PATHOLOGY TEAM
439

Revised & Approved by:
Shayma Abdullah Alghanoum
Faisal Alotaibi

جامعة الملك سعود
King Saud University
1957

Rapid Progressive Glomeruloneph-ritis & CKD

GLOMERULAR DISEASES part 1for dr.ali
Part 2

Objectives:

- Recognize 2 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.

Index:
Important
NOTES
Extra Information

Clinical manifestations of kidney disease

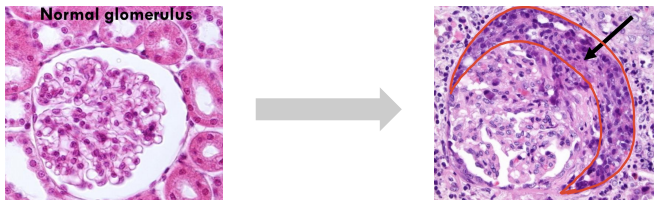
Nephritic syndrome	Results from glomerular injury leading to acute onset of hematuria (rbcs in urine), mild to moderate proteinuria, azotemia, edema & hypertension.
Nephrotic syndrome	heavy proteinuria (excretion of more than 3.5 g of protein/day in urine), hypoalbuminemia, severe edema, hyperlipidemia, 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 leading to 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)

Definition

RPGN is also known as "Crescentic glomerulonephritis" (**CRGN**). It is a clinical syndrome (not a final diagnosis, a collection of clinical features that could be caused by several things which will be the diagnosis). Its characterized by:

- ➢ Rapid progressive loss/decline of renal function within weeks to months
- ➢ Extensive glomerular crescent formation



In order for us to to call something as RPGN, sampled kidney biopsy must show **more than 50%** of glomeruli having crescents.

Histopathology

Commonly associated with:
Severe glomerular injury (reversible stage) with necrosis (irreversible stage), GBM rupture, subsequent proliferation of parietal epithelium (crescent formation).

Prognosis

Patients present with nephritic syndrome and progress to acute renal failure, the prognosis is poor **if untreated, even death.** (Poor prognosis)

Crescents

What are they?

Glomerular extracapillary parietal epithelial proliferations (which means proliferation outside the glomerular capillaries)

Why are they called crescents?

Because it has a crescent shape. شكل هلال

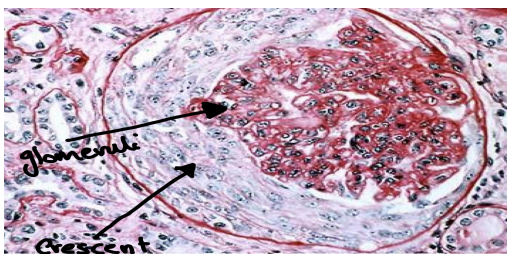
How are they formed?

1. proliferation of parietal epithelial cells that line the Bowman's capsule.
2. migration of monocytes/macrophages into Bowman's space.

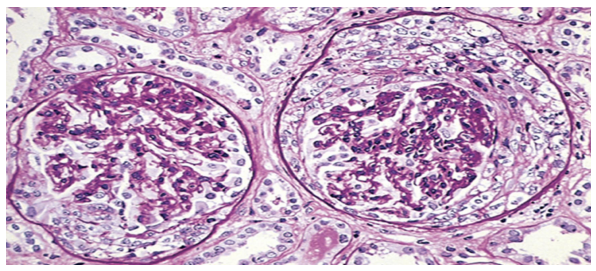
Light Microscopy

***Severe glomerular injury + presence of crecsents**

Crescent formation fills up bowman's space and compresses 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. (Instead of cells filling up bowman's space, the whole area will be fibrotic).



Clinical features

- Timely diagnosis is important.
- Some patients require long-term dialysis or transplantation.
- Proteinuria sometimes approaching nephrotic range may occur.
- 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).

dialysis :غسيل كلى

Types of RPGN or CRGN

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

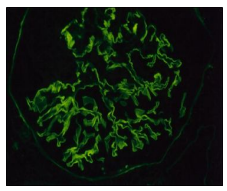
Type I RPGN (12%)
Anti-Glomerular Basement Membrane antibody disease (anti-GBM disease)

Overview

- A rare autoimmune disorder. It's characterized by presence of **auto-antibodies** directed **against an antigen** that is normally present **in the glomerular basement membrane** (GBM).

Diagnosis

- IF: **linear** staining or positivity **with IgG** immunoglobulin along the GBM.
- Patient's serum is **positive** for anti-GBM antibodies (helpful in diagnosis).
- Team 438: EM: negative.



Goodpasture's syndrome

- 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). In other words, it is the **involvement of both the kidneys and lungs**.

Treatment

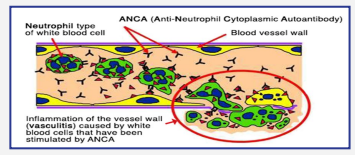
- responds well to plasmapheresis (it removes pathogenic antibodies from the circulation), steroids and cytotoxic agents.

Type II RPGN (44%)
Immune Complex Mediated Crescentic Glomerulonephritis

Overview

- 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. If any immune-mediated GN shows crescents it would fall under this category. Such as:
  - Poststreptococcal GN
  - Lupus nephritis (in systemic lupus erythematosus)
  - IgA nephropathy and Henoch-Schönlein purpura



Diagnosis
A consistent finding in this form of GN is that

- IF: shows positivity with various immunoglobulins and/or complements (depends on etiology, if IgA nephropathy we would see IgA antibodies in the mesangium).
- EM: shows electron dense immune deposits.

Treatment

- Type II RPGN **does not** respond well to plasmapheresis, the original underlying disease needs to be treated.

Type III RPGN (44%)
Pauci-Immune ANCA-associated GN

Overview

- Pauci= Few, It's called Pauci-Immune GN because there is
  - No anti-GBM antibody (not like type I)
  - Almost no immune complex deposition (not like type II)
  - RPGN type I and II are ANCA negative.
  - IF findings are negative/almost negative and EM shows no immune-complex deposits.

Etiology

- Due to circulating **A**ntineutrophil **C**ytoplasmic **A**utoantibodies (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 (especially glomerular capillaries)
  - Neutrophils release injurious products that promote endothelial injury, vascular inflammation (vasculitis and fibrinoid necrosis of arteries and arterioles) and crescentic GN.

Syndromes that is associated with:

- Pauci-immune crescentic GN is associated with systemic diseases like:
  - Granulomatosis with polyangiitis (formerly called Wegener's Granulomatosis) ⟶ **c**ANCA positive
  - Microscopic polyangiitis ⟶ **p**ANCA positive.

Treatment

- responds well to plasmapheresis (it removes pathogenic antibodies from the circulation), steroids and cytotoxic agents.

Chronic Renal Failure (CRF) or Chronic Kidney Disease (CKD)

Definition	Chronic kidney disease describes the slow or gradual loss of kidney function, can be a consequence of irreversible acute disease or progressive slow scarring in any type of chronic renal disease. The end result is **end stage kidney disease**.
End Stage Kidney Disease	It's the scarring of all 4 renal compartment:(regardless of the original site of injury) 1. Glomerulus: glomerular sclerosis. 2. Tubules: tubular atrophy. 3. Interstitium: interstitial fibrosis . 4. Blood vessels: arteriosclerosis.
Prognosis	Poor. Patients need dialysis or transplantation otherwise death from uremia will result. Dialysis and kidney transplantation allow long-term survival
Common Etiology	1. Chronic glomerulonephritis like RPGN, membranous GN, membranoproliferative GN, FSGS, IgA nephropathy, etc. 2. Diabetic Nephropathy 3. Hypertension 4. Reflux nephropathy in children 5. Polycystic kidney disease 6. Kidney infections & obstructions 7. Others

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.

Morphology

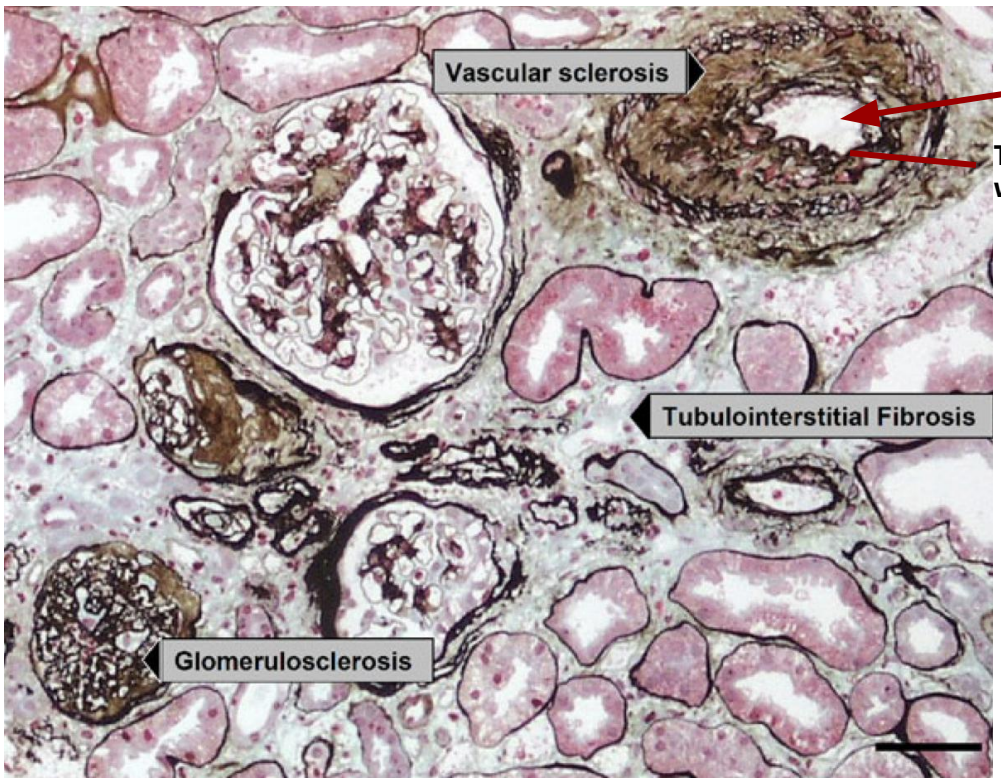
Grossly	Microscopically
The kidneys are **small** and contracted with **granular surface.** Markedly damaged kidneys are designated "end-stage kidneys".	❖ **Glomeruli**→ most of the glomerular are sclerosed (fibrosed/scarred) called glomerulosclerosis. ❖ **Tubules**→ show prominent atrophy with thyroidization of tubules (tubules are filled with eosinophilic hyaline casts resembling colloid in thyroid gland). ❖ **Interstitium**→ prominent interstitial fibrosis with lymphocytic infiltrate ❖ **Blood vessels**→ show thick walled arteries and arterioles with narrowed lumen.

- - - ➤

Chronic Renal Failure (CRF) or Chronic Kidney Disease (CKD)

Morphology

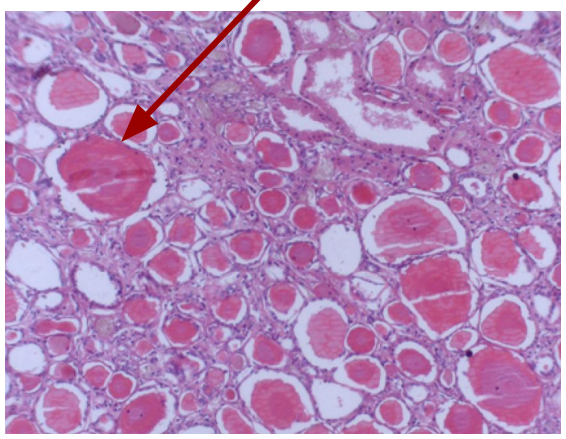
Microscopically



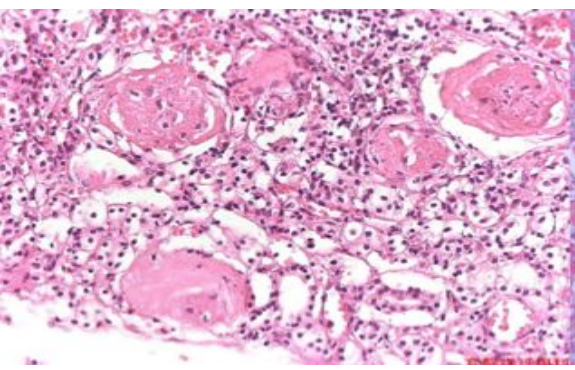
Narrowed lumen

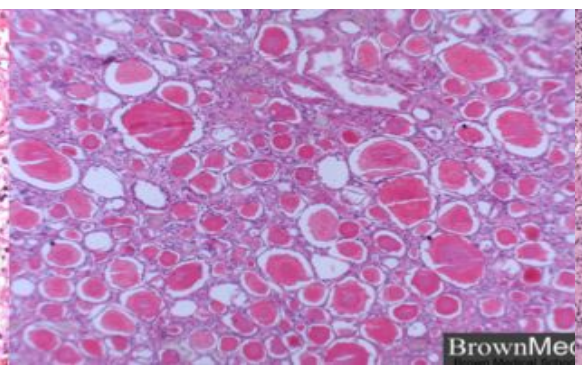
Thick wall

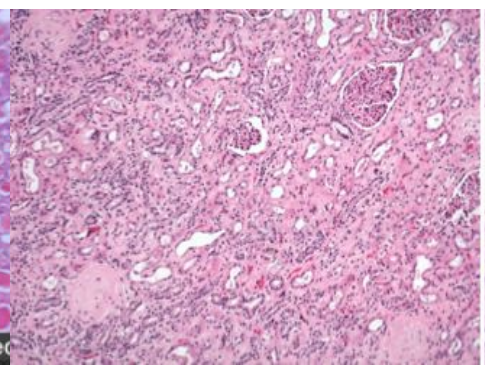
Thyroidization of tubules, look like thyroid gland

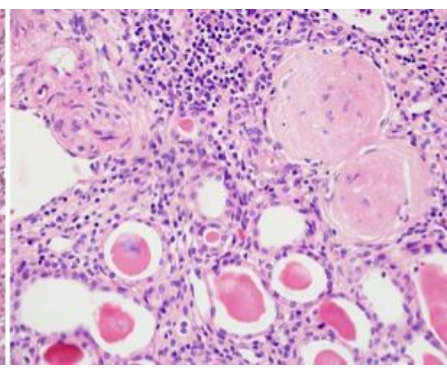


END STAGE KIDNEY

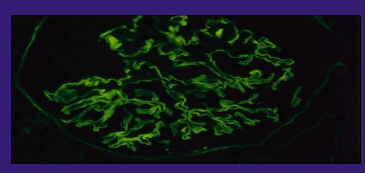








Qulz

1- A 65 year old male patient has a glomerular filtration rate of 55 mL/min and azotemia ,he suffered from pain in the bones and the electrolytes analysis shows low Ca2 , K2 in addition he has a low pH , The patient has a history of uncontrolled hypertension and coronary artery disease , what are the diagnosis?			
a- CHronic kidney disease	b- Acute Kidney injury	c- UTI	d- None
2- patient come to the hospital complaining from flank pain and have hematuria and mild proteinuria , doctors expecting RPGN and they discover that the patient have negative ACNA so what is possible could have ?			
a- I and II	b- I and III	c- II and III	d- All of them
3-biopsy for patient shows leukocytoclastic vasculitis in capillaries of skin and results of IF =negative for immune complexes and immunoglobulins Which one of the followings antibodies are frequently detected in patient ?			
a-Antistreptolysin O antibody	b-Anti-neutrophil cytoplasmic antibodies	c-Anti c3 nephritic factor	d-none
4- A 28-year-old man complains of nasal obstruction, bloody nose, cough, and bloody sputum. A chest X-ray displays cavitated lesions and multiple nodules within both lung fields. Urinalysis reveals 3+ hematuria and red blood cell casts. Laboratory studies show anemia and elevated serum levels of C-ANCA (antineutrophil cytoplasmic antibody). Peripheral eosinophils are not increased. A renal biopsy exhibits focal glomerular necrosis with crescents and vasculitis affecting arterioles and venules. What is the appropriate diagnosis? (cardiovascular block)			
a-Wegener granulomatosis.	b-Goodpasture syndrome	c-Hypersensitivity vasculitis	d-Polyarteritis nodosa
5-Which of the following best describes the renal disease of the patient described in Question 4?			
a-RPGN	b-Nephrotic syndrome	c-Type I membranoproliferative glomerulonephritis	d-Chronic nephritic syndrome
6-A 35-year-old man with a history of smoking presents with hematuria and bloody sputum. Over the next 2 days, he develops oliguria and renal failure, after which he is placed on dialysis. A renal biopsy is stained with fluorescein-conjugated goat antihuman IgG, and the results are shown. Which of the following best describes the pattern of direct immunofluorescence observed on this photomicrograph? 			
a-Linear along the glomerular basement membrane	b-Peripheral granular humps	c-Mesangial with a stalk predominance	d-Discontinuous and peripheral

1-A , 2-A , 3-B , 4-A ,5-A , 6-A

Summary

	The disease	LM	EM	IF	Characterized
RPGN	**Type I**, Anti-glomerular basement membrane antibody-mediated Crescentic GN	- Formation of many crescents - Crescents fill Bowman's space, compress glomeruli and can rupture the GBM - Segments of glomeruli may show necrosis. - With healing, crescents undergo fibrosis.		Linear staining/positivity with IgG immunoglobulin along the GBM	❖ Characterized by the presence of autoantibodies directed against the glomerular basement membrane.
	Type II, Immune complex mediated Crescentic GN		Electron dense immune deposits.	Presence of immune complexes (immunoglobulin and/or complement). Depending on the etiology	❖ Here the crescents are seen in renal disease in which is deposition of antigen antibody immune complex e.g. SLE, IgA nephropathy, past-infectious GN etc.
	Type III, (Pauci-immune) ANCA-Associated Crescentic GN		No deposits.	Negative/almost negative, no immune complex deposition.	❖ Characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) e.g. granulomatosis with polyangiitis (Wegener's) and Microscopic polyangiitis

	The disease	EM	IF	Characterized
Chronic Renal Failure (CRF)/ Chronic kidney disease (CKD) → End result: End-stage Kidney	- Glomerular sclerosis and scarring of most renal glomeruli. - 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.			Grossly, kidneys are symmetrically contracted with red-brown and diffusely granular surface.)

Team Leaders

-Rania Almutiri
- Hadi AlHemsi

Team members

عبدالرحمان الدويش
يزيد القحطاني
حمد الموسى
عبدالعزيز الربيعة
ابراهيم التميمي
عبدالعزيز السحيم
فيصل الفضل
عبدالرحمن بارشيد
ناصر السنبل
أحمد الحوامدة
عبدالإله الشمراني

Team members

فاطمة آل هلال
البندري العنزي
منى العبدلي
ريناد الحميدي
غادة العبدلي
نورة السالم
نورة الكثيري
ساره العبيد
لمى الأحمدي
الجوهرة البنيان
غيداء العسيري
ساره المقاطي
غادة العثمان
مريم الرحيمي
دعاء
غيداء المرشود
غادة السويلم

Editing File