Glomerular Diseases Part 1

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BUMC INTERNAL MEDICINE RESIDENT LECTURE

JANUARY 21, 2020

Learning Objectives

1. Distinguish nephrotic syndrome from nephritic syndrome.
2. Diagram the classic clinical presentations, laboratory findings, and associated systemic diseases (if any) of the following syndromes:
   - Immune-Complex GN (Subcategorize diagnoses within the category of Immune-complex GN)
   - Anti-Glomerular Basement Membrane (GBM) Disease
   - Pauci-Immune Glomulonephritis (ANCA positive)
   - Minimal Change Disease
   - Focal Segmental Glomerulosclerosis
   - Membranous Glomerulonephropathy
   - Diabetic nephropathy
   - Lupus nephritis
3. Subcategorize which GNs present with hypocomplementemia and distinguish which complement is low in each.
4. Choose first line treatments for reduction of proteinuria, including those based on specific pathologies.

Nephrotic Syndrome

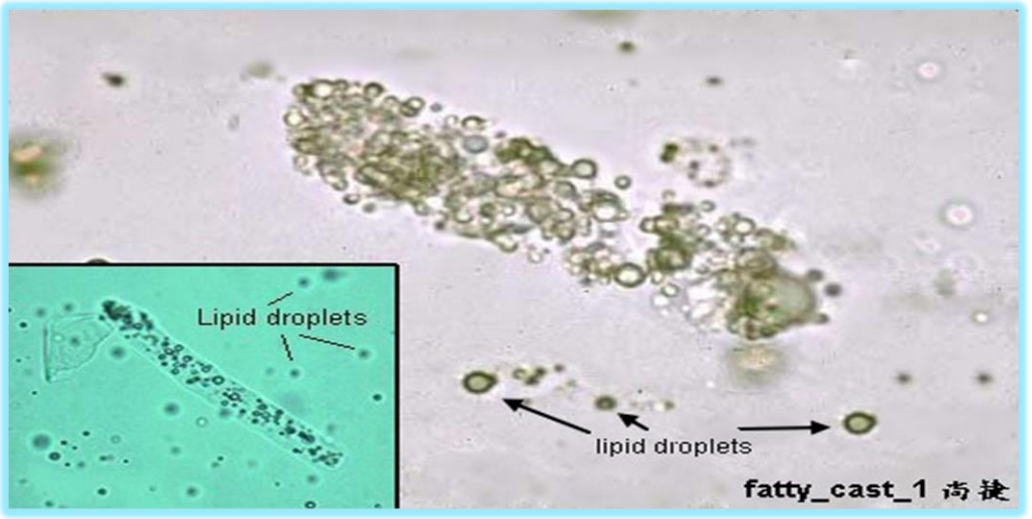
- Nephrotic-range proteinuria
  - > 3.5 gm / 24 hr urine
  - > 3-3.5 gm on UPC
- Lipiduria
- Hypoalbuminemia
- Edema
- Hyperlipidemia

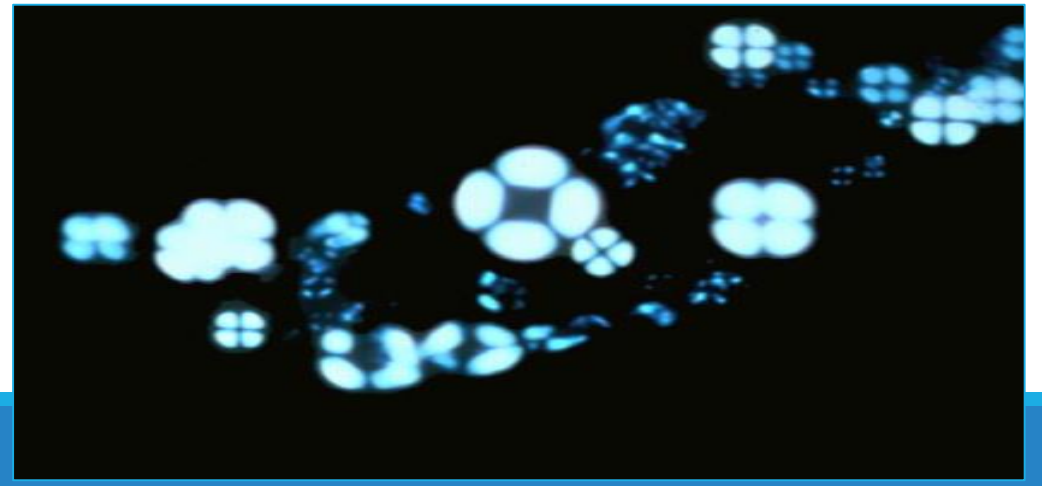
Normal or decreased renal function

Hypercoaguable state due to ATIII loss in urine

Increased risk of infection (loss of IG in urine)

Thyroid dysfunction (loss of thyroid hormones in urine)





Question

Which of the following mechanisms explains the reason for edema in Nephrotic Syndrome?

A. Increased sodium excretion in the ENAC

B. Splanchnic vasodilatation leading to decreased effective circulating volume

C. Inactivation of the RAAS system, leading to sodium/water retention

D. Reduced intravascular oncotic pressure & shift of plasma into interstitium

Answer

D. Reduced intravascular oncotic pressure & shift of plasma into interstitium

Nephrotic Syndrome: Edema

“Underfill” Hypothesis

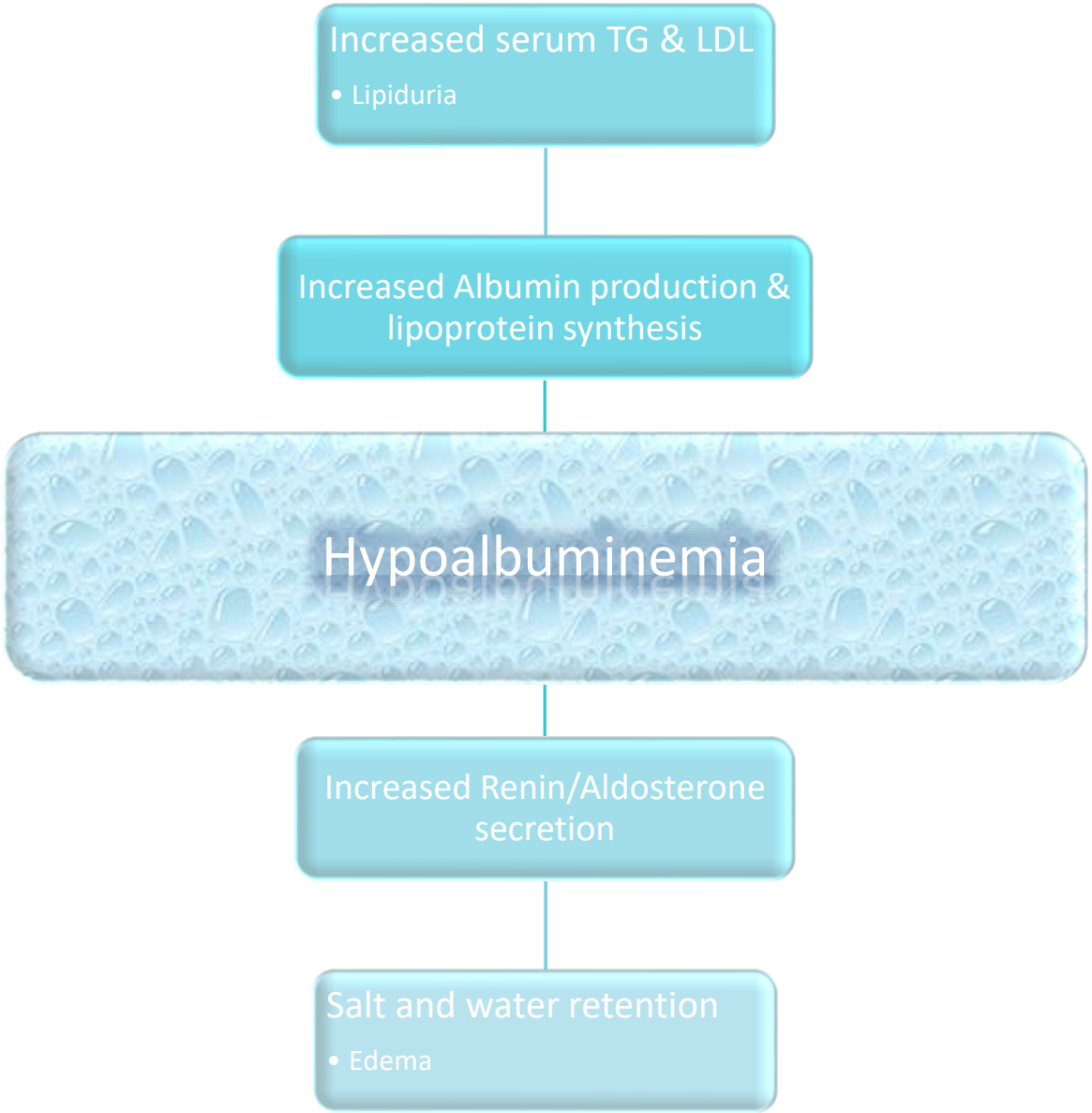
- Low serum albumin leads to reduced intravascular oncotic pressure & shift of plasma into interstitium
- This effective intravascular volume depletion activates RAAS, promoting Na/H20 retention

“Overfill” Hypothesis

- Abnormal filtered proteins leading to sodium retention at the collecting duct

Underfill Hypothesis:

Reduced oncotic pressure → Loss of fluid into interstitial space



Causes of Nephrotic Syndrome

- Minimal change disease
  - #1 cause in children, steroid-responsive
- Focal segmental glomerulonephritis
  - HIV, obesity, African Americans
- Membranous glomerulonephritis
  - #1 cause in white adults
- Diabetic nephropathy
- Deposition Diseases

Question

You are seeing an 82 year-old woman for complaint of new onset dependent edema that began suddenly 3 weeks ago. She says it is difficult to walk and she has gained 4.5 kg (10 pounds) in the past several weeks. History is significant for back pain, for which she has been taking Naproxen 2-3 times per day for the past 2 months.

On physical examination, vital signs are normal. BMI is 25. There is no rash. There is 3 mm bilateral dependent edema stopping just below the abdomen; it is equal on both sides. The remainder of the exam is unremarkable.

Laboratory Studies:

Albumin 2.1 g/dL

Creatinine 1.3 mg/dL

Urine protein/creatinine ratio 25,000 mg/g

Kidney biopsy shows normal LM and IF, but severe podocyte effacement on EM and superimposed acute tubular necrosis.

Question Continued

In addition to initiating diuretic and ACEI therapy, which of the following is the most appropriate treatment ?

A. Cyclosporine

B. High-dose oral prednisone

C. Rituximab

D. No additional treatment

Answer

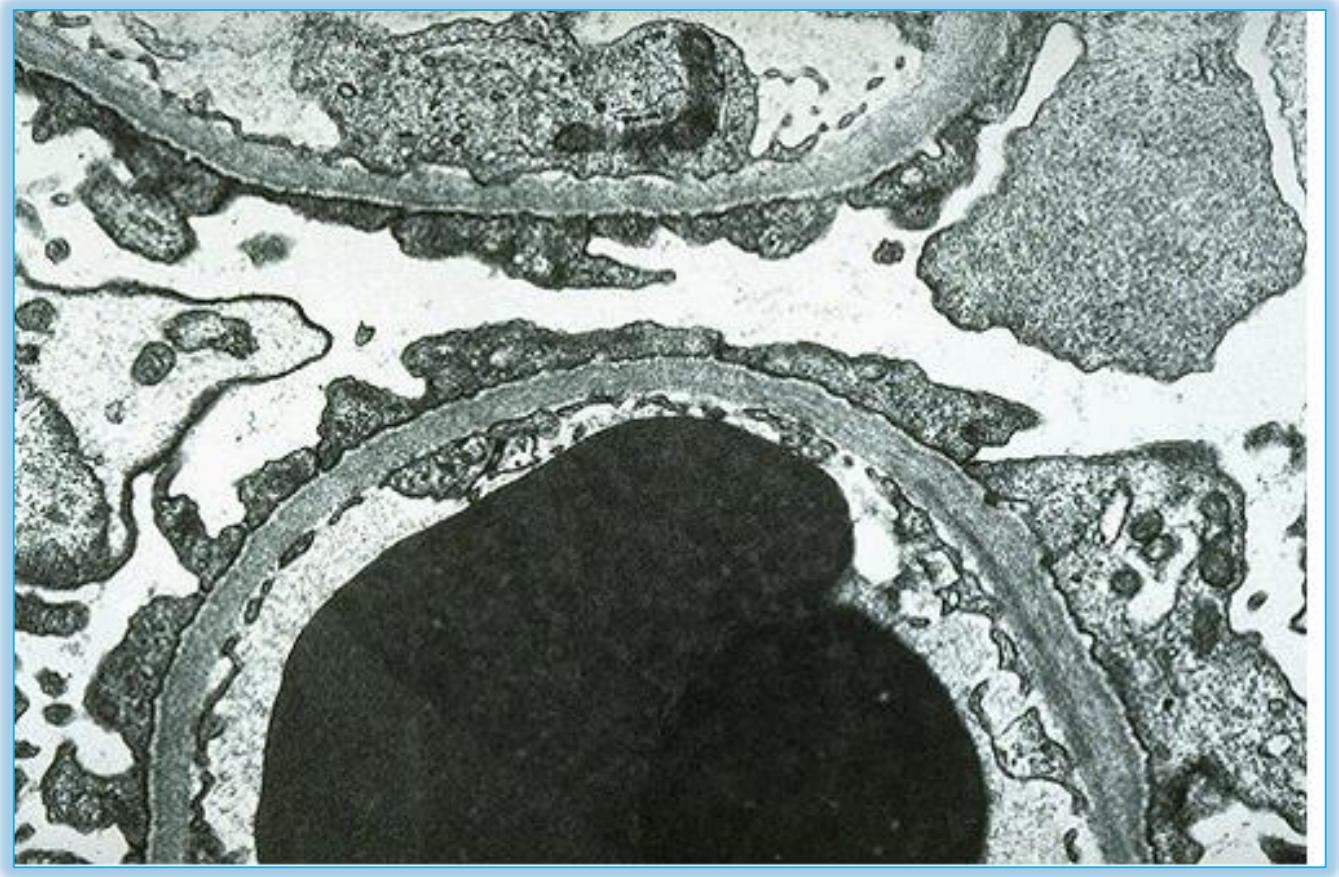
B. High-dose oral prednisone

Minimal Change Disease

- Most common cause of NS in children
- Extremes of age: young and very old
- Typically secondary in adults
  - Causes: NSAIDs, Hematologic malignancies (NHL) and Thymoma
- Severely nephrotic
- Tx: Steroid-responsive

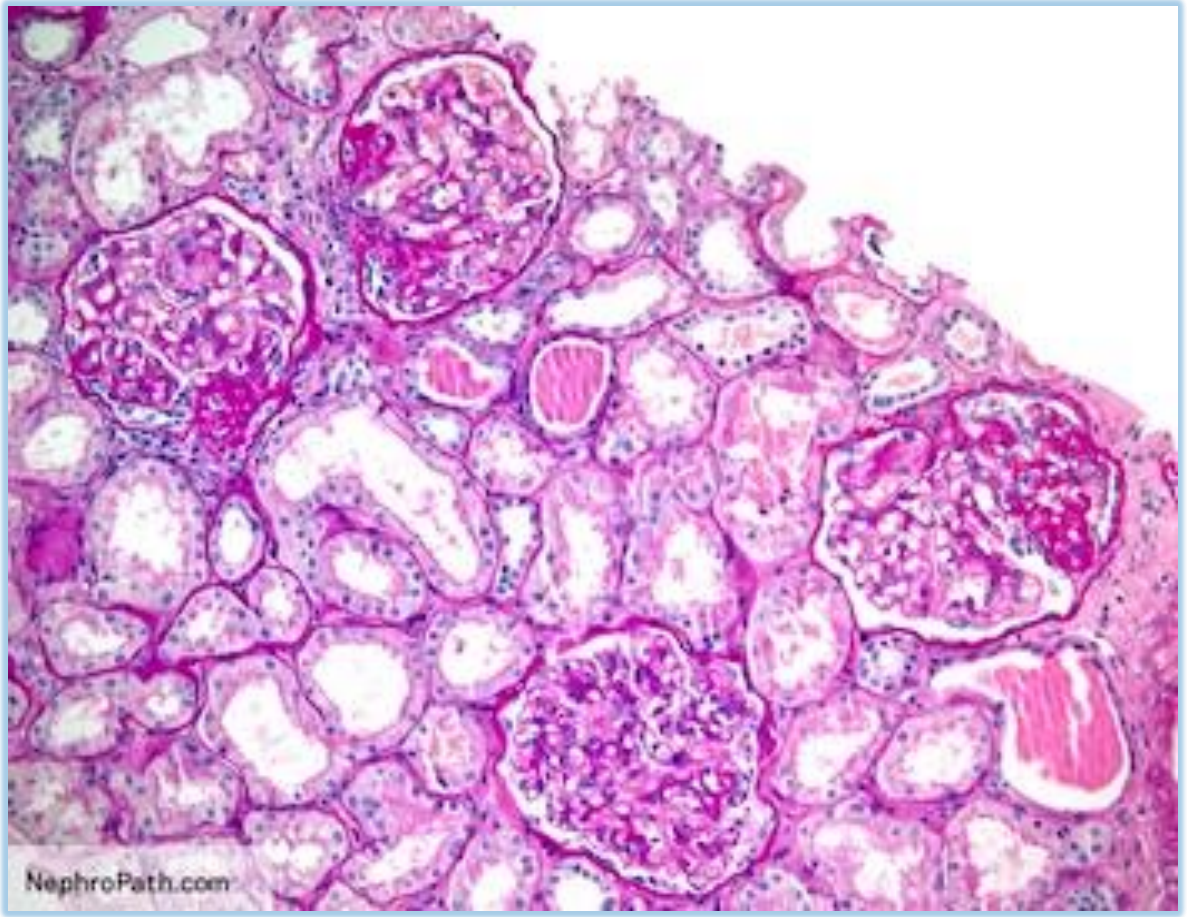
Minimal Change Disease

Podocytopathy on EM, otherwise normal pathology



Focal Segmental Glomerulosclerosis

- Most common GN pathology associated with ESRD in the US
- A morphological / histological pattern of injury stemming from podocyte injury leading to podocyte detachment/death
- **Sclerotic** lesions in glomeruli that are *focal* (< 50% of all gloms on LM) and *segmental* (< 50% of the glomerular tuft affected)
- Podocyte effacement
- Further LM classification: tip, cellular, collapsing, perihilar, and NOS
  - Collapsing: worst prognosis
  - Tip: steroid-responsive, best prognosis



Which of the following is associated with FSGS?

A. White race

B. APOL1 gene

C. Cocaine use

D. Hepatitis B

Answer

B. APOL1 gene

FSGS Causes

Most common in those of African descent – 5 times greater risk

Primary / Idiopathic

- Typically presents as *nephrotic syndrome*
- May be associated with a circulating **podocyte** toxin
- HTN, microhematuria, renal dysfunction common
- Poor prognosis: progression to ESRD over 5-10 years
- Can recur rapidly post-transplant
- Tx: ACEI/ARB, steroids; 2nd line: Cytoxan, CNI, MMF

Secondary

- *Sub-nephrotic proteinuria*
- Genetic: **APOL1 gene**, NPHS1/2
- Viral: **HIV**, Parvovirus B19
- Drugs: **Heroin**, Pamidronate, Interferon, Sirolimus, Lithium
- Adaptive changes/hyperfiltration
  - Obesity
  - Nephron loss/solitary kidney
  - Reflux nephropathy
  - HTN
- Tx: ACEI/ARB, tx underlying cause

Question

A 72 year-old man is evaluated during a follow up visit for a 4 week history of progressive worsening new onset edema, weight gain and foamy urine. He otherwise has been well and denies any other symptoms. He has a 50 pack year history of cigarette smoking and ongoing tobacco use.

On physical examination, vital signs are normal. Severe pitting edema to the knees is present.

Laboratory Studies:

Albumin 2.8 g/dL
C3 Normal
C4 Normal
Creatinine 0.8 mg/dL
RPR Normal
Antinuclear antibodies Negative
Hepatitis B antibodies Negative
Hepatitis C antibodies Negative
24 hour urine protein excretion 12,200 mg/ 24 h

Kidney Ultrasound shows normal appearing kidneys with no evidence of thrombus in renal veins. Lower extremity Doppler ultrasound shows no deep venous thrombosis.

Question Continued

Kidney biopsy shows membranous glomerulopathy with negative staining for the phospholipase A2 receptor (PLA2R) on immunofluorescence.

Which of the following is the most appropriate management?

A. Age and sex appropriate cancer screening

B. Initiation of immunosuppressive therapy

C. Prophylactic anticoagulation

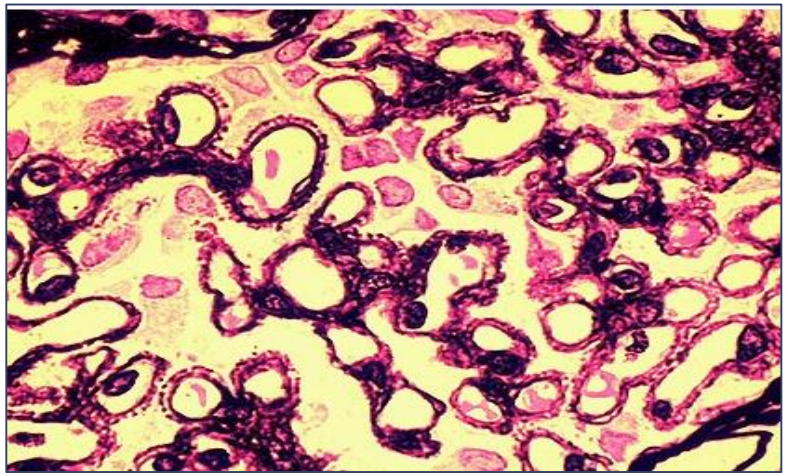
D. Serological testing for anti-PLA2R antibodies

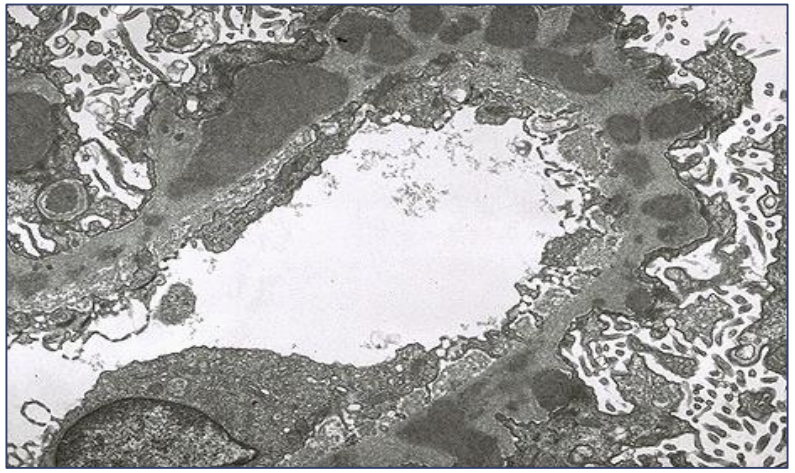
Answer

A. Age and sex appropriate cancer screening

Membranous Glomerulonephritis

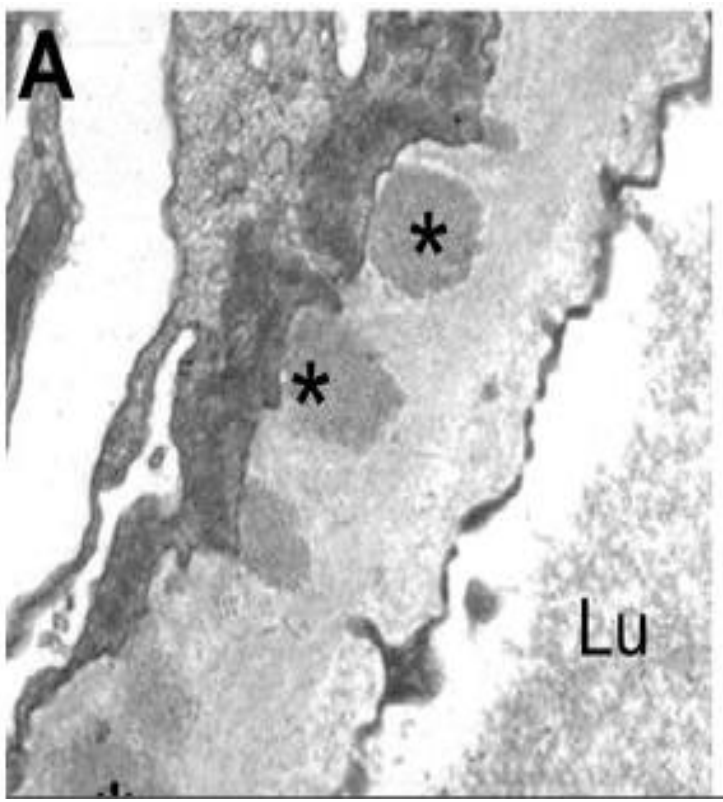
- May be primary vs secondary
- Primary associated with PLA2 R antigen
- Secondary associated with **solid tumor malignancy**, Hepatitis B, penicillamine, gold
- Tx: Primary – ACEI/ARB, steroid+alkylating agent vs CNI; Secondary – tx underlying cause



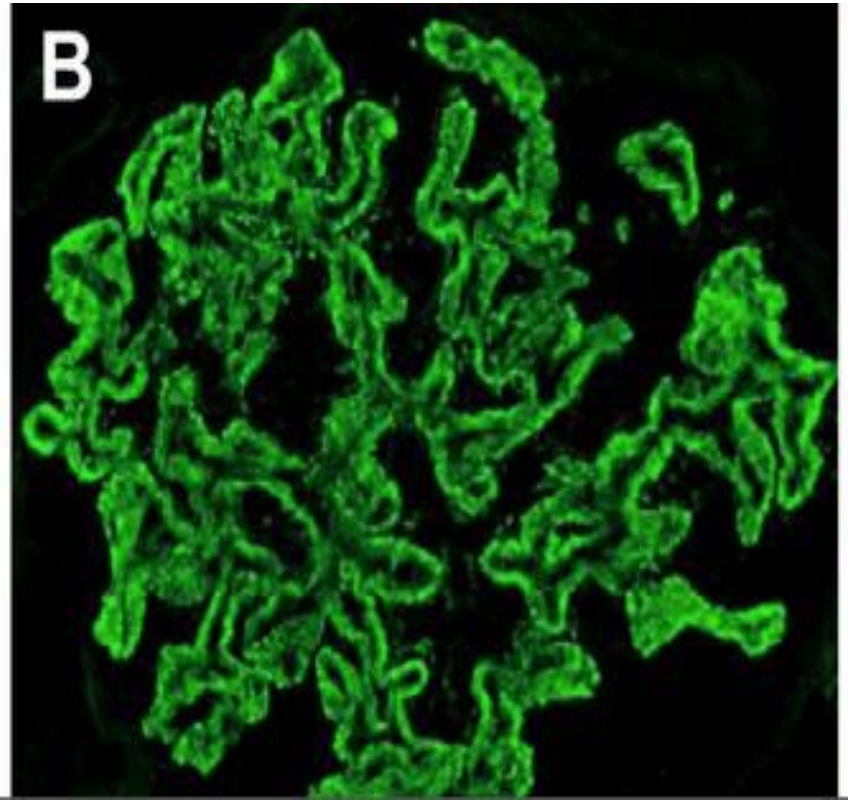


Spike-like GBM deposits seen on LM & EM

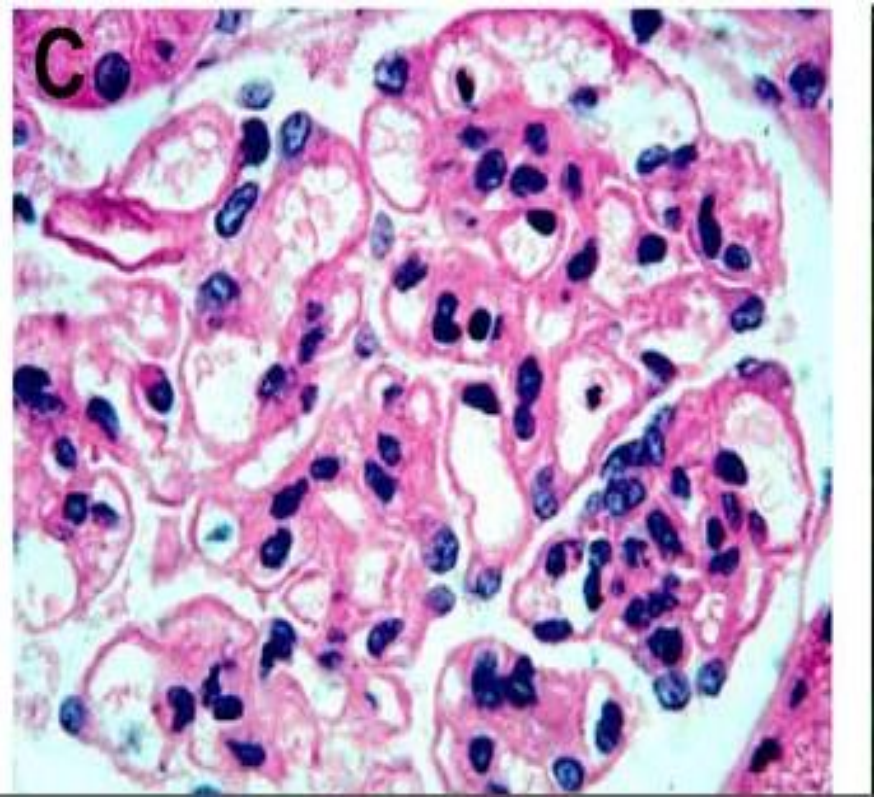
Membranous GN: EM/IF/LM



Subepithelial electron dense deposits and podocyte effacement



+IgG & Anti-PLA2R Ab along capillary wall



Thickened capillary walls

Question

A 33 year-old man is hospitalized for a headache, hypertension, and an elevated serum creatinine level. He has a 10 year history of poorly controlled type 2 diabetes mellitus and hypertension. Medications include insulin glargine, insulin lispro, atorvastatin, amlodipine and low dose aspirin.

On physical examination, blood pressure is 145/94 mm Hg; other vital signs are normal. Fundoscopic examination reveals nonproliferative diabetic retinopathy. There is 1+ pitting edema of the lower extremities to the ankles, equal on both sides. Dorsalis pedis pulses are decreased bilaterally and sensation is diminished in the feet bilaterally.

Laboratory Studies:

CBC	Normal
Albumin	3.3 mg/dL
Creatinine	1.8 mg/dL
HgA1c	8.1 %
Antinuclear antibodies	Negative
Hepatitis B virus antibodies	Negative
Hepatitis C virus antibodies	Negative
HIV antibodies	Negative
Urinalysis	No blood; 3+ protein
Urine protein/creatinine ratio	6700 mg / g

Kidney ultrasound reveals mildly increased echogenicity bilaterally and both kidneys enlarged at 12 cm.

Question Continued

In addition to improved glycemic control, which of the following is the most appropriate management?

A. Add an ACE inhibitor

B. Obtain ANCA titers

C. Obtain serum and urine electrophoresis

D. Schedule a kidney biopsy

Answer

A. Add an ACE inhibitor

Systemic Diseases → Glomerular Disease

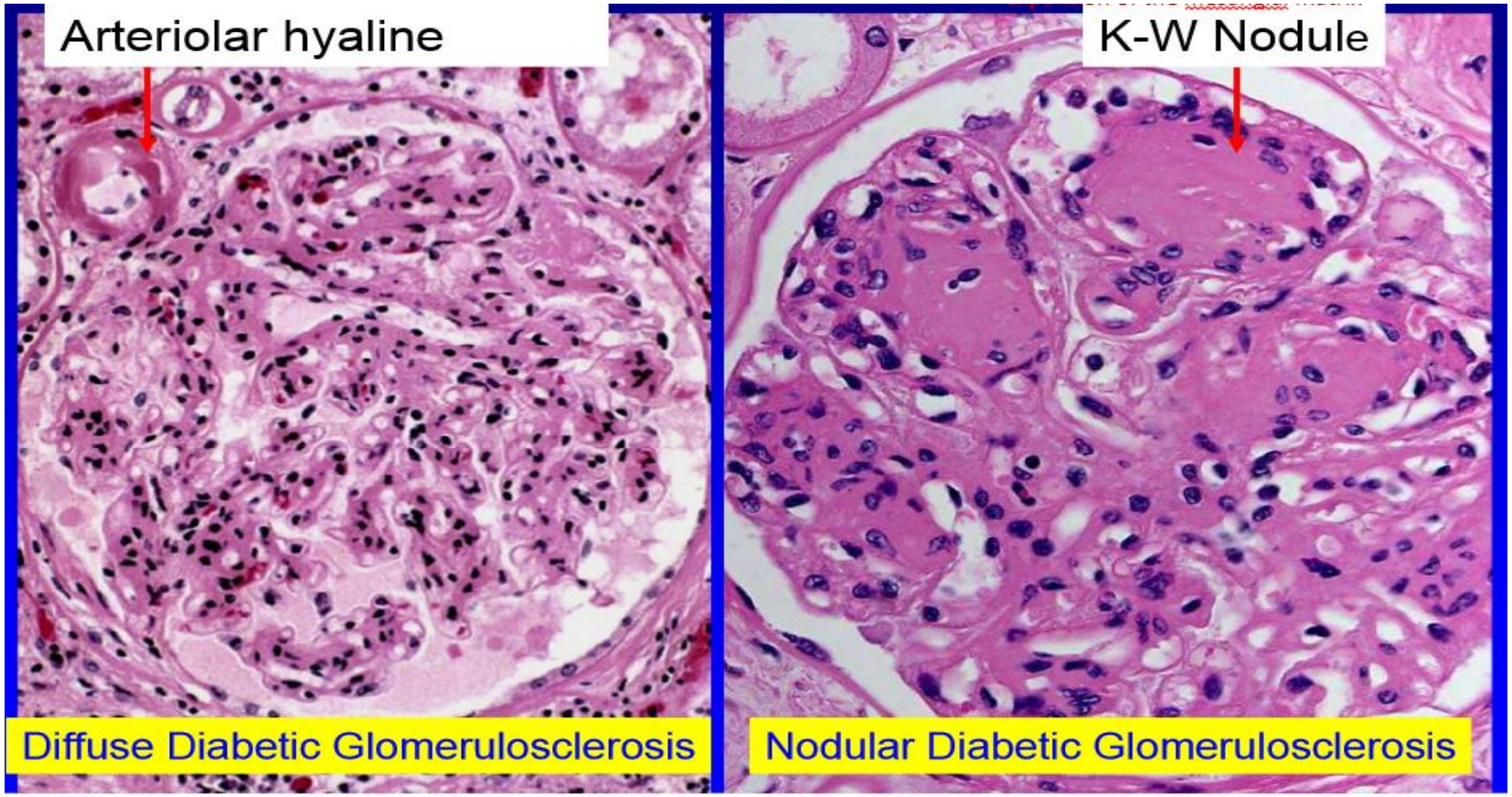
- Diabetes mellitus
- Systemic lupus erythematosus
- Deposition Diseases

Diabetic Nephropathy

- # 1 cause of kidney disease in the U.S.
- Type 2: develops after 10-12 years
- Type 1: develops after 20 yrs
- Annual screening with UACR
- Initially a hyperfiltrative state, high GFR, “microalbuminuria”
- Clinically can be subnephrotic or nephrotic
  - Degree of proteinuria prognostic indicator

Pathology in DN: Diffuse *or* Nodular Glomerulosclerosis

- Basement membrane thickening and increased mesangial matrix
- Profound hyalinization of afferent arterioles
- Caused by damage as a result of non-enzymatic glycosylation of proteins (leading to formation of advanced glycation end products).

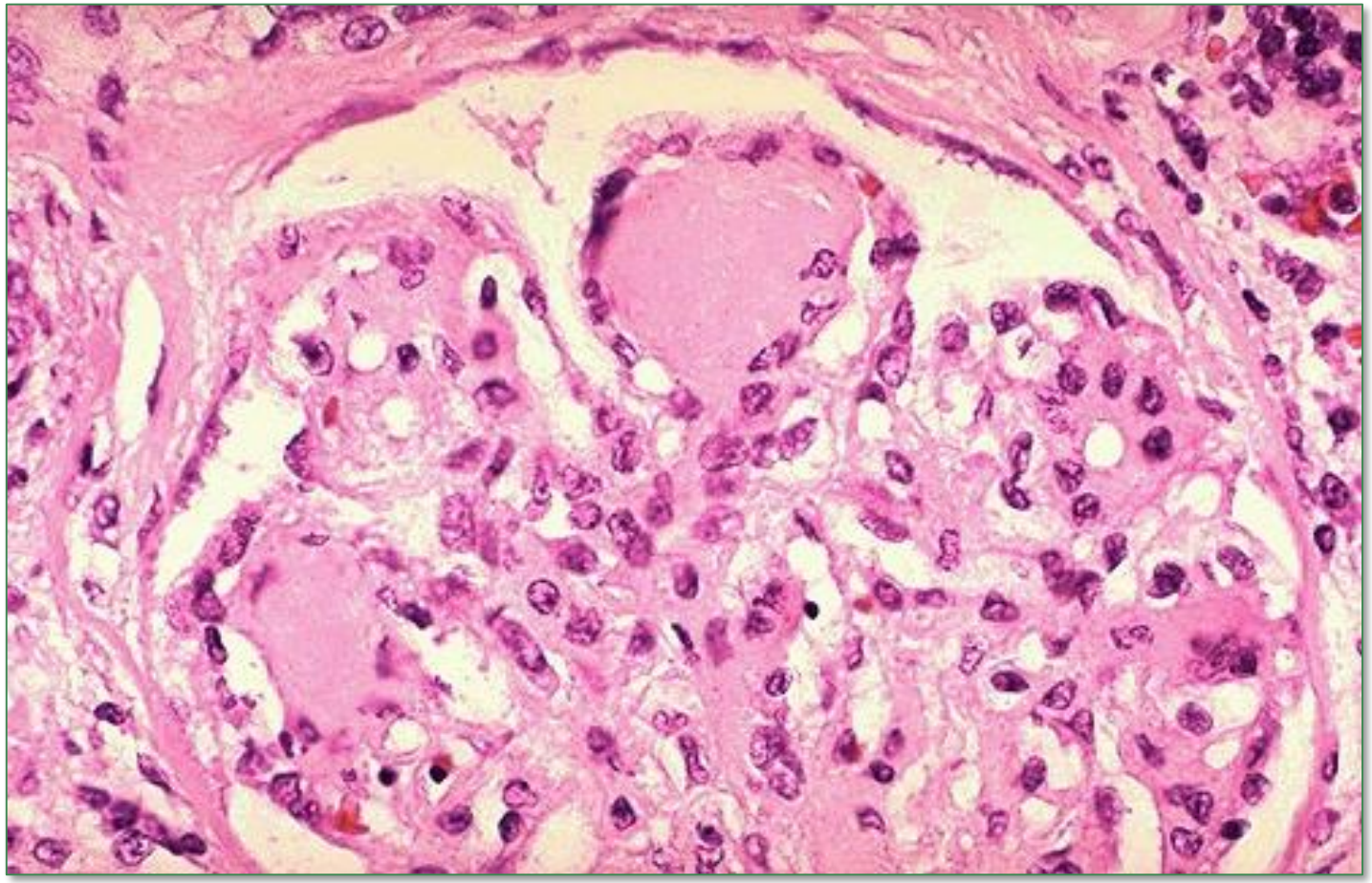


~ 50% Nodular

Diabetic “Nodular Glomerulosclerosis”

Nodular glomerulosclerosis

- “Kimmelstiel-Wilson” lesion: spherical nodules of hyaline material form in regions of glomerular capillary loops; PAS+
- **Pathognomonic** for DN



Lupus Nephritis

- 60 % of adults with SLE will develop renal abnormalities
- 6 different histopathological classes
  - Prognosis and treatment depends on LN Class
  - May change classes over time or have > 1 class on patholog
- Membranous lupus nephritis (class V) can be a cause of NS

Which of the following is a systemic disease which causes glomerular pathology and nephrotic syndrome?

A. Myeloma cast nephropathy

B. Renal amyloid

C. Tuberous sclerosis

D. Monoclonal gammopathy of unknown significance

Answer

B. Renal amyloid

Deposition Diseases/Paraproteinemias

- Diverse renal pathology, subnephrotic vs nephrotic
- Tubular pathology
  - Myeloma cast nephropathy
- Glomerular pathology
  - MIDD, MPGN, C3GN, Crystalline podocytopathy
- AL Amyloid
- AA Amyloid
- Fibrillary GN and Immunotactoid glomerulopathy
  - Larger than amyloid

Questions?

References

1. Korbet, Stephen M. Treatment of Primary FSGS in Adults. JASN November 2012, 23 (11) 1769-1776.

2. Brenner's The Kidney.

3. Forbes, Josephine et al. Role of Advanced Glycation End Products in Diabetic Nephropathy. JASN August 2003, 14 (suppl 3) S254-S258.