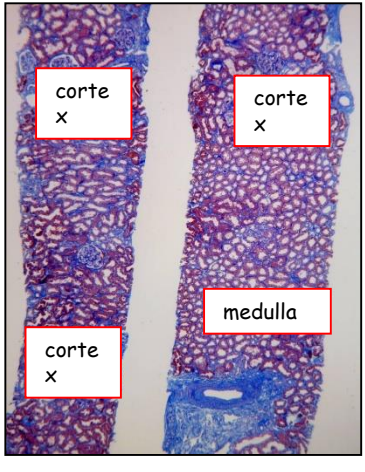
Mechanisms and Patterns of Glomerulonephritis

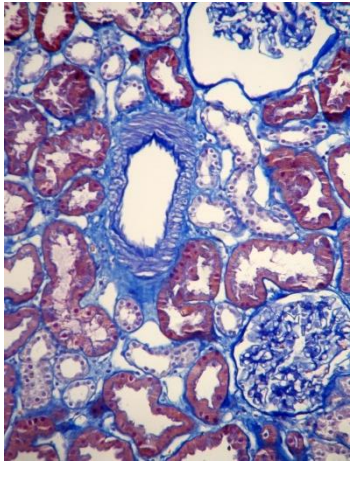
A Comprehensive Clinical Review

Nephrology Education Series

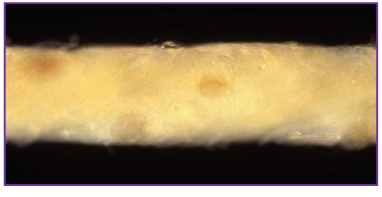
THICK NEEDLE BIOPSY OF THE KIDNEY



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

Glomerulonephritis: Clinical Significance

> **GN represents immune-mediated kidney diseases with diverse presentations requiring integrated diagnostic approach**

- **Immune-Mediated Disease:** Multiple pathogenic mechanisms affecting glomerular components
- **Clinical Spectrum:** Asymptomatic hematuria to nephrotic syndrome to RPGN
- **Diagnostic Triad:** Clinical presentation + serologies + renal biopsy (LM, IF, EM)
- **Therapeutic Implications:** Mechanism-based targeted therapies emerging

Pattern of injury and diagnosis of the disease

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.

nephrologist perspective

Clinical pattern: nephrotic syndrome

In pathologist perspective :

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

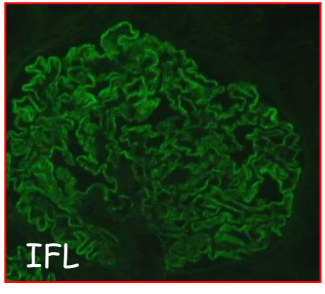
pathologist perspective

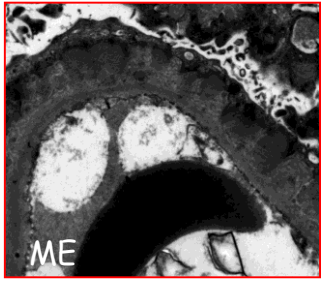
The disease: IgA nephropathy

In nephrologist perspective :

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

Various diseases may express by the same histopathological pattern





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

Three Major Mechanisms of Glomerular Immune Injury

Understanding mechanisms guides targeted immunotherapy

1

Antibody-Mediated

Anti-GBM (linear IF), immune complexes (granular IF)

2

Complement Activation

Alternative pathway (C3 glomerulopathy), classical pathway (lupus, post-infectious)

3

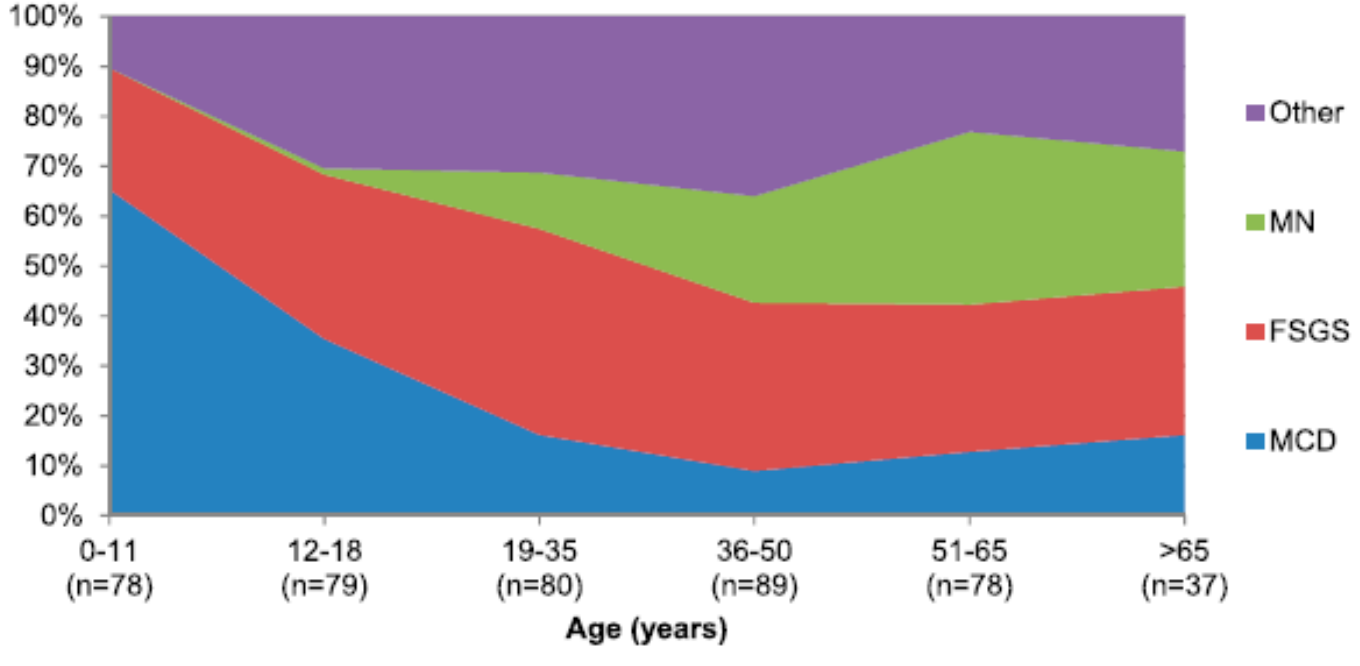
Cell-Mediated

T-cell injury, podocyte injury (MCD, FSGS)

Major Histopathological Patterns and Associated Diseases

Pattern	Associated Diseases
Proliferative	IgA nephropathy, post-infectious GN, lupus nephritis
Membranous	Primary membranous nephropathy, secondary (malignancy, SLE, infections)
MPGN Pattern	Immune complex MPGN, C3 glomerulopathy (DDD, C3GN)
Sclerosing	Primary FSGS, secondary FSGS (adaptive, genetic, viral)
Minimal Change	Primary MCD (idiopathic), secondary (NSAIDs, lymphoma)

Histopatological patterns underlying nephrotic syndrome by patients age



Minimal Change Disease: Clinical and Pathological Features

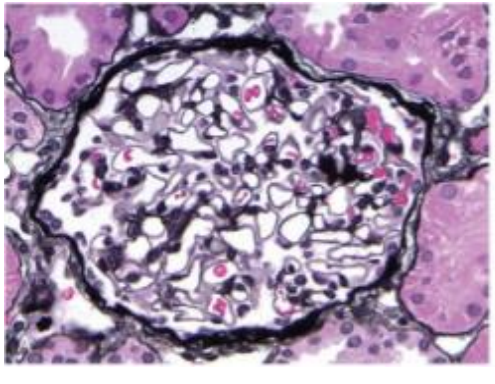
Clinical Features

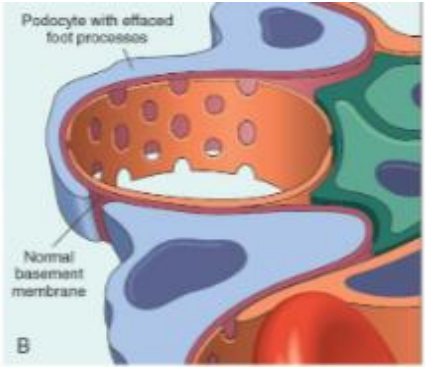
- **Epidemiology:** 90% of nephrotic syndrome in children, 10-15% in adults
- **Presentation:** Sudden onset nephrotic syndrome, normal BP, normal renal function
- **Proteinuria:** Highly selective (albumin), typically over 3.5 g/day

> **Pearl: 90% steroid-responsive in children, 75% in adults**

Pathology

- **Light Microscopy:** Normal glomeruli (hence minimal change)
- **Immunofluorescence:** Negative or minimal mesangial IgM
- **Electron Microscopy:** Diffuse podocyte foot process effacement





FSGS: Classification and Clinical Spectrum

Classification

- **Primary:** Idiopathic, circulating permeability factor
- **Secondary:** Adaptive (obesity, reduced nephrons), genetic (podocin, nephrin), viral (HIV, CMV)

Clinical Features

- **Presentation:** Nephrotic syndrome (60-70%), sub-nephrotic proteinuria, HTN, renal insufficiency
- **Demographics:** African Americans higher risk, adults more than children

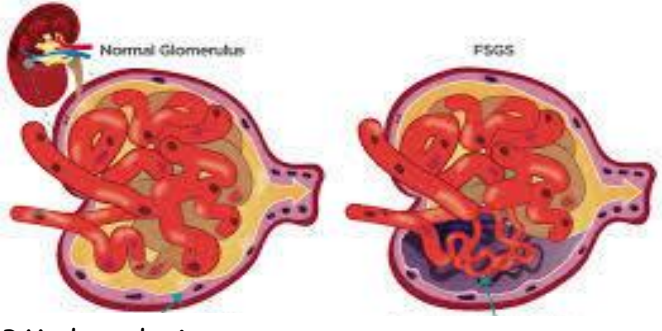
Pathology

- **LM:** Focal and segmental sclerosis; Columbia types (tip, perihilar, cellular, collapsing, NOS)
- **IF:** IgM and C3 in sclerotic segments
- **EM:** Foot process effacement

Prognosis: 50% progress to ESRD in 10 years; collapsing variant worst prognosis

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



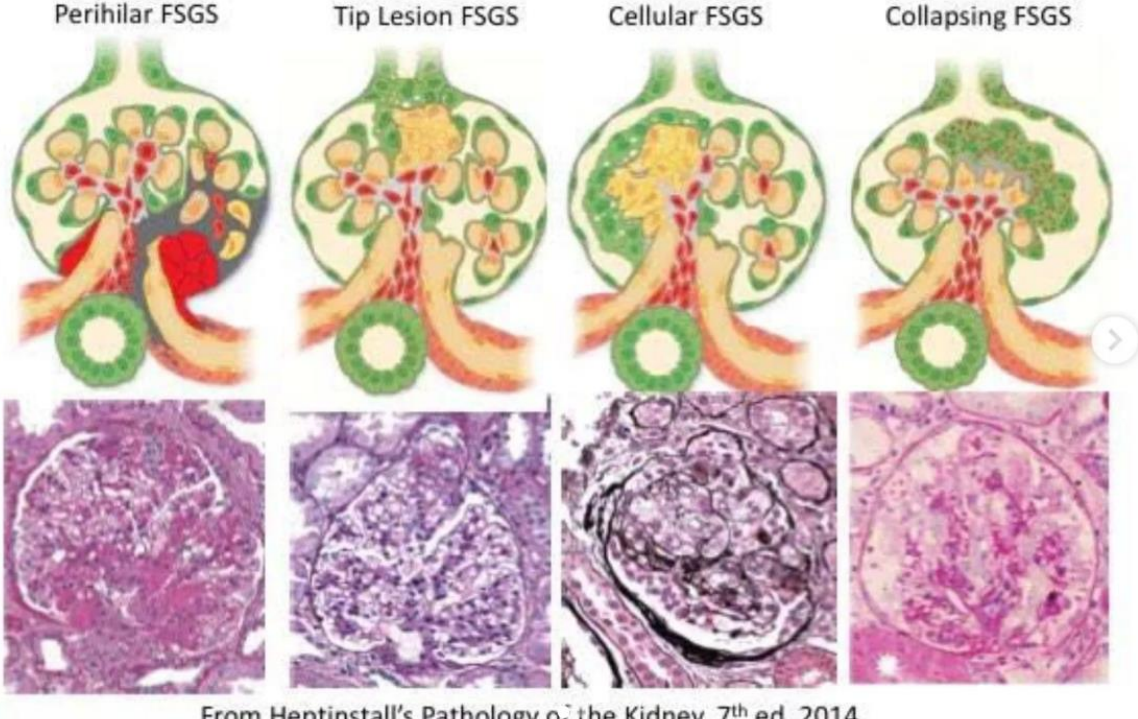
GBM denudation

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 REGENERATE/PROLIFERATE

Histopathologic subtypes of FSGS



From Heptinstall's Pathology of the Kidney, 7th ed, 2014

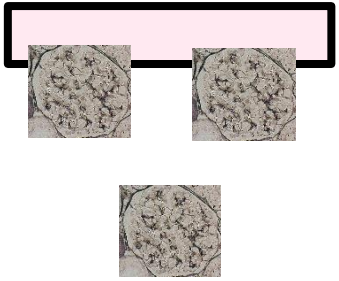
SECONDARY FSGS

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.

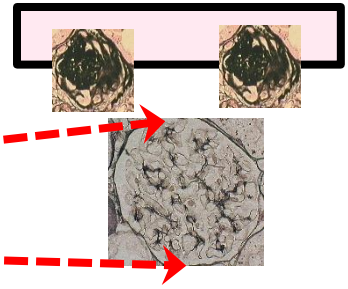
ADAPTIVE MECHANISM IN A PROGRESSIVE KIDNEY DISEASE

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



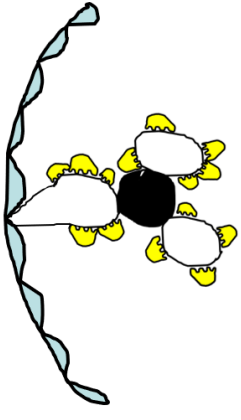
3 normal glomeruli in a portion of kidney cortex

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

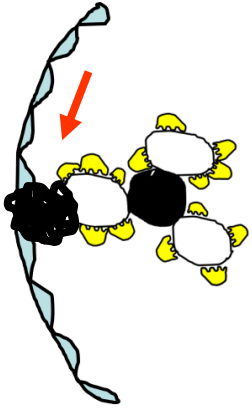


- The remaining glomerulus takes over the function of the two sclerosed ones. It enlarges and has increased filtration pressure in its capillaries, in consequence the blood volume filtered in this glomerulus per time unit rises.
- UNFORTUNATELY this mechanism causes secondary sclerotization of hypertrophied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

Concequences of the compensatory hypertrophy of the glomerulus

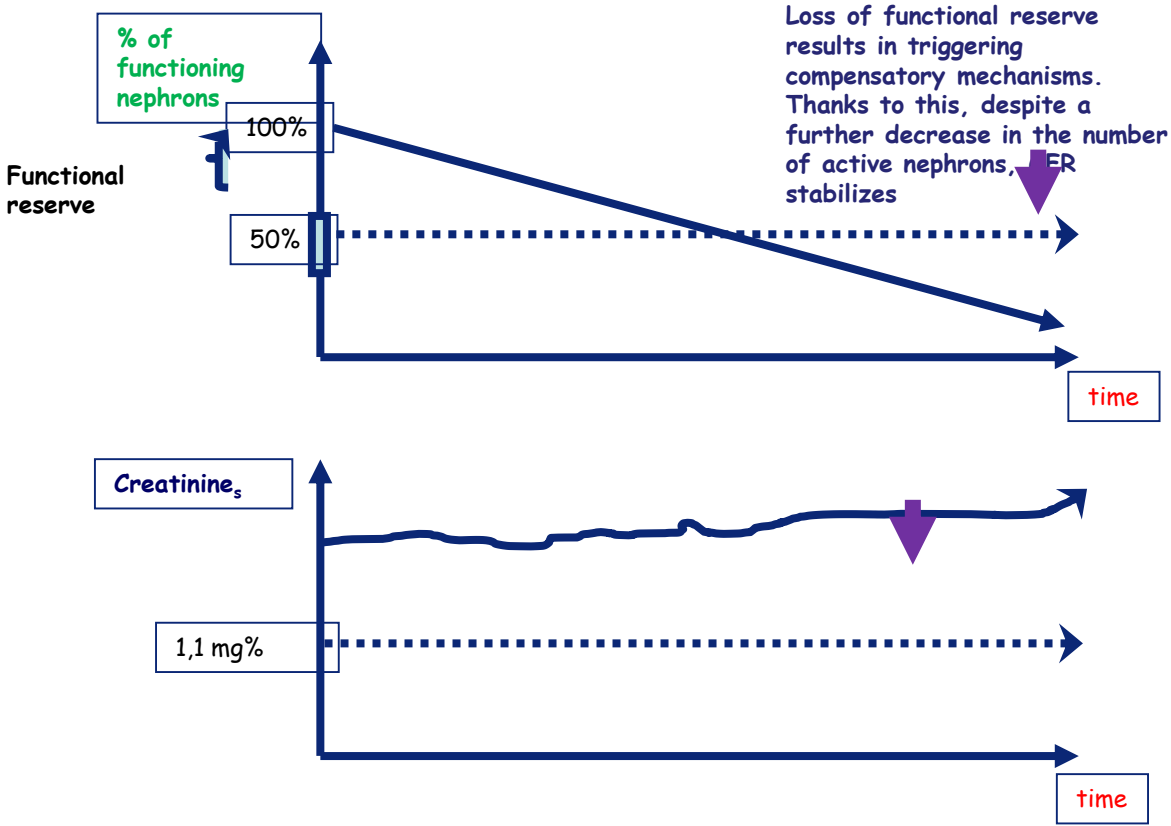


Denudated GBM is highly protein permeable and "tends" to be covered by the epithelium lining Bowman's capsule



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

PROGRESSIVE CHRONIC KIDNEY DISEASE



IgA Nephropathy: Clinical Features and Diagnosis

Epidemiology and Clinical Presentation

- **Most common primary GN worldwide** (40% of biopsies in Asia)
- **Classic:** Episodic gross hematuria with URTI (synpharyngitic - pathognomonic)
- **Common:** Asymptomatic microscopic hematuria with proteinuria
- **Severe:** Nephrotic syndrome (5%), RPGN with crescents (rare)

Pathology

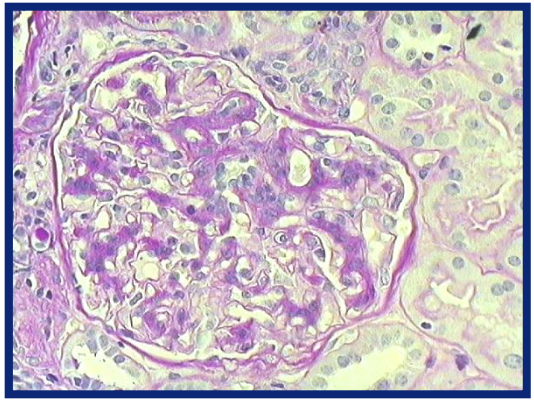
- **LM:** Mesangial hypercellularity and matrix expansion; crescents in severe cases
- **IF:** Dominant or co-dominant mesangial IgA deposits (DIAGNOSTIC)
- **EM:** Mesangial electron-dense deposits

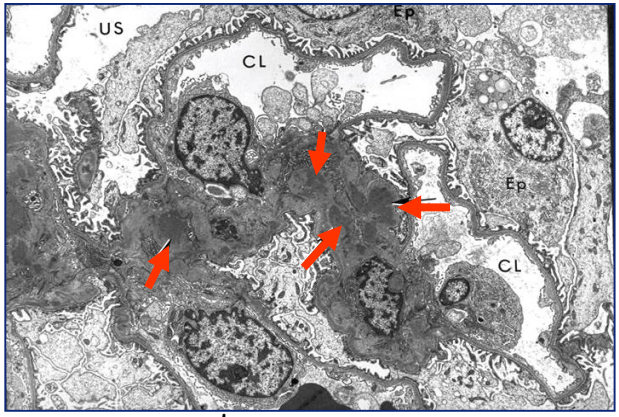
Oxford Classification (MEST-C) - Prognostic

- M (mesangial hypercellularity), E (endocapillary), S (segmental sclerosis), T (tubular atrophy), C (crescents)

Poor Prognosis: Proteinuria over 1 g/day, hypertension, reduced GFR, crescents

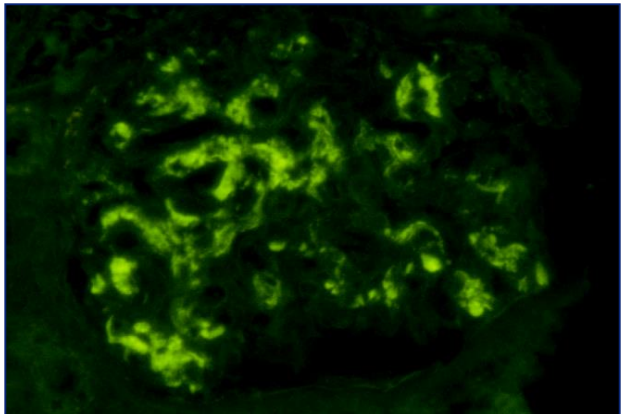
IgA Nephropathy





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

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



Membranous Nephropathy: Etiology and Diagnosis

Classification

- **Primary (75%):** Anti-PLA2R antibodies (70%), anti-THSD7A (3%), others
- **Secondary (25%):** Autoimmune (SLE, Sjogren), infections (HBV, HCV, syphilis), malignancy, drugs (NSAIDs, gold)

Clinical Features

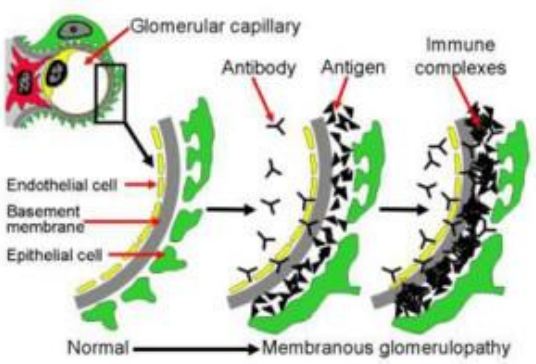
- **Presentation:** Nephrotic syndrome (80%), sub-nephrotic proteinuria
- **Demographics:** Adults 40-60 years, M:F = 2:1
- **Complications:** Thromboembolism, renal vein thrombosis (25-30%)

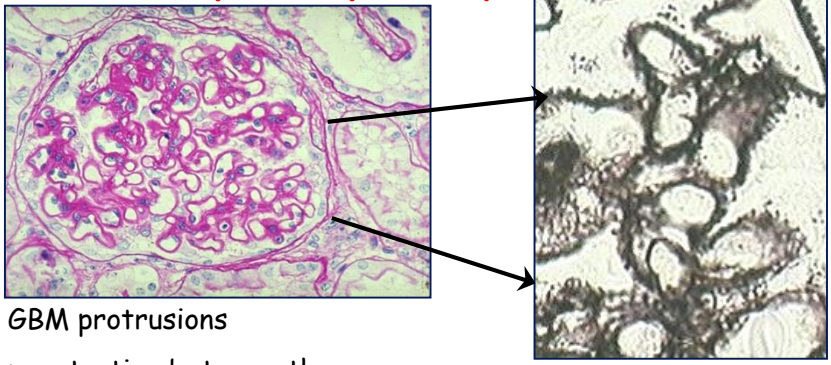
Pathology

- **LM:** Thickened GBM with spikes on silver stain; stages I-IV
- **IF:** Granular capillary loop IgG and C3
- **EM:** Subepithelial electron-dense deposits (stage-dependent)

Serology: Anti-PLA2R (70% sensitivity, 99% specificity). Prognosis: 30% spontaneous remission, 30-40% progressive

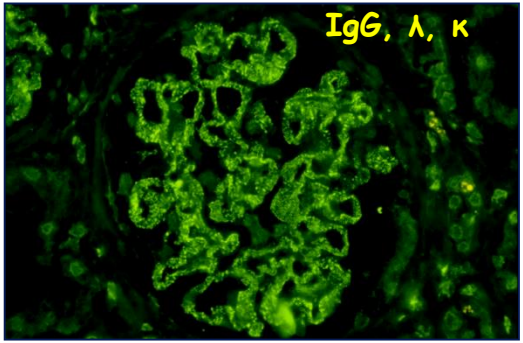
Membranous nephropathy



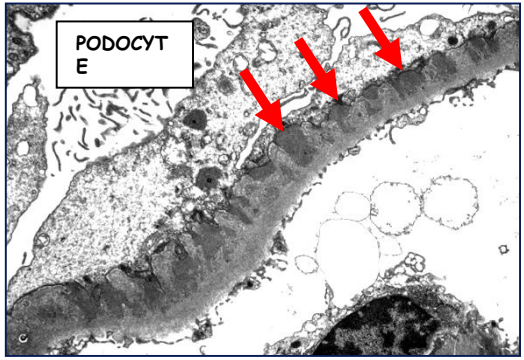


GBM protrusions

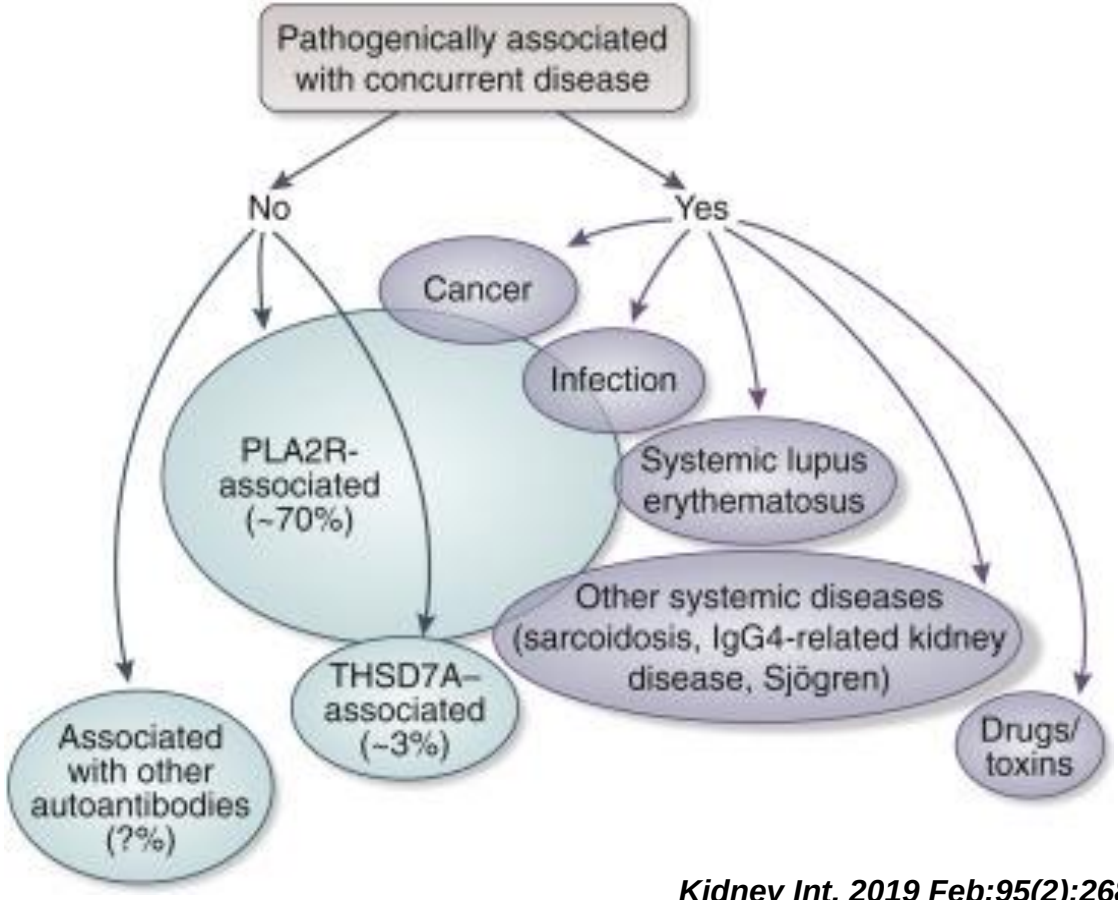
penetrating between the deposits



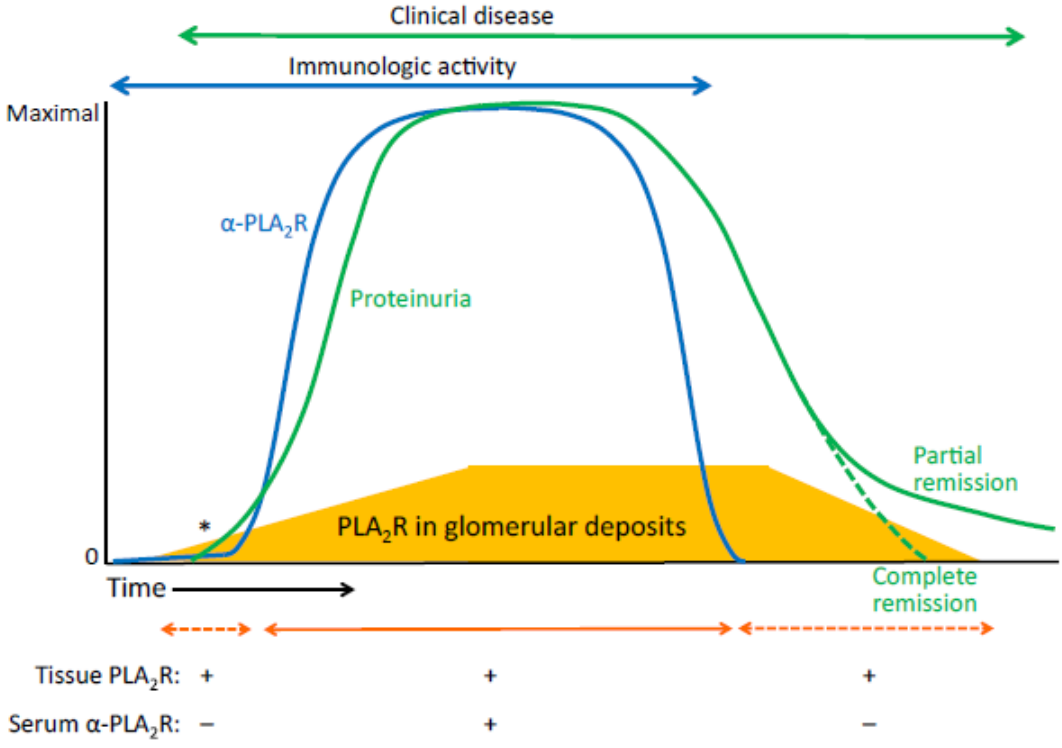
Deposits of IC form grains along the GBM



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

MPGN: New Classification and Clinical Approach

New Mechanism-Based Classification

- **Immune Complex-Mediated:** Infections (HCV, HBV), autoimmune (SLE, cryoglobulinemia), monoclonal gammopathy
- **Complement-Mediated (C3 Glomerulopathy):** Dense deposit disease (DDD), C3 GN

Clinical Features

- **Presentation:** Nephrotic-nephritic syndrome (mixed), hematuria plus proteinuria
- **Lab:** Low C3 (persistent in C3 glomerulopathy, transient in immune complex)

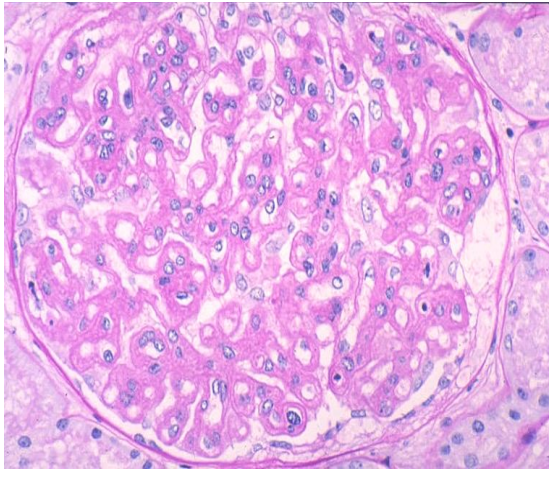
Pathology

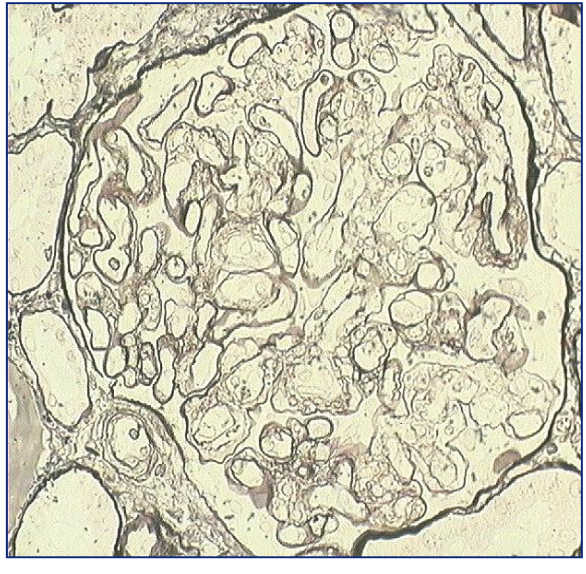
- **LM:** Mesangial proliferation with GBM thickening, double contours (tram-tracking)
- **IF:** C3 dominant (C3 glomerulopathy) vs. Ig plus C3 (immune complex)
- **EM:** Subendothelial deposits (immune complex), intramembranous dense deposits (DDD)

Workup: Complement panel (C3, C4, CH50, alternative pathway), monoclonal protein screen, infectious serologies

Membrano-proliferatve glomerulonephritis

It is characterized by thickening (double contours) of the glomerular capillaries





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

Integrated Diagnostic Algorithm for Glomerulonephritis

Step 1: Clinical Syndrome Identification

Nephrotic vs. Nephritic vs. RPGN vs. Asymptomatic urinary abnormalities

Step 2: Serological Testing

ANA, ANCA, anti-GBM, complement (C3, C4), anti-PLA2R, cryoglobulins

Step 3: Renal Biopsy (LM + IF + EM)

Timing critical in RPGN (within 24-48 hours) and nephrotic syndrome

Step 4: Pattern Recognition and Integration

Combine clinical presentation, serologies, and histopathology for diagnosis

Renal Biopsy Interpretation: Key IF and EM Patterns

Immunofluorescence Patterns

Linear IgG	Anti-GBM disease
Granular IgG/IgA/IgM	Immune complex GN
Dominant IgA	IgA nephropathy
C3 dominant	C3 glomerulopathy
Negative IF	Pauci-immune (ANCA), MCD

EM Deposit Locations

Subepithelial	Membranous nephropathy
Subendothelial	Lupus (IV), MPGN
Mesangial	IgA nephropathy, Lupus (II)
Intramembranous	Dense deposit disease

Prognostic Factors Across Glomerular Diseases

Universal Poor Prognostic Factors

- Elevated serum creatinine at presentation
- Severe proteinuria (over 8-10 g/day)
- Hypertension
- Tubulointerstitial fibrosis on biopsy
- Crescents (over 50% circumferential)

Disease-Specific Prognostic Factors

- **FSGS:** Collapsing variant, African American race
- **IgAN:** Oxford MEST-C score, persistent proteinuria over 1 g/day
- **Membranous:** Anti-PLA2R titer over 150 RU/mL, persistent nephrotic syndrome
- **C3 Glomerulopathy:** Dense deposit disease worse than C3GN

Advances in GN: Biomarkers and Targeted Therapies

Novel Biomarkers

- **Anti-PLA2R:** Diagnosis and monitoring in membranous nephropathy
- **Urinary biomarkers:** Podocyte proteins, tubular injury markers
- **Genetic testing:** FSGS gene panel (NPHS1, NPHS2, TRPC6, INF2)

Targeted Therapies

- **B-cell depletion:** Rituximab (membranous, FSGS)
- **Complement inhibition:** Eculizumab, avacopan (C3 glomerulopathy, ANCA-GN)
- **SGLT2 inhibitors:** Nephroprotection across GN types
- **Endothelin antagonists:** Sparsentan (FSGS, IgAN)

Clinical Pearls: Practical Points for Practice

- **MCD:** Consider empiric steroids in classic presentation; biopsy if atypical features
- **FSGS:** Distinguish primary from secondary; genetic testing in young patients with family history
- **IgAN:** Synpharyngitic hematuria is pathognomonic; optimize RAAS blockade
- **Membranous:** Check anti-PLA2R before biopsy; screen for malignancy in elderly patients
- **MPGN:** New classification is mechanism-based; complement workup essential
- **Biopsy Timing:** Urgent in RPGN (within 24-48 hours); early in nephrotic syndrome
- **Triple Assessment:** Always correlate LM, IF, and EM findings for accurate diagnosis

Summary: Approach to Glomerulonephritis

Pattern Recognition

Clinical syndrome + serology + biopsy pattern = diagnosis

Mechanism Matters

Guides therapy selection (immunosuppression vs. complement inhibition)

Biopsy is Gold Standard

LM + IF + EM are complementary and essential

Risk Stratification

Identify high-risk patients for aggressive therapy

Personalized Medicine

Biomarkers and genetic testing enable targeted approaches