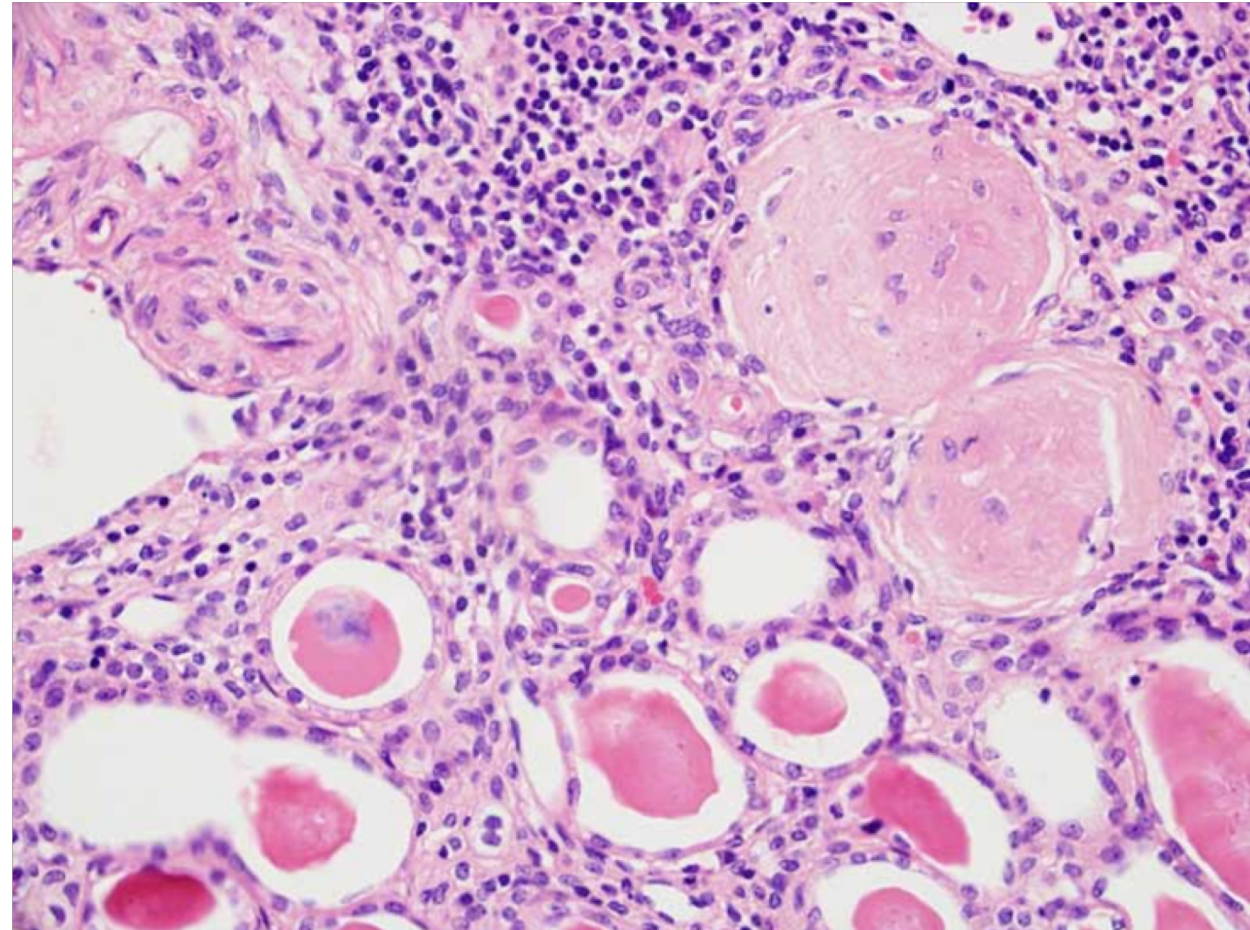


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End stage kidney



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