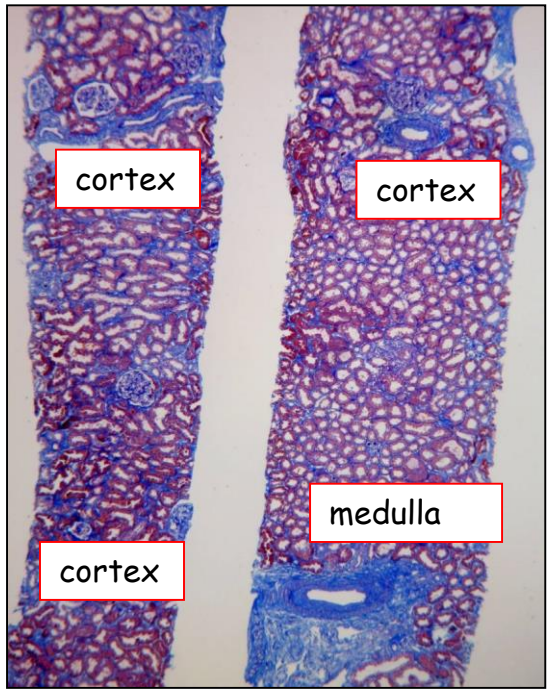
Primary glomerulopathies

dr hab. n. med. Joanna Pazik

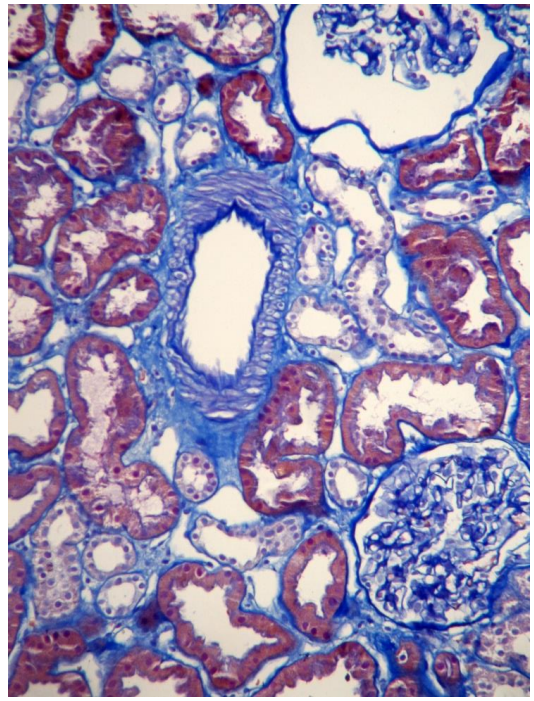
Klinika Medycyny Transplantacyjnej, Nefrologii i Chorób Wewnętrznych
Warszawski Uniwersytet Medyczny

THICK NEEDLE BIOPSY OF THE KIDNEY

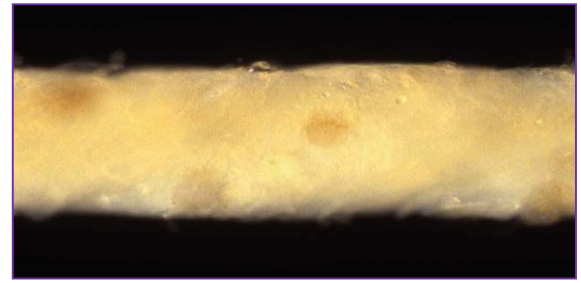
AFOG staining



Two biopsy speciments contaning kidney cortex and medulla



Kidney cortex specimen with healthy artery (A), tubuli and two glomeruli



Light microscopy

Immunomorphological examination (most commonly IF)

Electron microscopy

Pattern of injury and diagnosis of the disease

Diseases most often manifest themselves in a non-specific way.

In diagnostics, we usually start with determining the PATTERN (manifestation), which directs / narrows down the further search for something highly characteristic-unique, a specific etiological factor / cause / substrate), i.e. the search for DISEASE.
Different diseases can take a similar manifestation (PATTERN).
The same PATTERN can be found in various diseases.

In nephrologist perspective :

Clinical pattern: nephrotic syndrome

In pathologist perspective :

Underlying disease: amyloidosis, IgA nephropathy, lupus nephritis ……

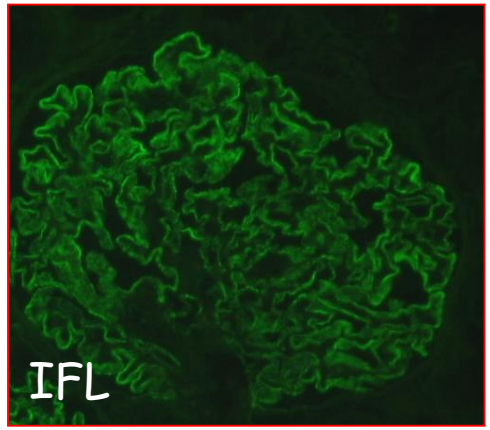
In pathologist perspective :

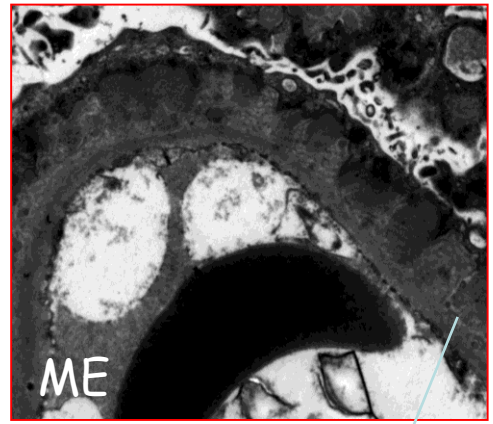
The disease: IgA nephropathy

In nephrologist perspective :

Pattern: isolated erythrocyturia, non-nephrotic proteinuria and erythocyturia, nephritic syndrome

Various diseases may express by the same pattern





HP PATTERN/DISEASE MANIFESTATION is the same in all 5 cases

Membranous glomerulonephritis (immune-complex deposition disease)

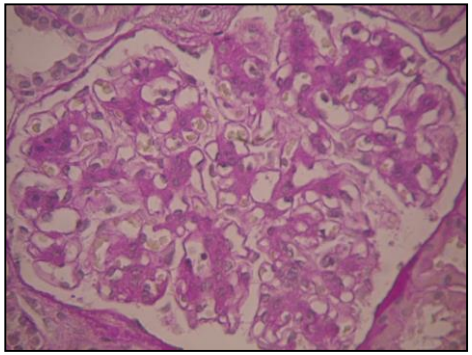
Immune complexes in the localization typical for MEMBRANOUS GN

- Patient with SLE
- Patient with RA treated with gold+ penicillamine
- Patient with local (glomerular) autoimmune disorder (PLA2R Ag/AntyPLA2R)
- Patient with adenocarcinoma of the colon
- Patient with chronic B hepatitis

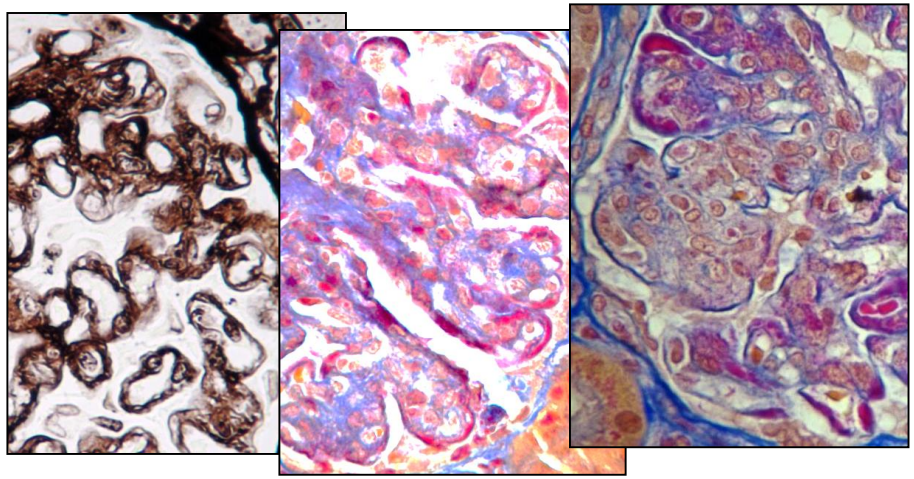
Different patterns may be seen in a course of the same disease….

ex. lupus nephritis –three different HP pattens

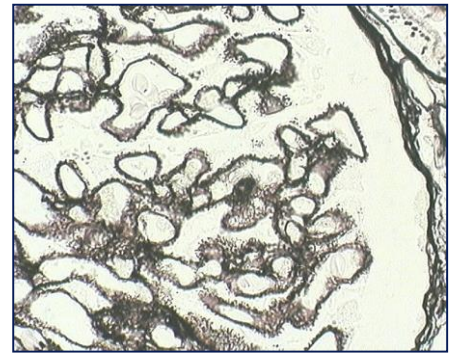
Class II
mesangial
proliferation



Class III,IV
proliferation/endocapillary
inflamation
Membrano-proliferative



Class V
membranous
injury



THE CLINICAL SYNDROMES

1. The acute (abruptly developing) Nephrotic Syndrome
2. The acute Nephritic Syndrome
3. Rapidly progressive glomerulonephritis
4. Asymptomatic hematuria / proteinuria
5. The chronic nephritic syndrome (chronic renal failure)

THE BASIC STRUCTURAL PATTERNS OF GLOMERULAR INJURY

1. Epithelial Cell Disease (Minimal Change Disease)
2. Focal Segmental Glomerulosclerosis
3. Membranous Nephropathy
4. Diffuse Proliferative Glomerulonephritis
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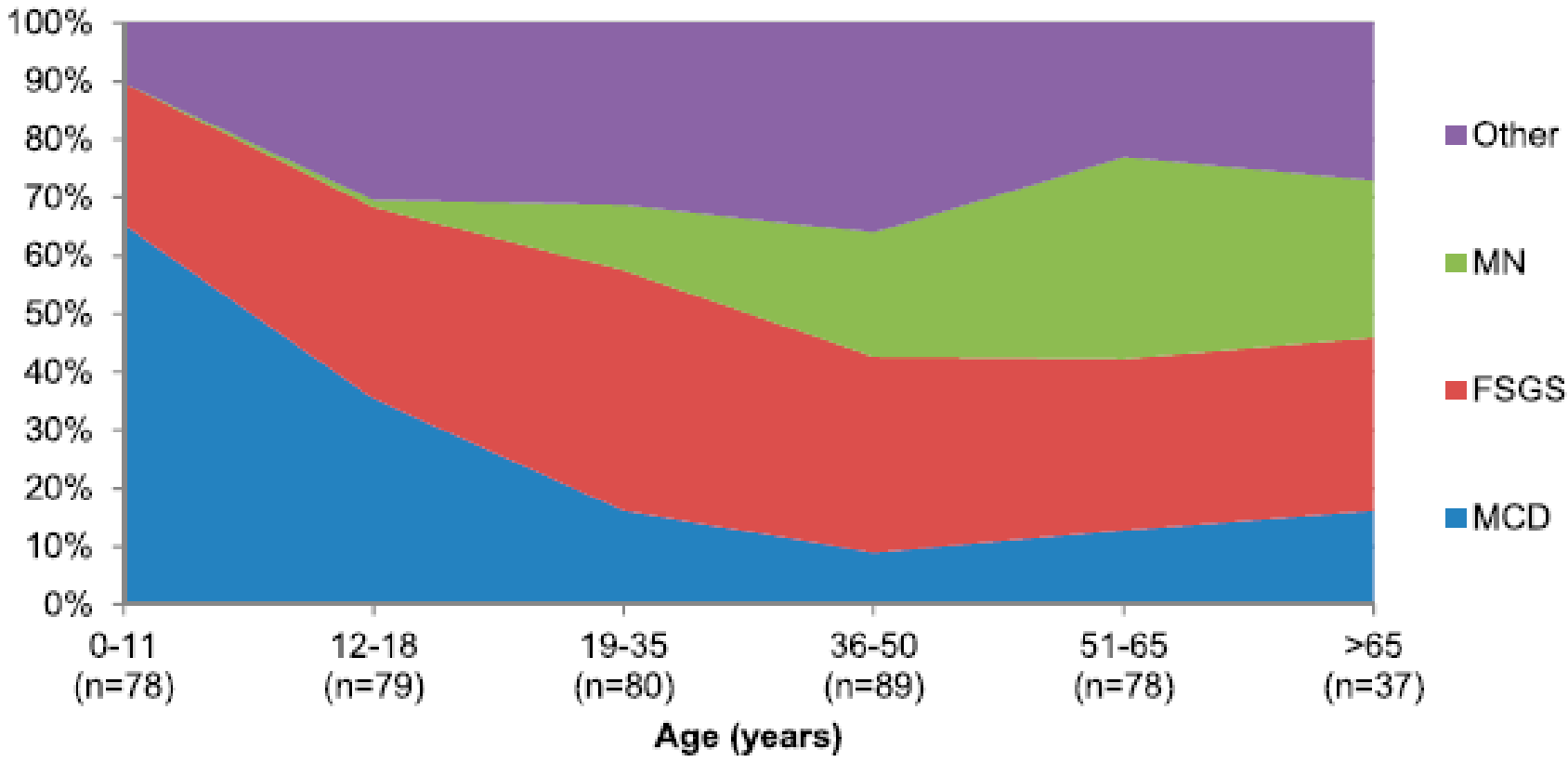
9. Basement Membrane Abnormalities
10. Focal Global Glomerulosclerosis, tubulointersitial inflamation/fibrosis, arteriosclerosis

Histopatological patterns underlying nephrolitic syndrome by patients age



Gipson D Nephrotic Syndrome Study Network CJASN 2016

In the following slides I will refer to typical clical patterns of GN presentation

and

corresponding histopathological patterns that may occur

With special attention given to how histopathology changes translate into clinical smptoms

Trigger Case 1

A 5-year-old boy presents to the emergency room with a 1-week history of generalized edema and fatigue. Your history reveals that he suffered from a viral URI 1 week before this visit. Serum and urine studies reveal massive proteinuria, hyperlipidemia, and hypoalbuminemia. You suspect that a renal biopsy would show ...

What is the Diagnosis?

THE CLINICAL SYNDROMES

1. The acute (abruptly developing) Nephrotic Syndrome
2. The acute nephritic syndrome
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THE NEPHROTIC SYNDROME

A syndrome associated with a such a loss of protein with the urine that the system (particularly liver) is not able to compensate with an enhanced proteins production.

Hence, the prerequisites for the diagnosis of NEPHROTIC SYNDROME are proteinuria and hypoproteinemia.

In an otherwise heathy people with normal synthetic liver function symptoms of the inability to compensate for proteinuria appear after exceeding the value of 3.5 g / day.
In people with liver dysfunction nephrotic syndrome symptoms nay occur even when proteinuria is lower than 3.5 g/day

Nephrotic syndrome includes:

- **Proteinuria usually >3.5 g/d (diagnostic criterion)**
- **hypoproteinemia / hypoalbuminaemia NS (diagnostic criterion)**
- oedema (they do not always occur)
- dyslipidemia
- Thrombophilia

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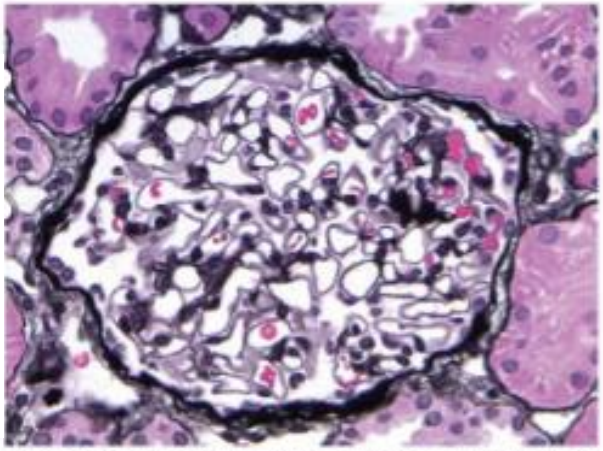
Minimal Change Disease

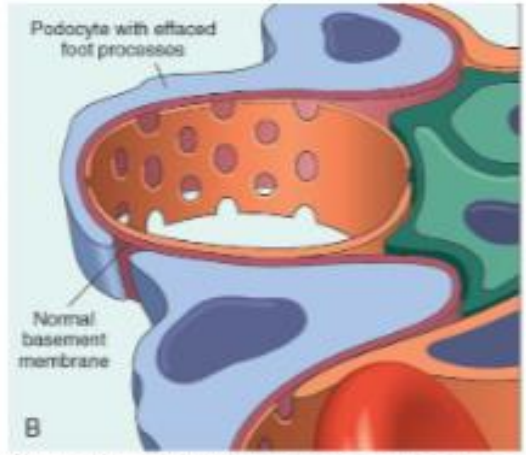
In other words: NIL disease (nothing in light microscopy)

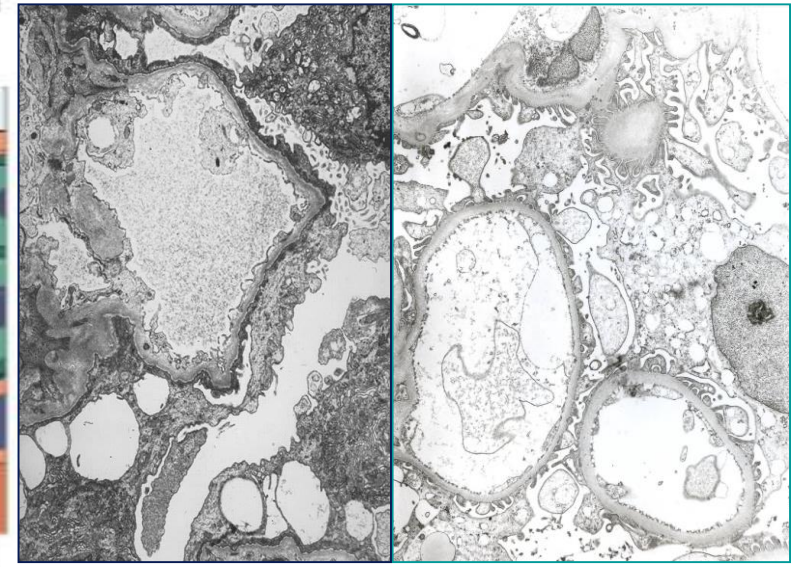
MCD

(A) When viewed with a LM, silver methenamine–stained glomerulus appears normal, w a delicate basement membrane.

(B) Schematic diagram illustrating diffuse **effacement of foot processes** of podocytes with no immune deposits.







Kumar V, Abbas AK, Aster JC. *Robbins and Cotran Pathologic Basis of Disease, 9th ed. Philadelphia:* Saunders-Elsevier, 2015.

MINIMAL CHANGE

One of the patterns of injury

Some patients experience multiple episodes of nephrotic syndrome.

Non-progressive injury

May be idiopathic (genetic predisposition),

Or secondary (drugs toxicity, limphoproliferative disorders, systemic diseases).

Main cause of nephrotic syndrome in children in young adults.

MCD pathogenesis

systemic T cell dysfunction

patients with Hodgkin lymphoma

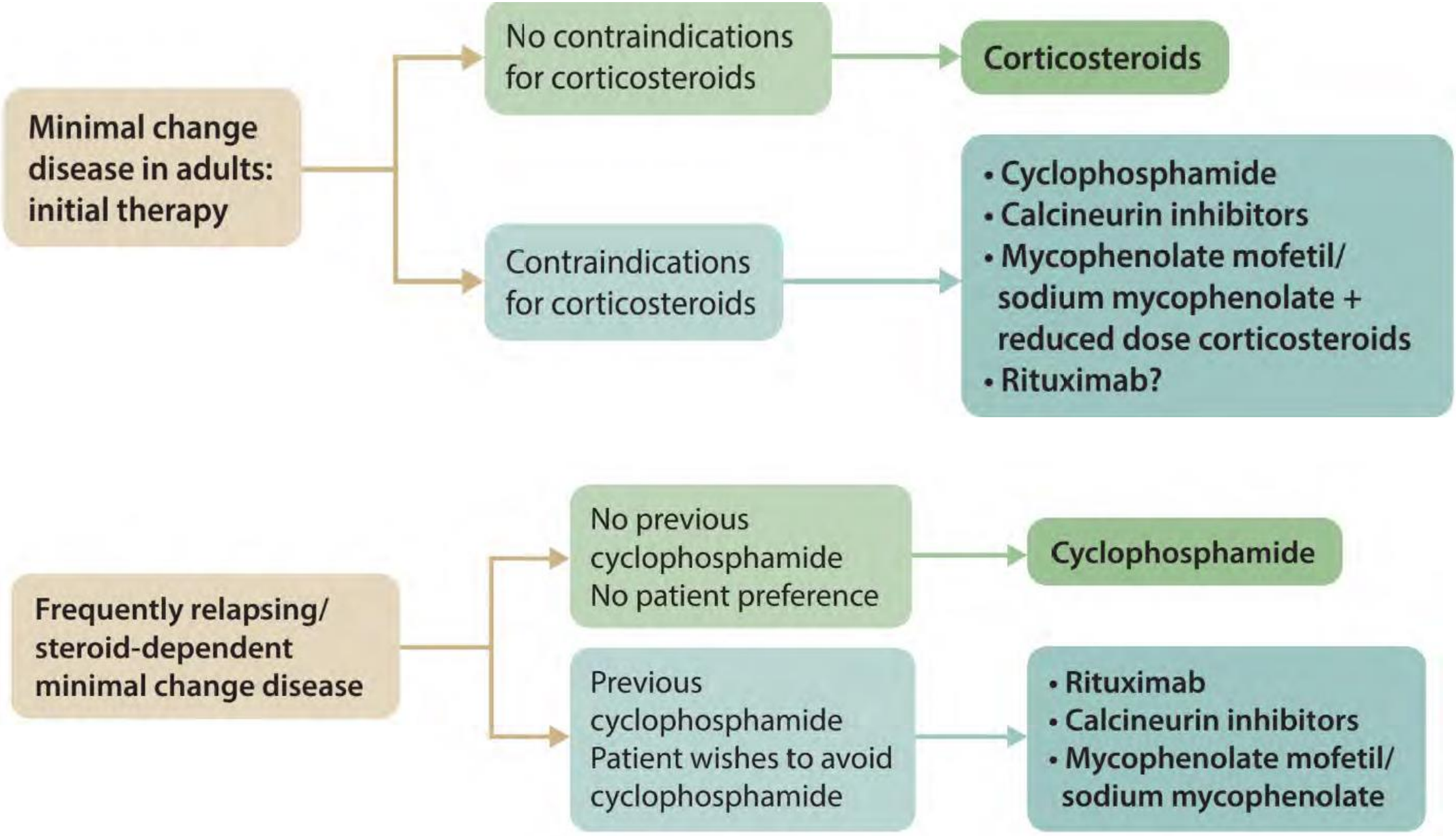
patients with atopic disease

B cell dysfunction

rituximab efficacy

glomerular permeability factor

Neoplasms, infections, allergy, other glomerular diseases


Minimal change disease in adults: initial therapy
No contraindications for corticosteroids
Corticosteroids
Contraindications for corticosteroids
• Cyclophosphamide
• Calcineurin inhibitors
• Mycophenolate mofetil/ sodium mycophenolate + reduced dose corticosteroids
• Rituximab?
Frequently relapsing/ steroid-dependent minimal change disease
No previous cyclophosphamide
No patient preference
Cyclophosphamide
Previous cyclophosphamide
Patient wishes to avoid cyclophosphamide
• Rituximab
• Calcineurin inhibitors
• Mycophenolate mofetil/ sodium mycophenolate

Trigger case 2

57 year old man who presents to your office with a chief complant of increased swelling in his legs. Recent laboratory studies show proteinuria, hypoalbuminemia hyperlipidemia. You suspect that a renal biopsy would demonstrate ……..

What is the diagnosis?

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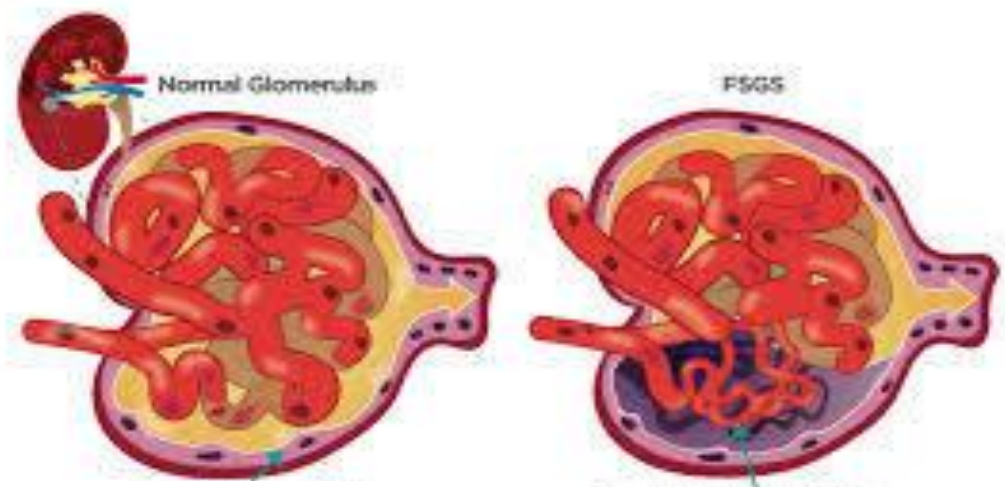
Clinically the beginning is the same as in MINIMAL CHANGE: the abrupt evolution of nephrotic proteinuria,

Morphologically: in the beginning the same as in MINIMAL CHANGE: diffuse flattening of podocyte foot processes



GBM denudation

sclerotization is a spot where glomerular tuft forms adhesion with Bowman's capsule

In FSGS injurious factor causes not only foot processes flattening but also podocyte death the number of podocytes decreases gradually

PODOCYTES DO NOT HAVE THE CAPACITY TO REGENERATE/PROLIFERATE

FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

Idiopathic or primary FSG

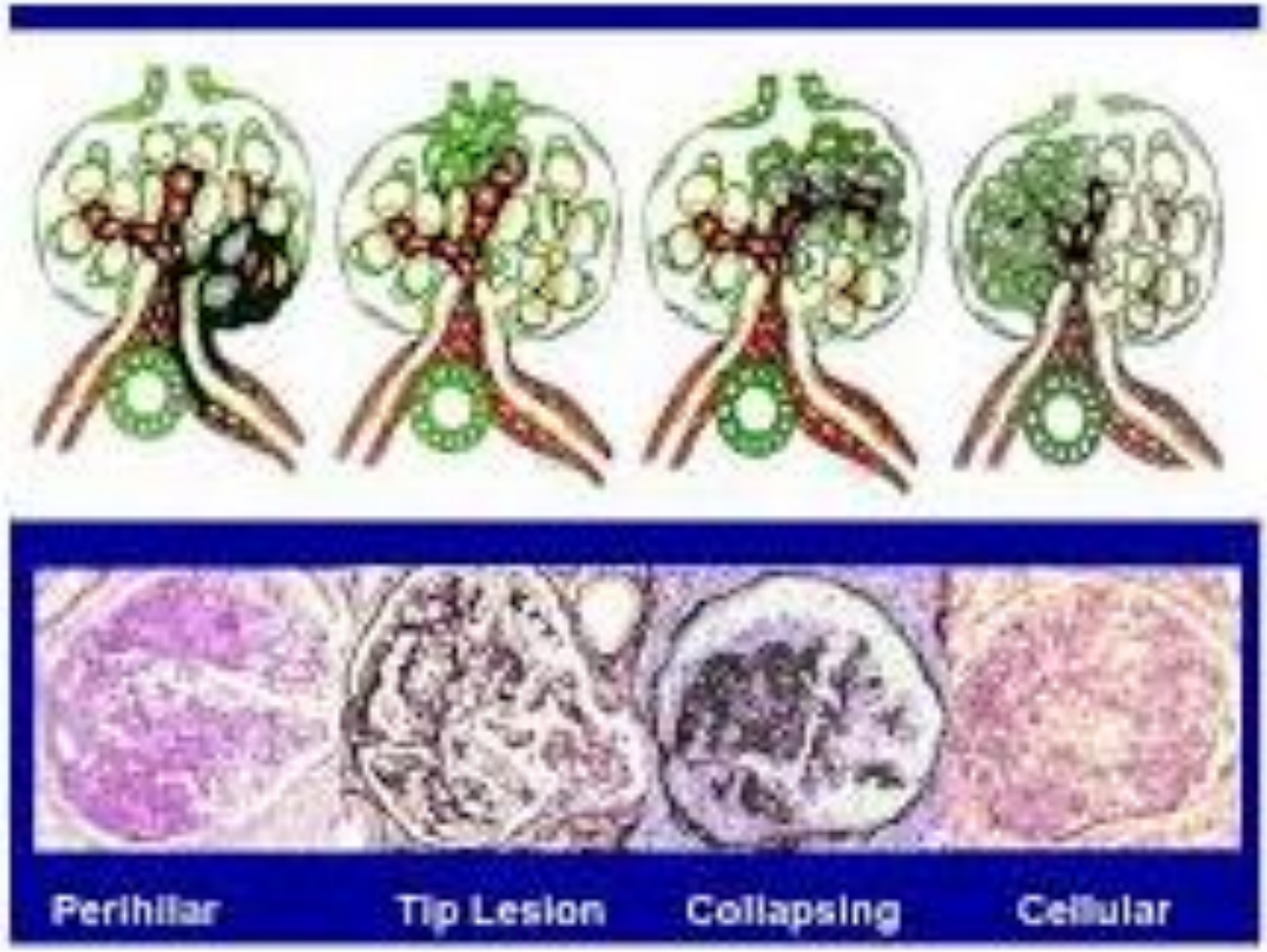
-background: due to the presence of circulating permeability factor that damages podocytes

-**manifestation: acute nephrotic syndrome (+/-erythrocyturia), edema**

-morphologically: diffuse, global fusion of podocyte foot processes, progressive tuft sclerotization

- genetically determined
- secondary to other forms of kidney injury

Histologic Variants on FSGS



Treatment	Dose and duration
Corticosteroids	**Starting dose:** • High dose corticosteroid therapy with prednisone at daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg)
	High dose corticosteroid treatment duration: • Continue high dose corticosteroid therapy for at least 4 weeks and until complete remission is achieved, or a maximum of 16 weeks, whichever is earlier • Patients who are likely to remit will show some degree of proteinuria reduction before 16 weeks of high dose treatment • It may not be necessary to persist with high-dose corticosteroid therapy until 16 weeks if the proteinuria is persistent and unremitting, especially in patients who are experiencing side-effects
	Corticosteroid tapering: • If complete remission is achieved rapidly, continue high dose corticosteroid treatment for at least 4 weeks or for 2 weeks after the disappearance of proteinuria, whichever is longer. Reduce prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months • If partial remission is achieved within 8 to 12 weeks of high dose corticosteroid treatment, continue until 16 weeks to ascertain whether further reduction of proteinuria and complete remission may occur. Thereafter, reduce the dose of prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months • If the patient proves to be corticosteroid-resistant or develops significant toxicities, corticosteroids should be rapidly tapered as tolerated and treatment with alternative immunosuppression like a CNI should be considered
Calcineurin inhibitors	**Starting dose:** • Cyclosporine 3–5 mg/kg/day in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/day in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml • Tacrolimus target trough level: 5–10 ng/ml
	Treatment duration for determining CNI efficacy: • Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 6 months, before considering the patient to be resistant to CNI treatment
	Total CNI treatment duration: • In patients with partial or complete remissions, cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 12 months to minimize relapses • The dose of cyclosporine or tacrolimus can be slowly tapered over a course of 6–12 months as tolerated

In cases of steroid-resistant FSGS

Treatment	Dose and duration
Calcineurin inhibitors	**Starting dose:** • Cyclosporine 3–5 mg/kg/day in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/day in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml • Tacrolimus target trough level: 5–10 ng/ml
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Inability to tolerate or contraindications to calcineurin inhibitors	• Lack of quality evidence for any specific alternative agents • Mycophenolate mofetil and high-dose dexamethasone, rituximab, and ACTH have been considered • Treatment will need to be personalized and is dependent on availability of drugs and resources, as well as the benefits of further treatment and risks of adverse effects of immunosuppression • Patients should be referred to specialized centers with the appropriate expertise, and should be evaluated on the appropriate use of alternative treatment agents or to discontinue further immunosuppression

Secondary FSGS due to …

Potential causes of FSGS:

- Mutations of genes coding for proteins that make up the filtration barrier (Nephrins, Podocins, Laminin, Collagen IV, CD2AP)
- Viral infections (HIV, parvovirus)
- Toxic effect of certain drugs (bisphosphonates, anabolic steroids)
- Sclerosis secondary to glomerulonephritis, bundle necrosis,
- Compensatory mechanisms secondary to relevant or irrelevant deficit in the number of nephrons

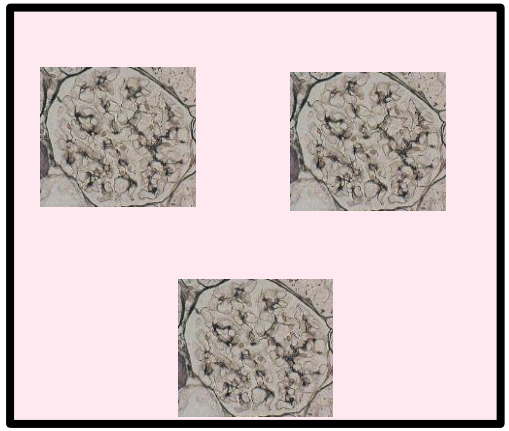
Apart from all mentioned causes of SECONDARY FSGS

SEPARATE, VERY IMPORTANT etiological background of this injury evolutions is progressive loss of functioning renal tissue.

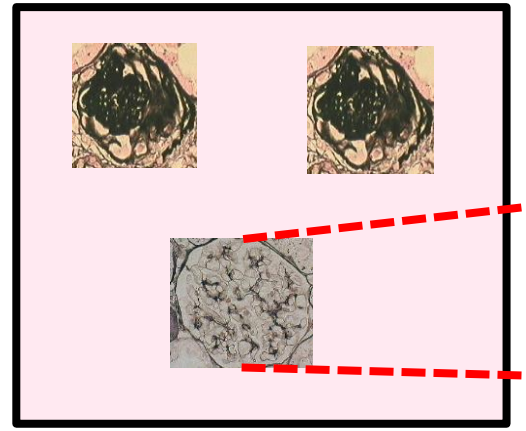
EVERY CASE OF PROGRESSIVE KIDNEY DISEASE is associated with secondary FSGS development.

ADAPTIVE MECHANISM IN A PROGRESSIVE KIDNEY DISEASE

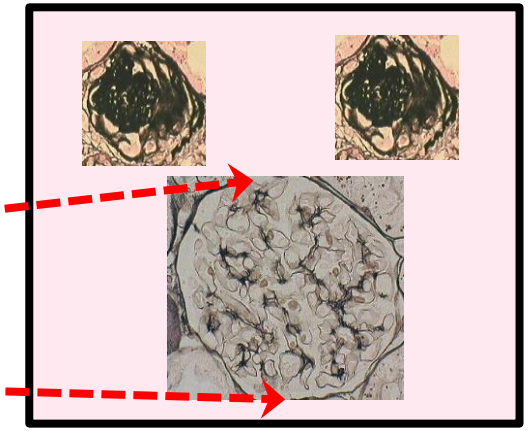
This mechanism allows for GFR stabilization despite ongoing drop in the numer of functioning glomeruli.



3 normal glomeruli in a portion of kidney cortex

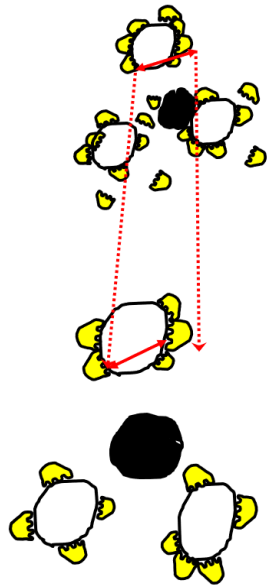


Let's assume that in a course of CKD two upper glomeruli become sclerosed

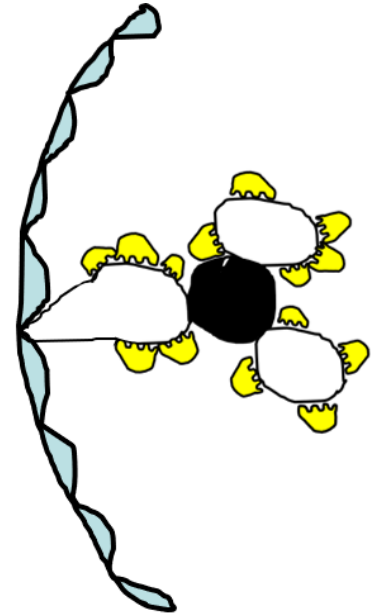


- The remaining glomerulus takes over the function of the two sclerosed ones. It enlarges and has increased filtration pressure in its capillaries, in consequence the blood volume filtered in this glomerulus per time unit rises.
- UNFORTUNATELY this mechanism causes secondary sclerotization of hypertrophied glomerulus.

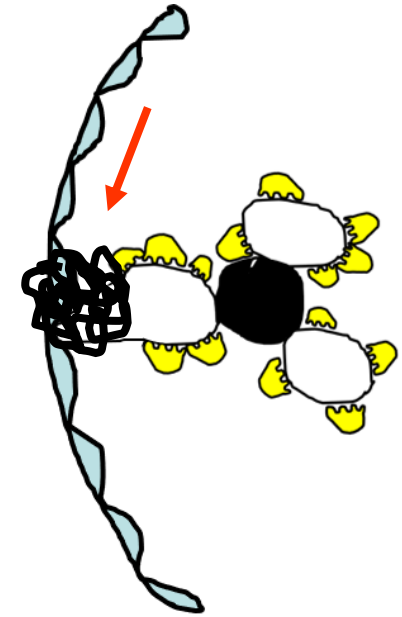
Concequences of the compensatory hypertrophy of the glomerulus



Increase of capillars diameter and their surface area

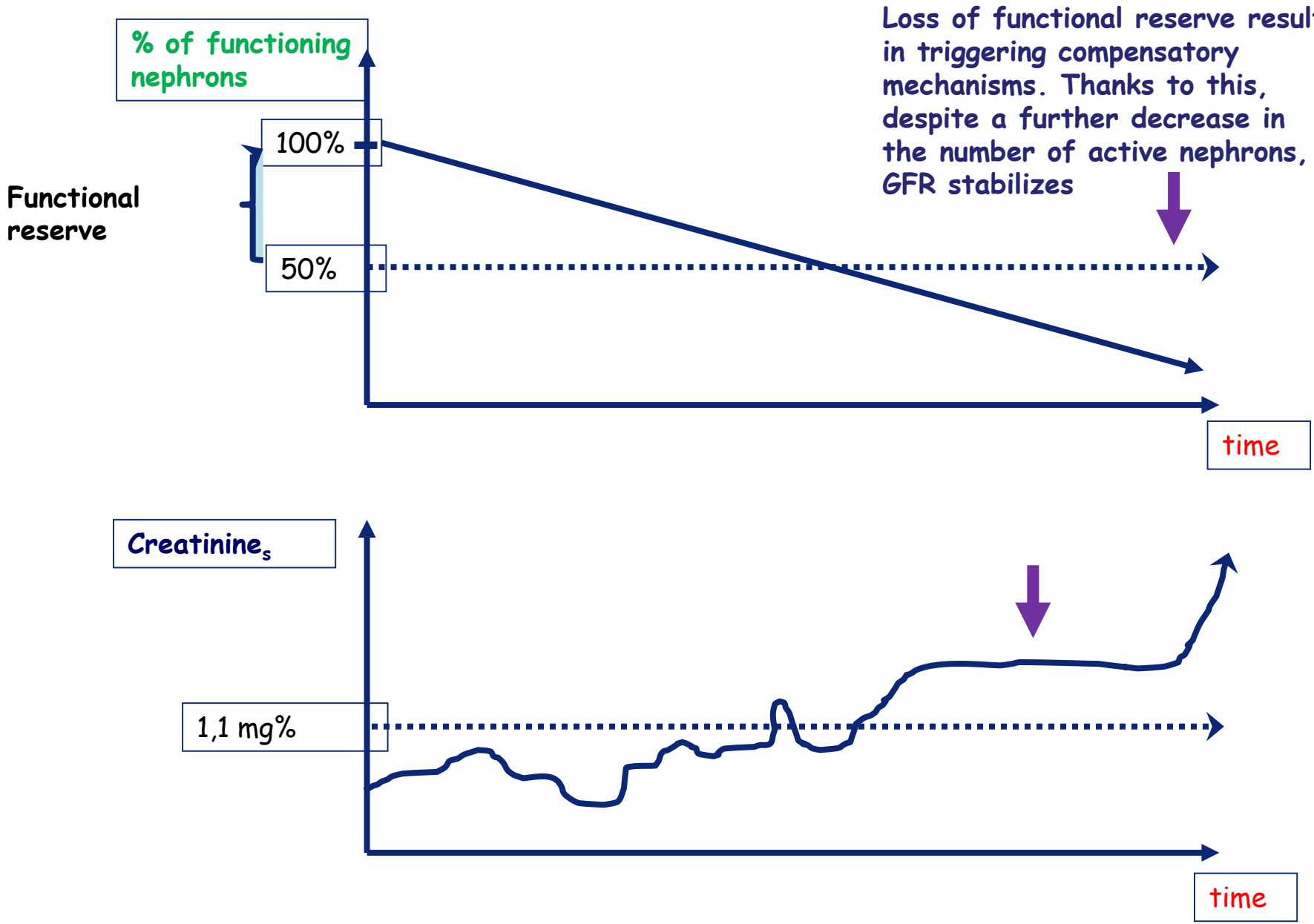


Denudated GBM is highly protein permeable and "tends" to be covered by the epithelium lining Bowman's capsule



At the site of adhesion between the vascular loop with Bowman's capsule, the sclerosing of the vascular bundle begins

PROGRESSIVE CHRONIC KIDNEY DISEASE



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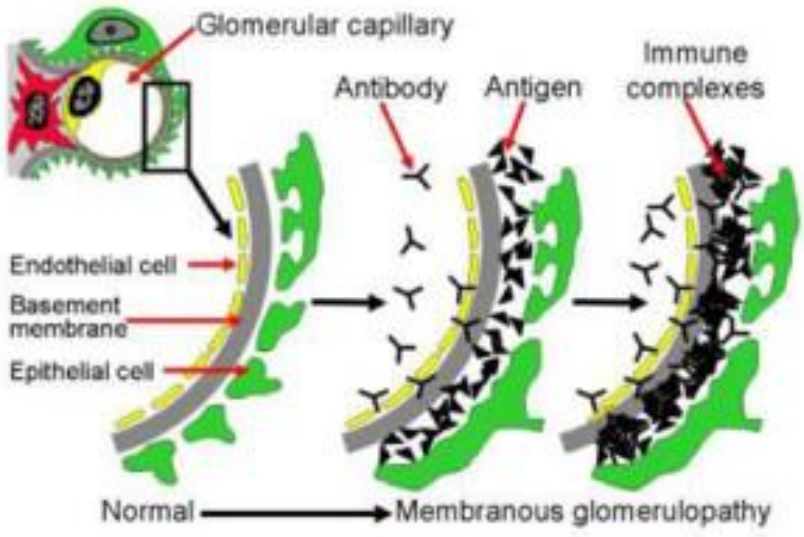
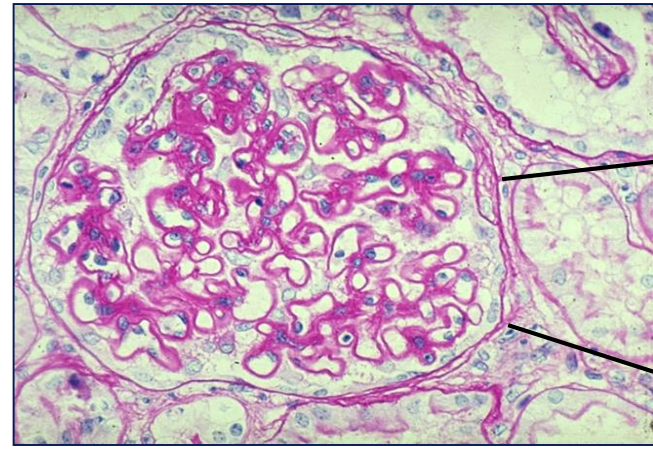
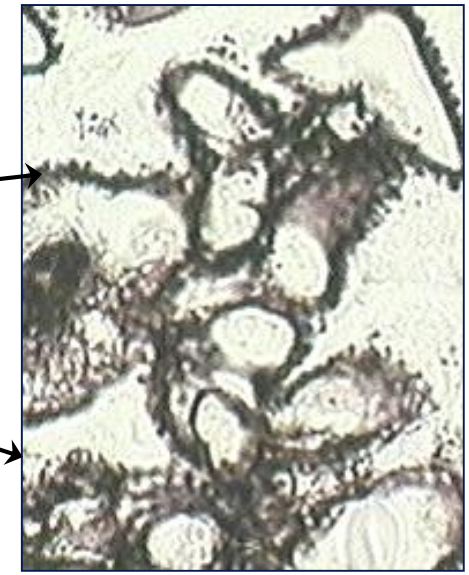
Membranous nephropathy

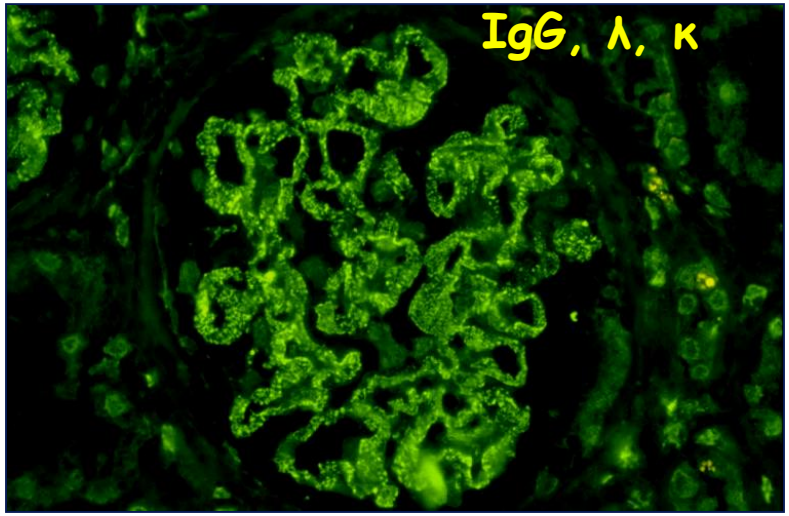




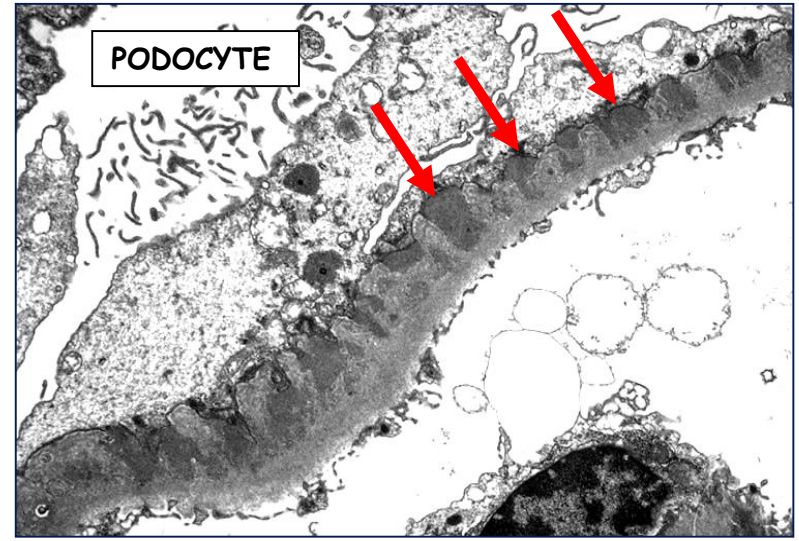


GBM protrusions

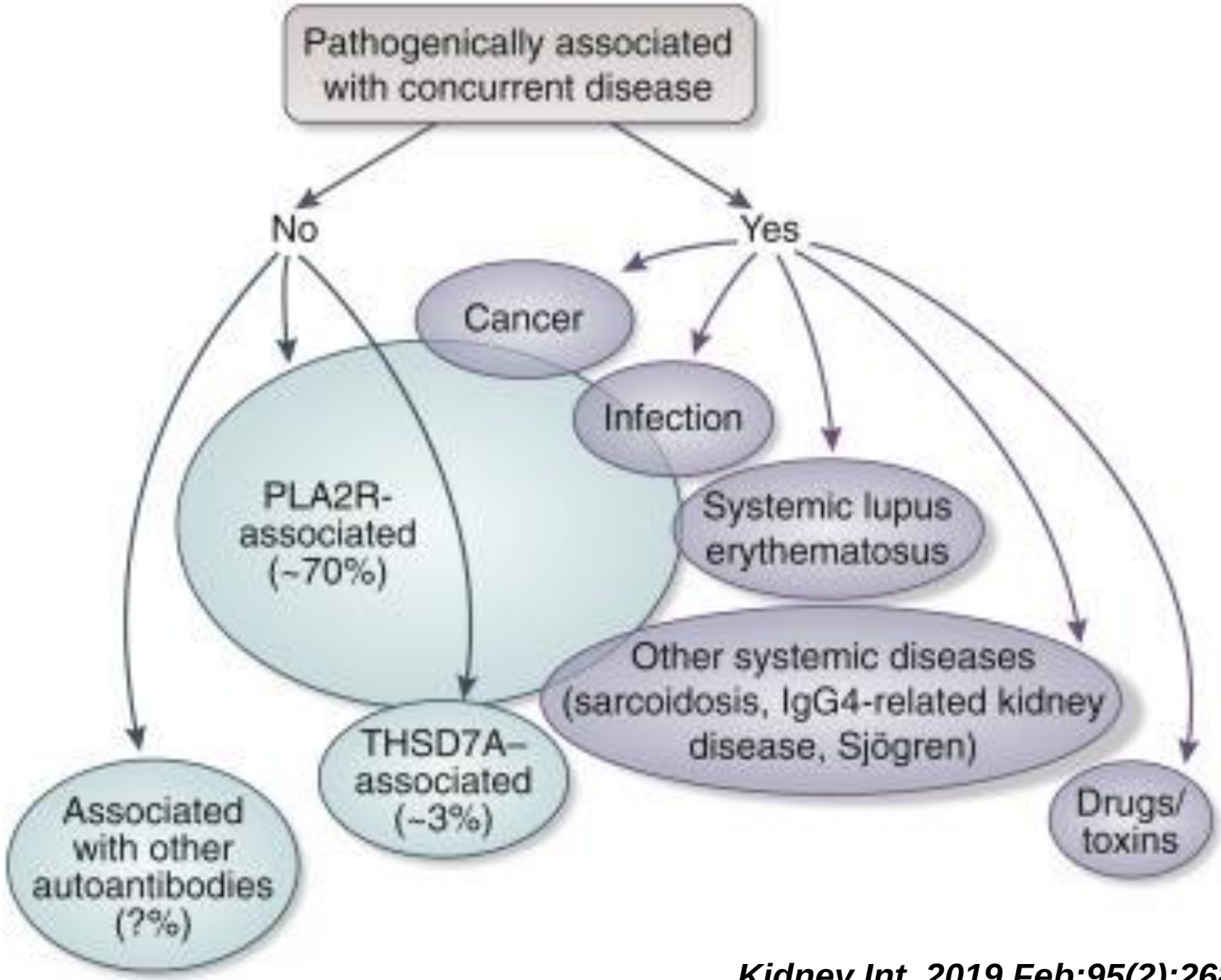
penetrating between the deposits



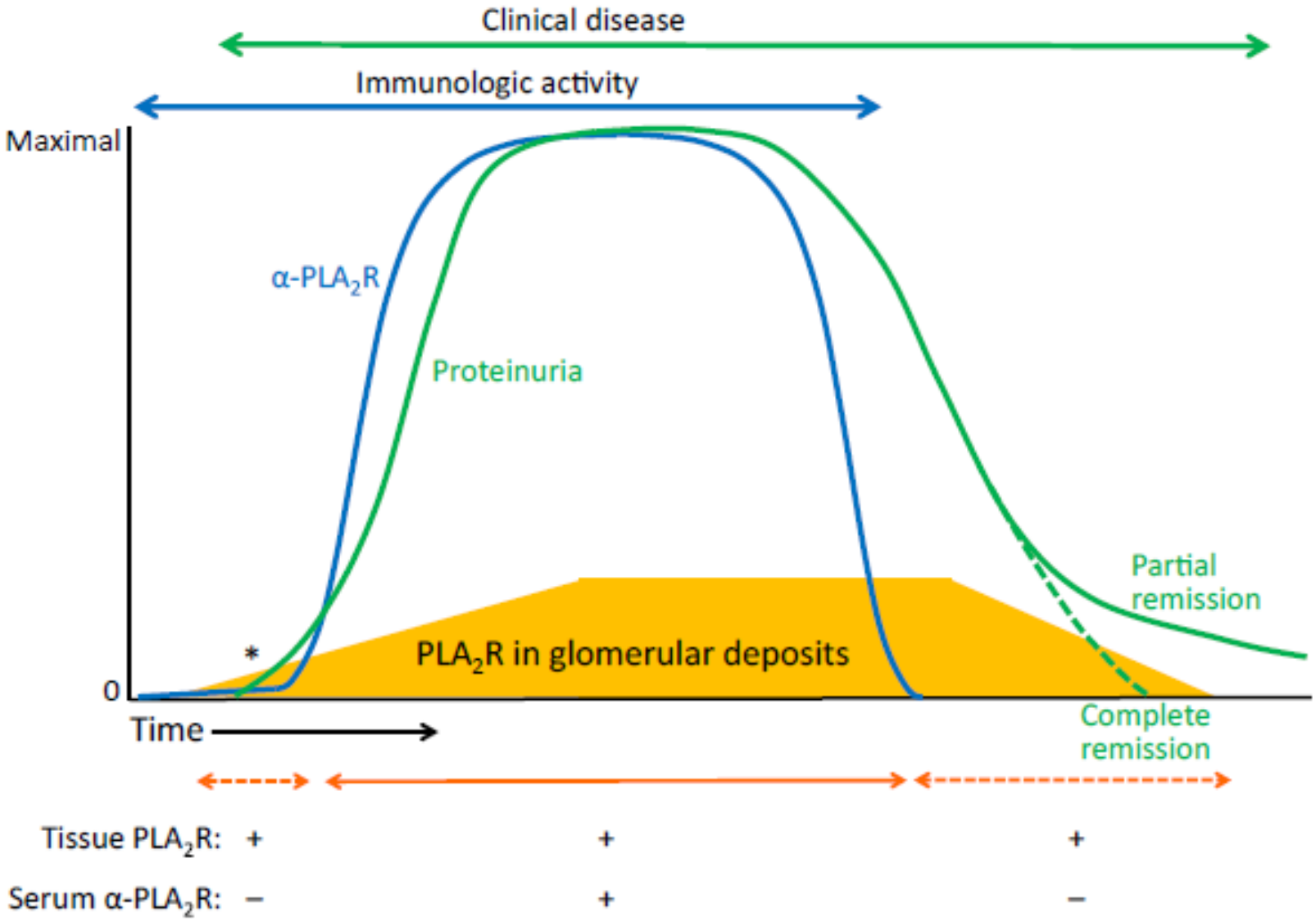
Deposits of IC form grains along the GBM



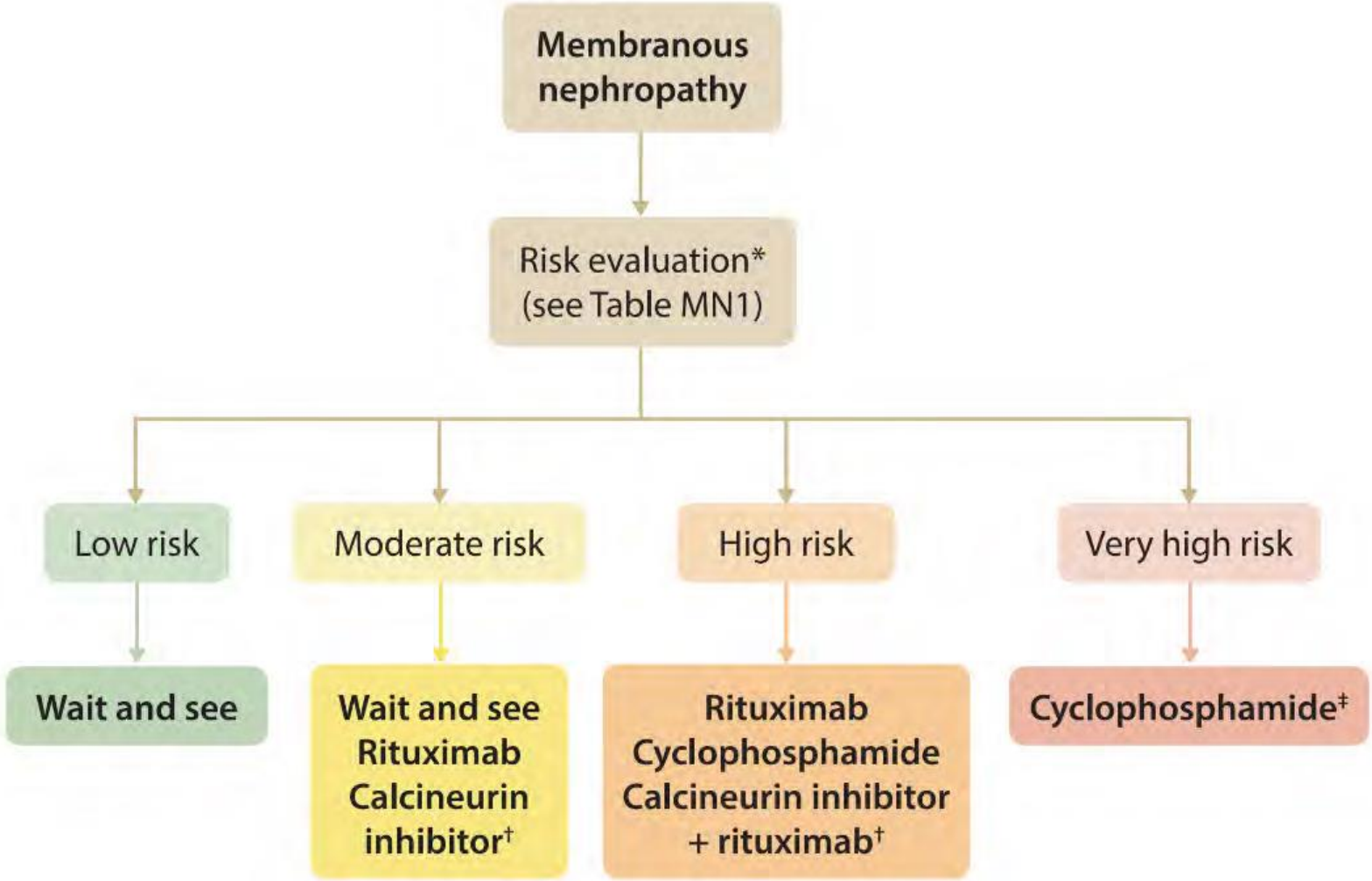
Deposits of IC form dark fields on the outer GBM contour



Kidney Int. 2019 Feb;95(2):268-280



Francis JM, Beck LH Jr, Salant DJ. Am J Kidney Dis. 2016 Apr 13


Membranous nephropathy
Risk evaluation* (see Table MN1)
Low risk
Moderate risk
High risk
Very high risk
Wait and see
Wait and see
Rituximab
Calcineurin inhibitor†
Rituximab
Cyclophosphamide
Calcineurin inhibitor + rituximab†
Cyclophosphamide‡

Trigger case 3

A 10-year-old girl presents to the clinic complaining od eye swelling. You note that the child was seen 3 weeks ago in the clinic for a chief complaint of sore throat. Upon taking the history and performing the physical you find that the patient has pronounced periorbital oedema, has been urinating very litte despite adequate fluid intake and has a blood pressure of 150/90. Laboratory findings include azotemia, hematuria, red cel casts in urine

What is the diagnosis?

What is the prognosis?

THE CLINICAL SYNDROMES

1. The acute (abruptly developing) Nephrotic Syndrome
2. The acute nephritic syndrome
3. Rapidly progressive glomerulonephritis
4. Asymptomatic hematuria / proteinuria
5. The chronic nephritic syndrome (chronic renal failure)

Acute nephritic syndrome

A common feature of all pathologies presenting with nephritic syndrome is damage to the endothelium of the glomerular capillaries, leading to the development of inflammation due to the presence of immune complexes (deposited or formed in situ).

Nephritic syndrome is defined by a rapid (within a few days) evolution of symptoms: active urine sediment, increased blood pressure control and a decrease in GFR

Mechanism: diminished GFR is secondary to a decrease in filtration area due to obstruction of the capillary lumen by inflammatory exudate and endothelial proliferation, often in combination with sodium retention, leading to hypervolemia, hypertension and edema.

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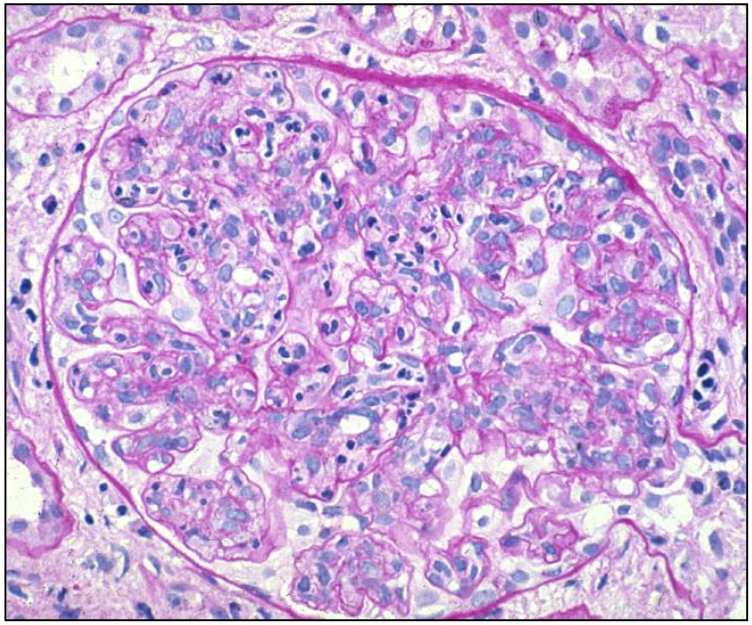
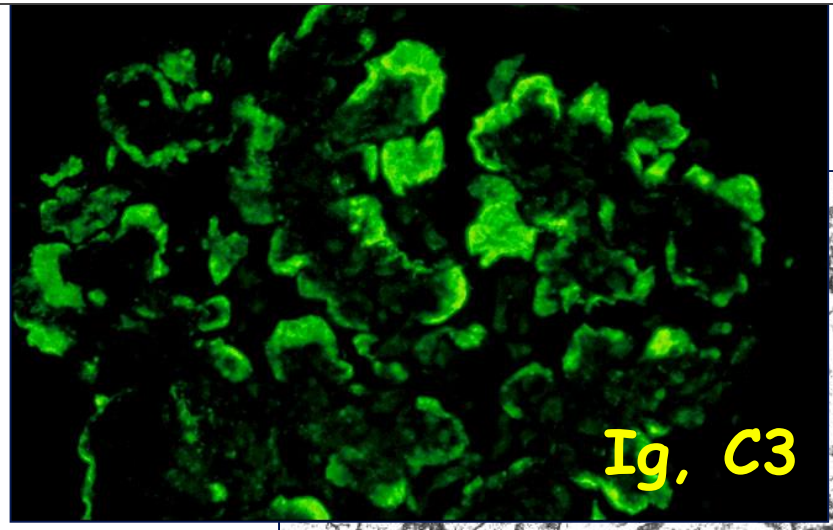
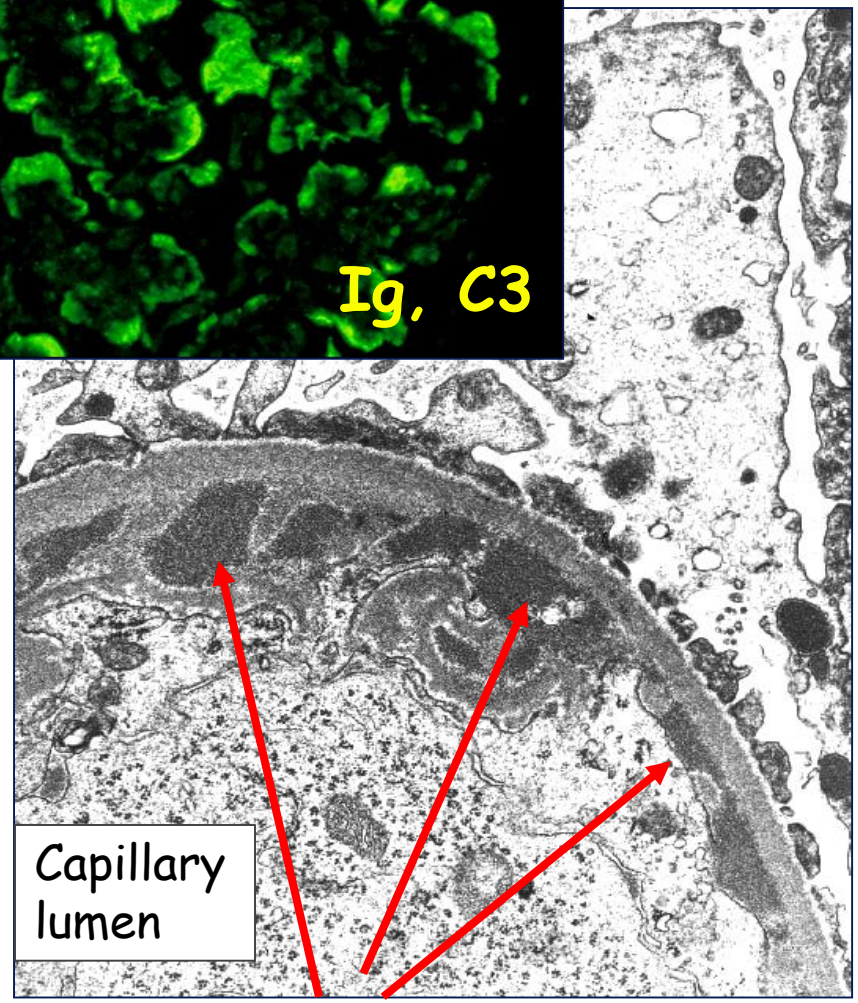
immune complexes deposited under the capillary endothelium

Diffuse Proliferative Glomerulonephritis







Electron-dense deposits in the subendothelial area

The activated complement components cause the accumulation of inflammatory cells (neutrophils and monocytes) in the glomerular capillaries, which hinders the contact of blood with GBM and the formation of ultrafiltrate.

Acute nephritic syndrome

Basic 3 mechanisms

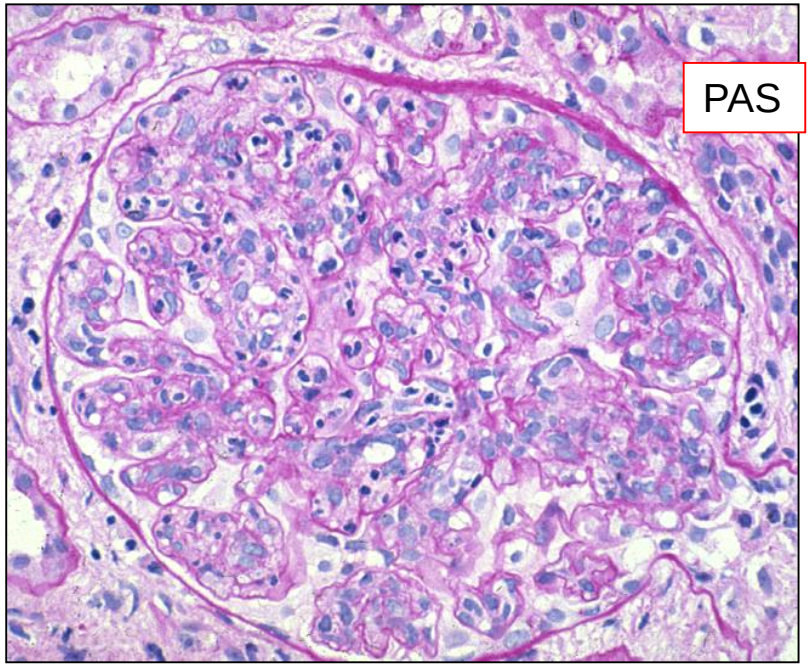
1. Formation of immune complexes in the subendothelial and / or mesangial region (IgA-N, SLE class II),
2. Binding of circulating antibodies to glomerular antigens (anti-GBM disease)
3. Necrotic inflammation due to the presence of ANCA antibodies

<u>Occurs mainly secondary to:</u>

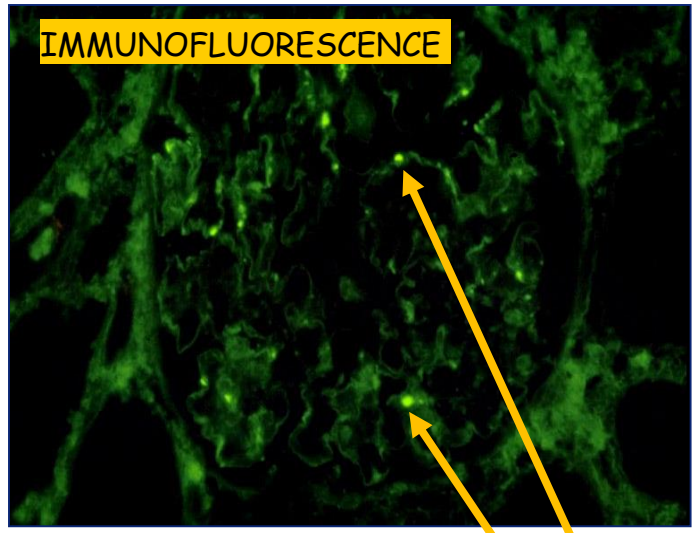
- infectious diseases
- autoimmune diseases
- hematological tumors

Diffuse Proliferative postreptococcal intracapillary Glomerulonephritis

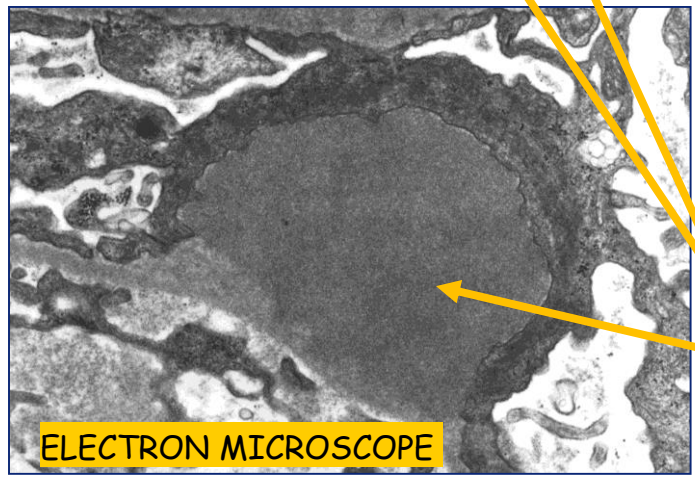
the most common cause of acute nephritic syndrome in the world, mainly in developing countries, mainly in children and adults > 50 years of age.



poststreptococcal inflammation takes the form of diffuse intra-capillary inflammation



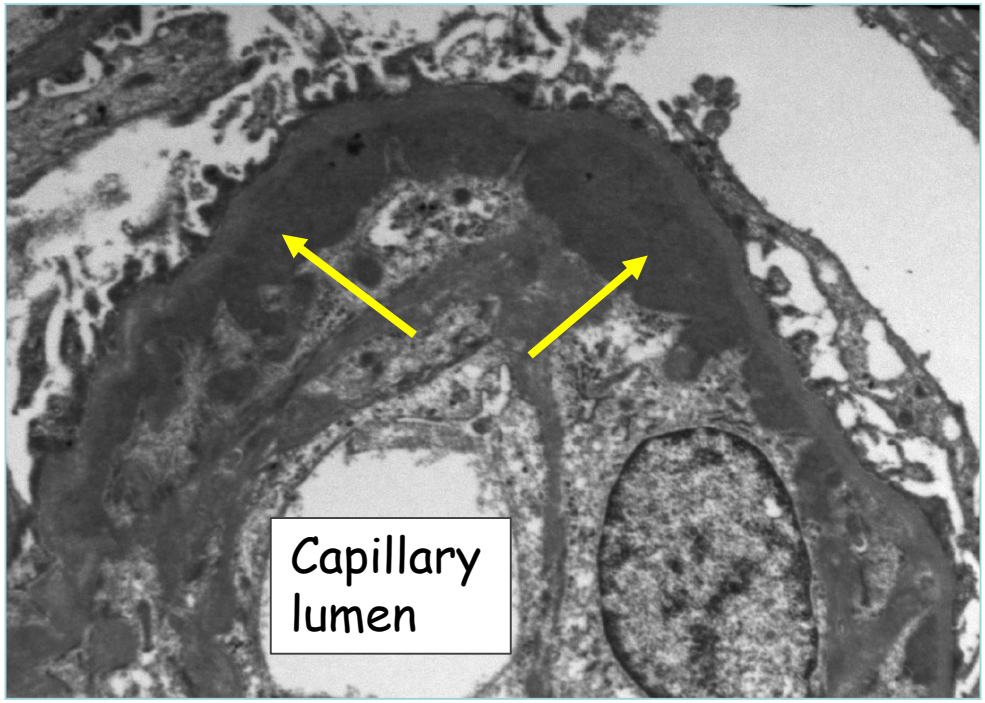
A distinguishing feature of intracapillary inflammation due to bacterial infection is the presence of subepitlelial deposits called humps



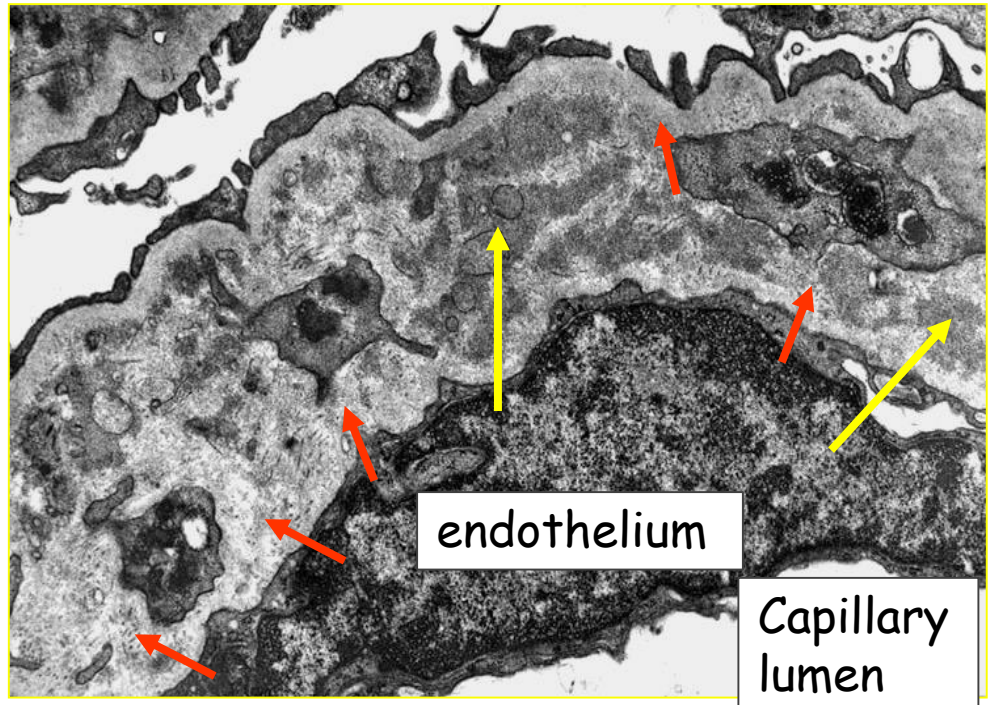
Subepithelial HUMPS

Membranoproliferative Glomerulonephritis

Endocapillary infammation



Membrano-proliferatve inflammation



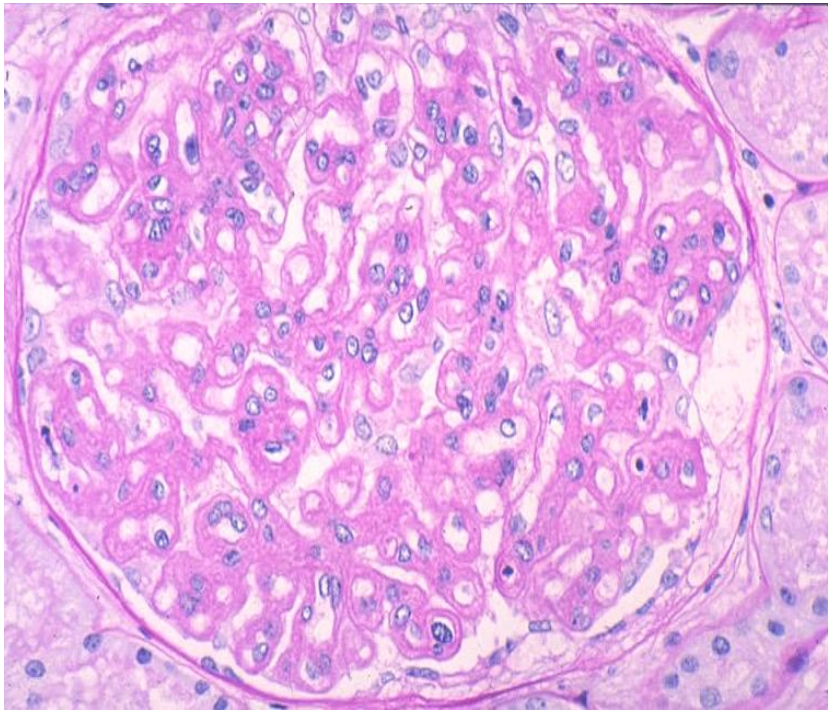
→ : immune complexes deposited in subendothelial area

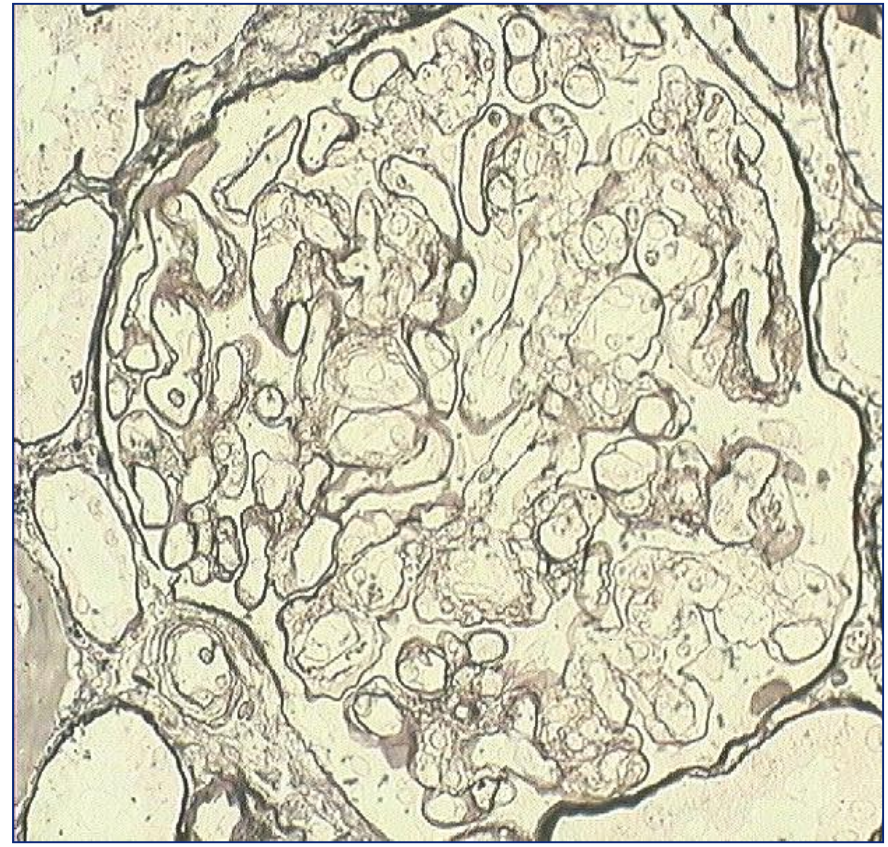
Prolonged deposition/presence od immune complexes between endotlelium and GBM provokes „new" basic mambrane sythesis (→), that separates them from the circulation and siliences complement activation

Membrano-proliferatve glomerulonephritis

It is characterized by

thickening (double contours) of the glomerular capillaries





Clinically:
Coincidence of nyphritic syndrome (manifests endocapillary inflamation) and nephrotic syndrome reflecting diffuse GBM thickening

Trigger case 4

A 40-year-old man is admitted to the hospital with a history of of blood in his urine, malaise, weight loss. On physical examination you find that his blood pressure is 165/95, on lab test erythrocyturia, proteinuria, anaemia, elevated ESR and kidney function tests . Fortunately two months ago he had medical check-up and you can see that his lab test were perfectly normal.

What is the primary diagnosis?

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Crescentic glomerulonephritis (proliferative extracapillary)

Idiopathic (primary) crescentic GN:

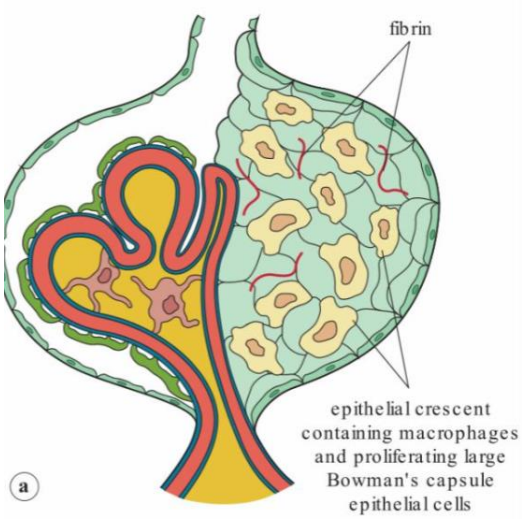
- Type I, disease with the presence of anti-GBM antibodies
- Type II, associated with immune complexes
- Type III, „pauci immune" (associated with ANCA antibodies)

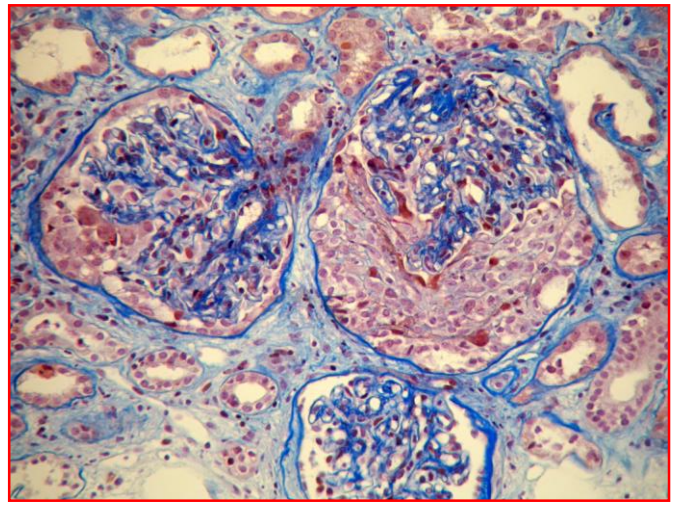
Complicating other forms of primary GN

ex. in the course of IgAN, MPGN, post-infectious GN

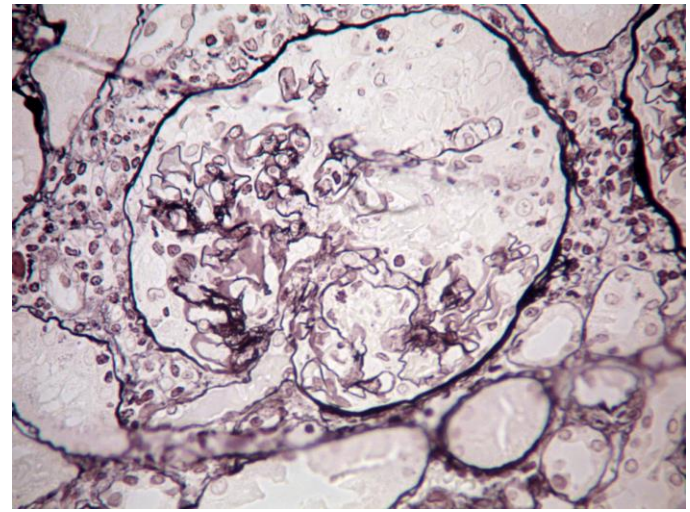
Complicating systemic autoimmune diseases (S-H syndrome, SLE)

GN with crescent formation

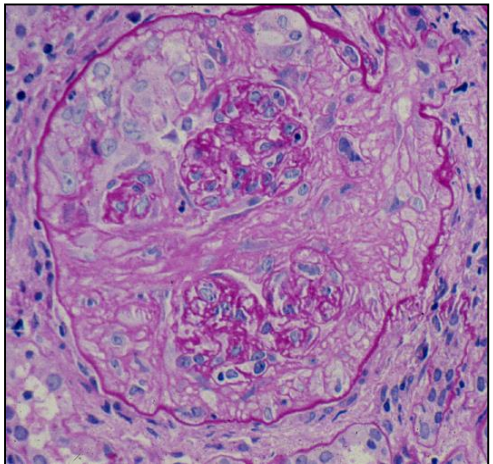




Cellular crescents
Potentially sensitive to immunosuppressive therapy



Breaks in GBM
Exsanquintion through the GBM defect stimulates the proliferation of the parietal epithelium



fibrous crescent - irreversible

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Non-nephrotic proteinuria and/or asymptomatic erythrocyturia/haematuria

- Diseases characterized morphologically by focal segmental, necrotic / inflammatory changes in the glomeruli or by GBM pathology.
- Ussualy present with preserved kidney function and normal blood pressure
- In a subset of cases, they do not reflect inflammation, but the susceptibility (often genetic) of GBM to damage.

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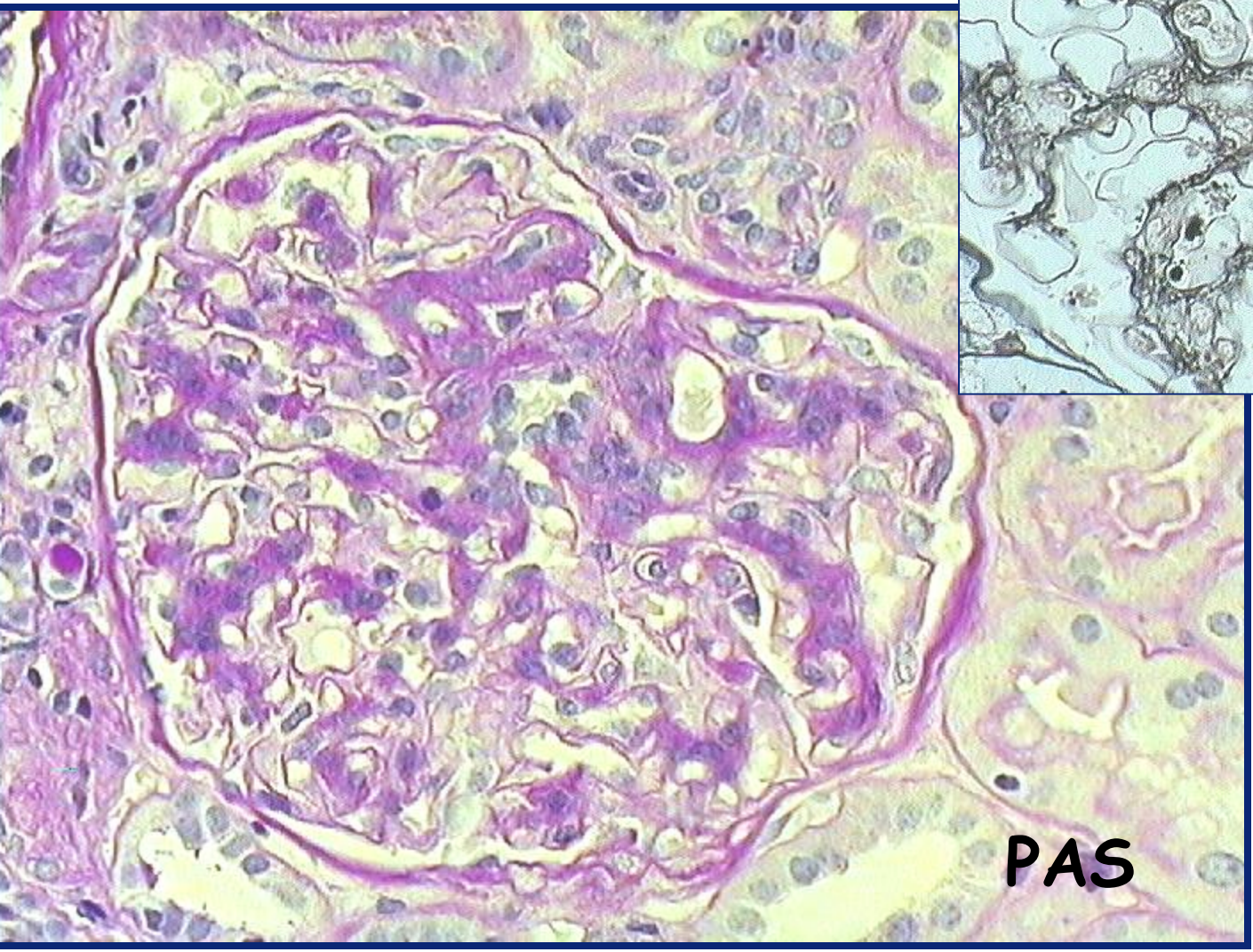
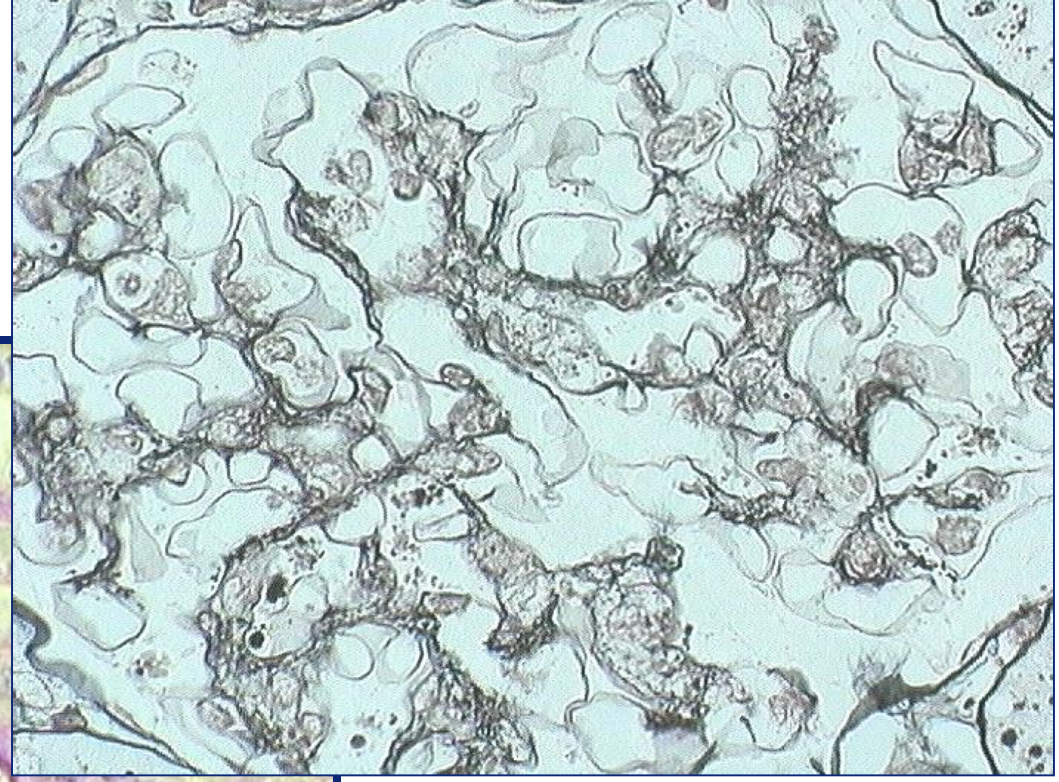
Mesangioproliferative glomerulonephritis

- IgA Nephropathy
- Idiopathic Mesangioproliferative GN
- Recovery phase of a postinfectious glomerulonephritis
- SLE WHO Class II, mesangial form and other IC-mediated diseases
- Some of the deposition diseases

Mesangial proliferation

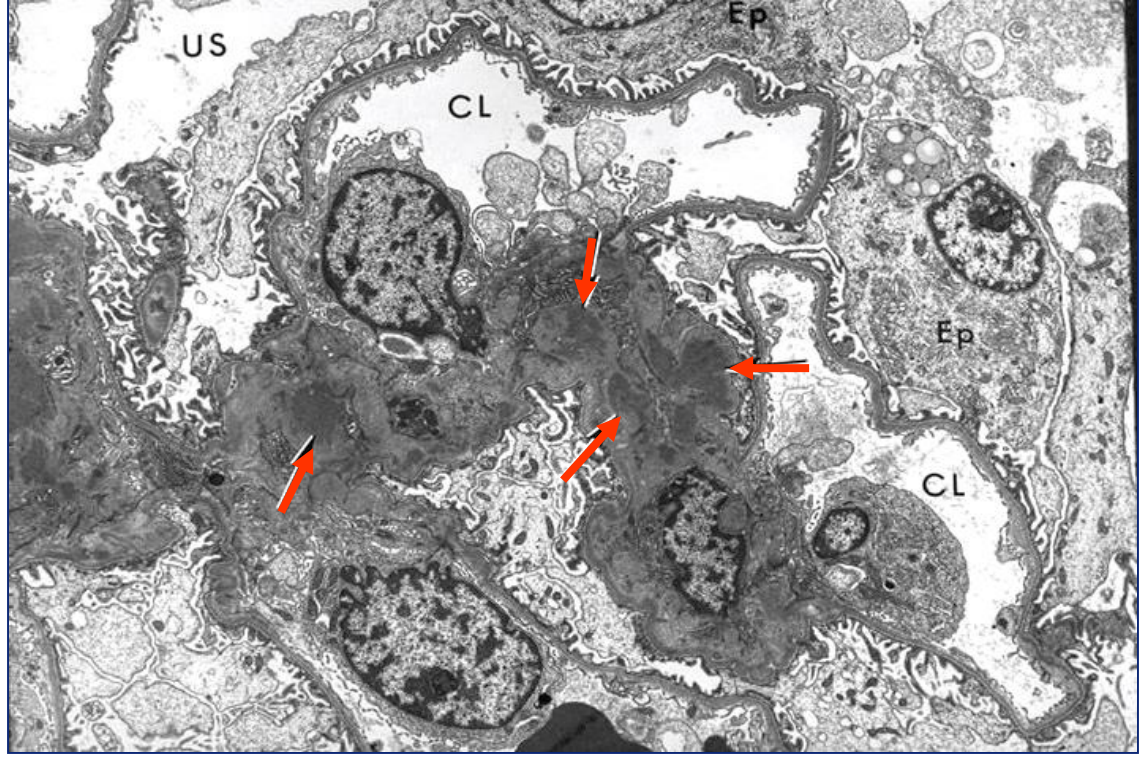


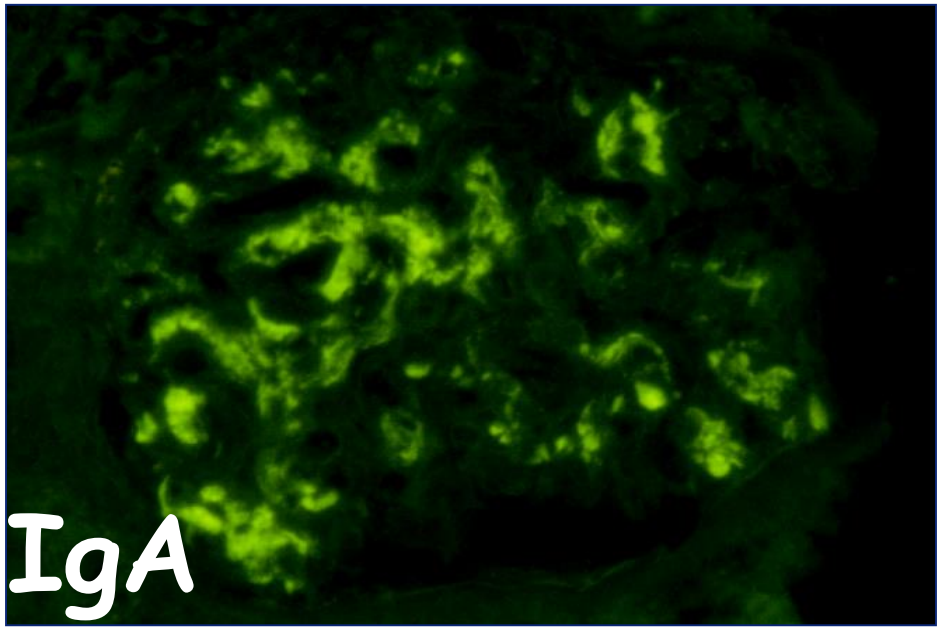


IgA Nephropathy

1. DISEASE defined as the (co) dominance of IgA deposits among all the deposits present in the glomeruli

1. The most common type of chronic gn in the world





The deposits in immunofluorescence correspond to electron-dense deposits in electron microscopy

IgA Nephropathy treatment

Not applicable to variant forms of IgA:
- IgA deposition with minimal change disease
- IgAN with acute kidney injury
- IgAN with a rapidly progressive glomerulonephritis

!

Proteinuria >1 g/24 h despite 3 months of optimized supportive care:
- **BP management**
- **Maximally tolerated dose of ACEi/ARB**
- **Lifestyle modification**
- **Address cardiovascular risk**

Not applicable to:
- IgA vasculitis
- IgA nephropathy secondary to:
  - Viral (HIV, hepatitis)
  - Inflammatory bowel disease
  - Auto-immune disease
  - Cirrhosis
- IgA-dominant post-infectious GN

!

eGFR <30 ml/min/1.73m^2

eGFR ≥ 30 ml/min/1.73m^2

Toxicity risk stratification:
- Advanced age
- eGFR <50 ml/min/1.73m^2
- Metabolic syndrome
- Morbid obesity
- Latent infection (TB, HIV)

Consider maximal supportive care

Corticosteroid if risk/benefit profile acceptable

CONDITIONS ASSOCIATED WITH GLOMERULAR BASEMENT MEMBRANE ABNORMALITIES

Disturbances in the GBM structure may cause lower mechanical strength, leading to cracks formation

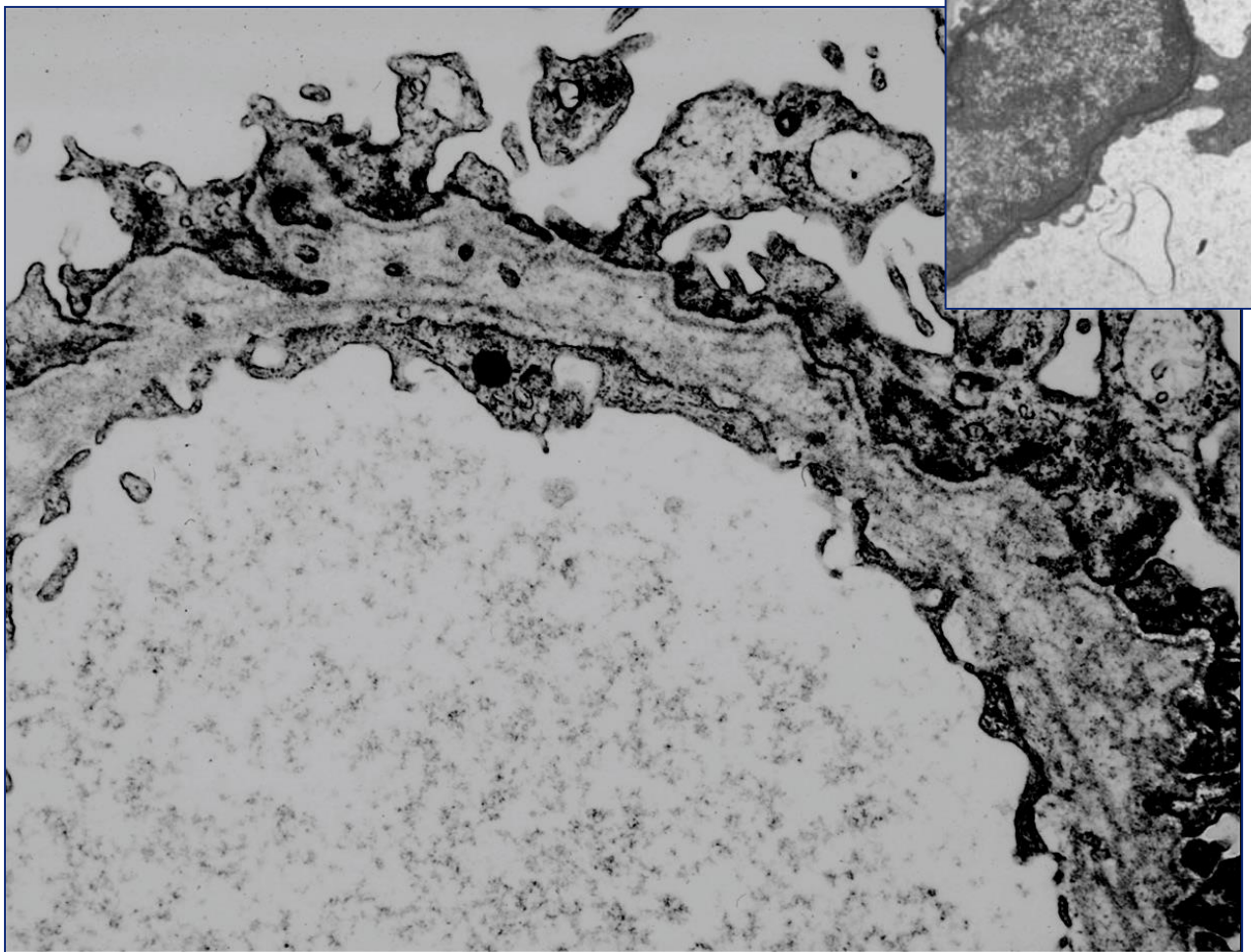
Congenital:

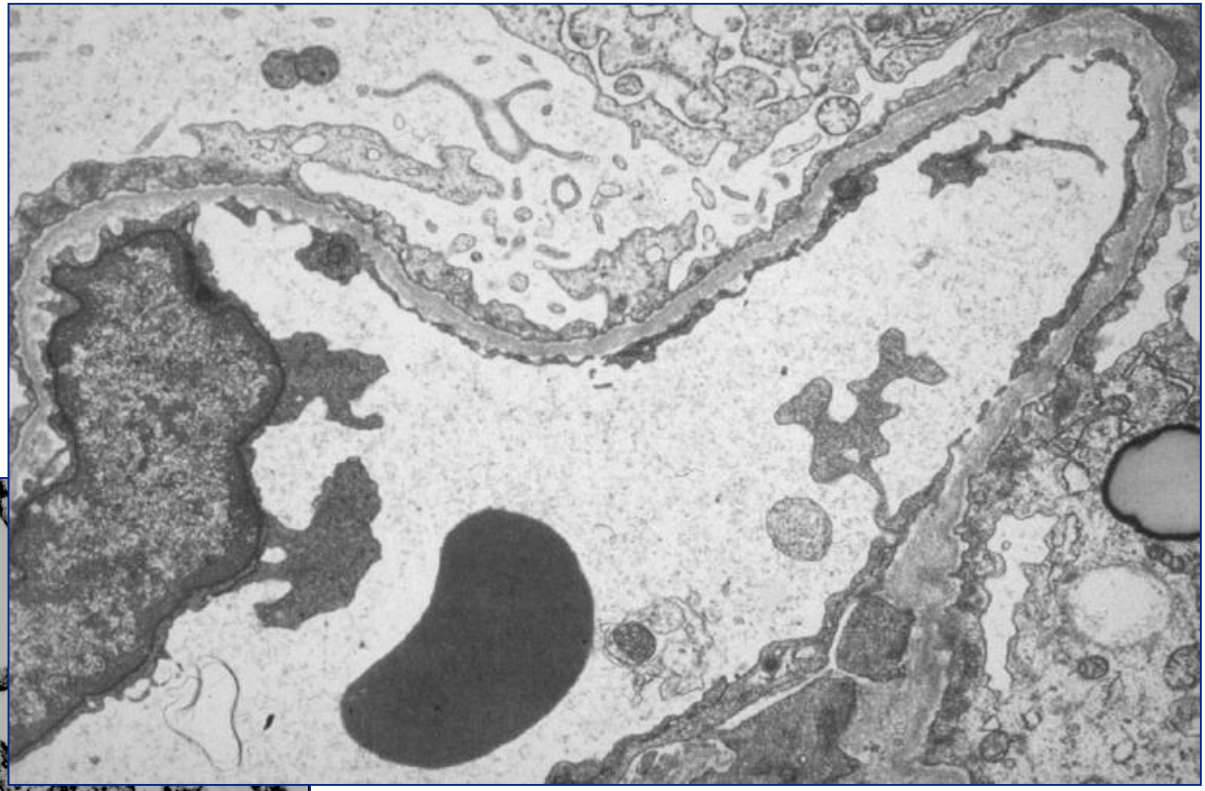
- collagen IV disease: Alport syndrome and thin membrane disease
- lecithin-cholesterol acetyltransferase deficiency (LCAT deficiency)
- nail-patella syndrome

Acquired structure disorders secondary to various glomerulopathies, mainly inflammatory

Collagen type IV disease

Alport syndrome





Thin membrane disease

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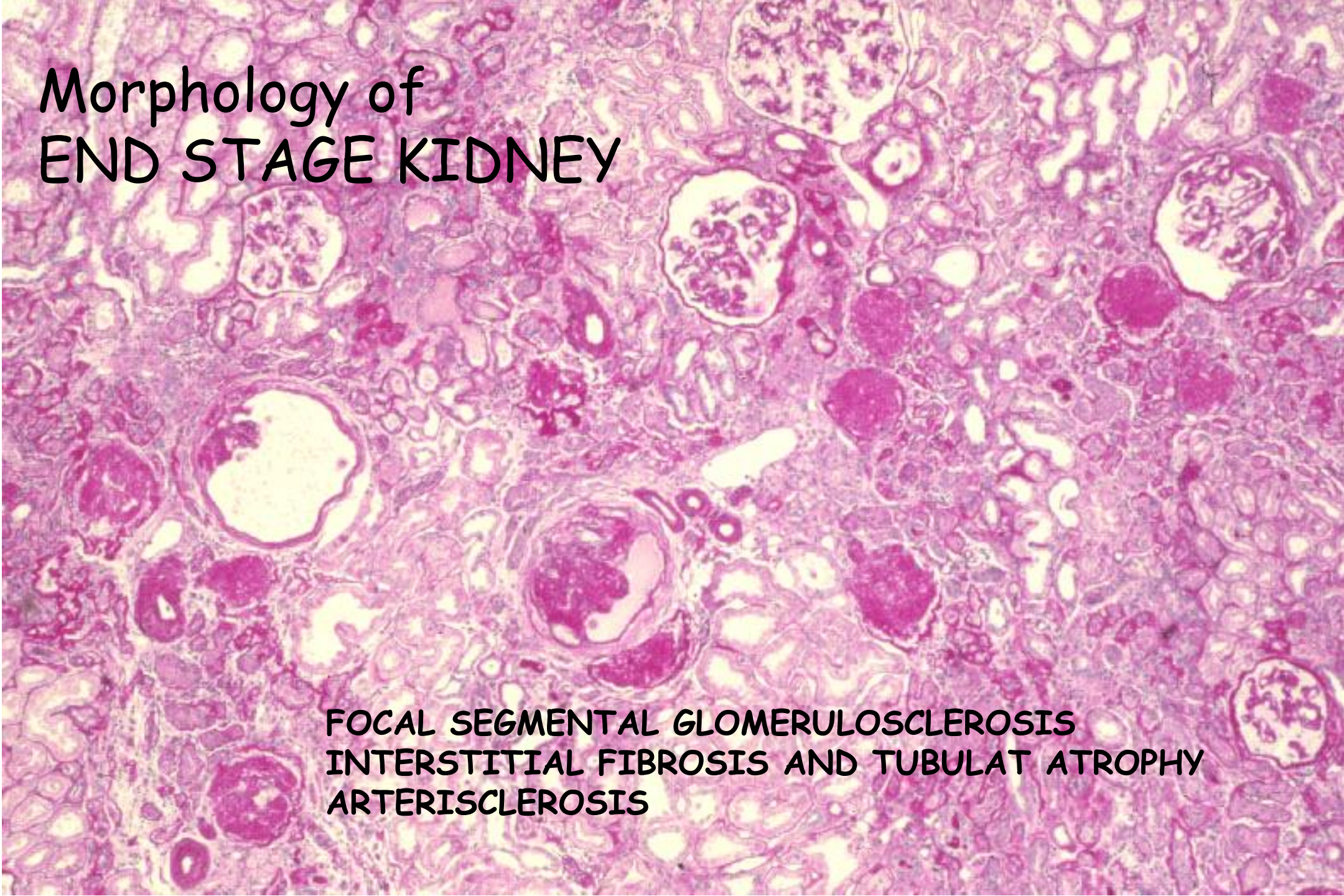
Chronic kidney failure
(chronic nephritic syndrome)

- Morphologically, this syndrome is associated with advanced chronic kidney damage in the form of glomerular sclerosis, interstitial fibrosis, tubular atrophy, arteriosclerosis and arteriolosclerosis, and arteriolar hyalinosis.
- The more advanced these nonspecific changes are, the more difficult it is to determine their etiology (primary disease).

Morphology of END STAGE KIDNEY



FOCAL SEGMENTAL GLOMERULOSCLEROSIS
INTERSTITIAL FIBROSIS AND TUBULAT ATROPHY
ARTERISCLEROSIS

Symptomatic treatment in GN

- Hypertension control is crucial in GN management

BP target of 125/75 mm Hg in the GN patient with proteinuria >1 g/d.

- Proteinuria reduction – RAS blockade, SGLT2 inhibitors
- Hyperlipidemia control – statins
- Hypercoagulability – ASA, warfarin, LMWH, non-vitamin-K antagonist oral anticoagulants
- Infection prophylactics

Immunosuppression in Glomerular Disease

- **Glucocorticoids** - anti-inflammatory and immunosuppressive effects
- **Mycophenolate acid** - antiproliferative agent
- **Cyclophosphamide -** antiproliferative agent
- **Calcineurin inhibitors** - inhibit T cell activation, have direct effects on the podocyte, stabilize the actin cytoskeleton
- **Rituximab-** depletion of circulating and tissue resident B cells
- **Eculizumab** - humanized IgGκ mAb that blocks the cleavage of complement C5, inhibiting formation of MAC (C5b-9) and release of the anaphylatoxin C5a

Glomerular diseases capsule

Nephritic syndrome—due to GBM disruption. Hypertension, ↑ BUN and creatinine, oliguria, hematuria, RBC casts in urine. Proteinuria often in the subnephrotic range (< 3.5 g/day) but in severe cases may be in nephrotic range.

- Acute poststreptococcal glomerulonephritis
- Rapidly progressive glomerulonephritis
- IgA nephropathy (Berger disease)
- Alport syndrome
- Membranoproliferative glomerulonephritis

Nephrotic syndrome—podocyte disruption → charge barrier impaired. Massive proteinuria (> 3.5 g/day) with hypoalbuminemia, hyperlipidemia, edema.

May be 1° (eg, direct podocyte damage) or 2° (podocyte damage from systemic process [eg, diabetes]).

- Focal segmental glomerulosclerosis (1° or 2°)
- Minimal change disease (1° or 2°)
- Membranous nephropathy (1° or 2°)
- Amyloidosis (2°)
- Diabetic glomerulonephropathy (2°)

Nephritic-nephrotic syndrome—severe nephritic syndrome with profound GBM damage that damages the glomerular filtration charge barrier → nephrotic-range proteinuria (> 3.5 g/day) and concomitant features of nephrotic syndrome. Can occur with any form of nephritic syndrome, but is most commonly seen with:

- Diffuse proliferative glomerulonephritis
- Membranoproliferative glomerulonephritis
- Lupus Nephropathy Type IV

GRAMS OF PROTEIN EXCRETED PER DAY (g/day)

0.25	3.5	> 3.5