NOTES
NEPHROTIC SYNDROME

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Collection of diseases caused by inflammation, damage to glomeruli of kidney; glomeruli become more permeable, allow proteins from blood into urine → proteinuria

Proteinuria

- Hallmark of nephrotic syndromes
  - Loss of protein (mostly albumin) → hypoalbuminemia; lowers oncotic pressure in blood → water moves out of vessels into interstitium → edema
  - ↓ proteins → ↑ lipids → hyperlipidemia; ↑ lipids filtered in glomeruli → lipiduria; fatty casts, foamy urine

CAUSES

- Immune-mediated, metabolic, hemodynamic disturbances
- *Primary:* kidney lesion
  - Minimal change disease, focal segmental glomerulosclerosis, membranous glomerulonephritis, membranoproliferative glomerulonephritis
- *Secondary:* systemic disease
  - Diabetic nephropathy, lupus nephritis

COMPLICATIONS

- *Loss of proteins (e.g. anticoagulants, iron-carrying proteins):* thromboembolism, renal vein thrombosis, microcytic hypochromic anemia, infections, hypocalcaemia

SIGNS & SYMPTOMS

- Proteinuria, hypoalbuminemia, edema, hyperlipidemia, lipiduria, hypercoagulability

DIAGNOSIS

LAB RESULTS

- Protein/blood in urine
- *Decreased glomerular filtration rate:* estimated from serum creatinine clearance

Kidney biopsy

- Changes under light/electron microscope, immunofluorescence
- *Blood test:* albumin, cholesterol levels

TREATMENT

MEDICATIONS

- Edema
  - Diuretics (furosemide), medical nutrition therapy
- Blood pressure control
  - Angiotensin converting enzyme (ACE) inhibitors
- Hyperlipidemia
  - Reduce cholesterol, saturated fat intake
- Hypercoagulability
  - Heparin
- Infections
  - Antibacterial drugs
- Immunosuppressants
  - Cyclophosphamide, prednisone

MNEMONIC: Protein LEAC

Nephrotic syndrome findings

Proteinuria
Lipid up
Edema
Albumin down
Cholesterol up

DIABETIC NEPHROPATHY

osms.it/diabetic-nephropathy

PATHOLOGY & CAUSES

- Kidney damage caused by Type I, Type II diabetes

CAUSES

Excess glucose in blood

- Overrides renal threshold for glucose (160–180mg/dl) → glycosuria
- Non-enzymatic glycation of proteins → basement membranes thicken → hyaline arteriosclerosis
- Hyaline arteriosclerosis, arteriole dilatation increases pressure in glomerulus → increased glomerular filtration rate (first stage)
- Thickening of basement membrane → glomerulus expands, filtration slits widen → increased permeability
- High-pressure state → supportive mesangial cells secrete more structural matrix → Kimmelstiel–Wilson nodules
- Damage glomeruli → decreased glomerular filtration rate (second stage)

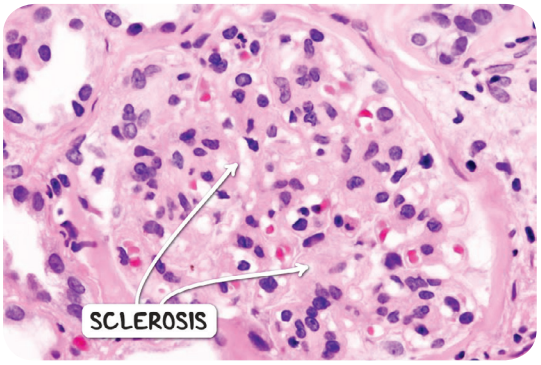

Figure 118.1 Histological appearance of the glomeruli in a case of diabetic nephropathy. There is diffuse sclerosis of the glomerulus.

RISK FACTORS

- Family history; poor control of diabetes, duration of diabetes (more common if developed at younger age); poor control of hypertension; obesity

SIGNS & SYMPTOMS

- Mostly asymptomatic

DIAGNOSIS

LAB RESULTS

- Microalbuminuria (30–300mg/day), macroalbuminuria (> 300mg/day)

TREATMENT

MEDICATIONS

- Control hyperglycemia
- *ACE inhibitors/angiotensin receptor blockers:* reduce constriction of efferent arteriole → lower pressure in glomerulus

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

osms.it/focal-segmental

PATHOLOGY & CAUSES

- Histologic finding of glomerular damage, not distinct disease.
- Affects parts (segmental) of some (focal) glomeruli of nephron; damage, scarring → proteinuria
- Foot processes of podocytes damaged → plasma proteins, lipids permeate glomerular filter
- Proteins, lipids trapped → build up inside glomeruli → hyalinosis (hyaline/glassy view on histology) → scar tissue (glomerulosclerosis)

CAUSE

- *Primary:* unknown
- *Secondary:* result of underlying cause
  - Sickle cell disease, HIV, renal hyperfiltration (e.g. unilateral renal agenesis), heroin abuse
- *Genetic forms:* FSGS 1–6

RISK FACTORS

- More common in black people of African descent/people of Latin American descent
- Morbid obesity
- Chronic kidney disease (congenital malformation)

COMPLICATIONS

- *End-stage renal failure:* inconsistent response with treatment; adults—more involved segments of kidney's glomeruli → kidney failure

SIGNS & SYMPTOMS

- Proteinuria, hypoalbuminemia, edema, hyperlipidemia, lipiduria, hypercoagulability

DIAGNOSIS

LAB RESULTS

- Protein in urine > 3.5g/L

Kidney biopsy: most definitive

- *Light microscopy:* segmental sclerosis, hyalinosis of glomeruli
- *Electron microscope:* effacement of foot processes of podocytes
- *Immunofluorescence:* nonspecific focal deposits of IgM, complement proteins not always seen (sometimes trapped in hyalinosis)

TREATMENT

MEDICATIONS

- Blood pressure reduction
  - ACE inhibitors
- Edema
  - Diuretics
- Prednisone/calcineurin inhibitors
  - Depend on nephrotic-range proteinuria, likelihood of reversibility

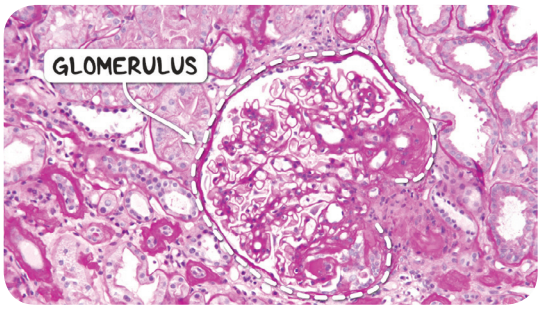

Figure 118.2 Histological appearance of focal segmental glomerulosclerosis. There is sclerosis and hyalinosis of only one part of the glomerulus, in this case the hilar part. The more distal part is normal.

LUPUS NEPHRITIS

osms.it/lupus-nephritis

PATHOLOGY & CAUSES

- Inflammation of kidney due to systemic lupus erythematosus.
- Focal (nephrons in one area)/diffuse (all nephrons in both kidneys)
- *Caused by antinuclear antibodies (anti-dsDNA):* bind to nuclear antigens, form antigen-antibody complexes
- Antigen-antibody complexes deposit in capillary walls, basement membrane, Bowman's space → initiate inflammatory response → Type III hypersensitivity reaction

TYPES

Class I
- Minimal mesangial glomerulonephritis

Class II
- Mesangial proliferative glomerulonephritis

Class III
- Focal glomerulonephritis

Class IV
- Diffuse proliferative nephritis

Class V
- Membranous glomerulonephritis

Class VI
- Advanced sclerosing lupus nephritis

COMPLICATIONS

- Renal vein thrombosis, pulmonary embolism, rapidly progressive glomerulonephritis

SIGNS & SYMPTOMS

- Nephrotic, nephritic syndrome
- *Nephritic syndrome:* hematuria, hypertension, edema, proteinuria, oliguria

DIAGNOSIS

LAB RESULTS

Kidney biopsy
- Microscopic presentation depends on class of lupus nephritis

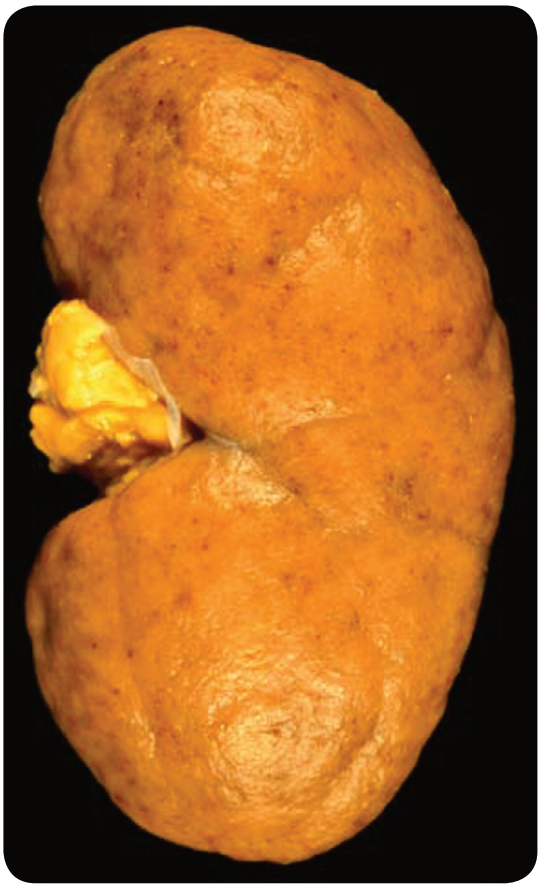

Figure 118.3 Gross pathological appearance of a kidney in case of lupus nephritis. The renal capsule has a characteritic flea-bitten appearance.

TREATMENT

MEDICATIONS

- Immunosuppressants
  - Corticosteroids; mycophenolate, cyclophosphamide

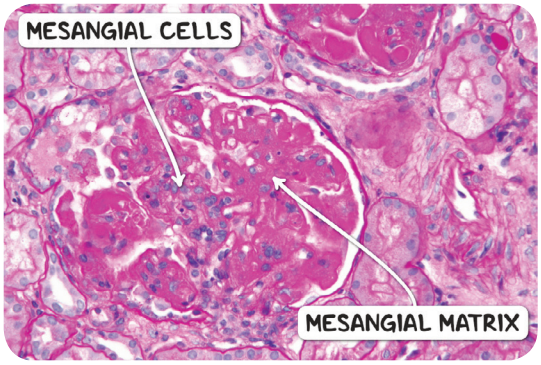

Figure 118.4 Histological appearance of the glomerulus in a case of lupus nephritis. There is global mesangial cell proliferation and abundant mesangial matrix.

LUPUS NEPHRITIS OVERVIEW

	MICROSCOPIC APPEARANCE	KEY FACTS
CLASS I (MINIMAL MESANGIAL GLOMERULONEPHRITIS)	Normal appearance under light microscope; mesangial deposits under electron microscope	Mild clinical symptoms
CLASS II (MESANGIAL PROLIFERATIVE GLOMERULONEPHRITIS)	Mesangial hypercellularity, matrix expansion	Microscopic haematuria with/ without proteinuria may occur
CLASS III (FOCAL GLOMERULONEPHRITIS)	Sclerotic lesions involving < 50% of glomeruli; subendothelial deposits under electron microscope	Haematuria, proteinuria with/ without nephrotic syndrome, hypertension, elevated serum creatinine
CLASS IV (DIFFUSE PROLIFERATIVE NEPHRITIS)	> 50% of glomeruli involved; subendothelial deposits under electron microscope	Haematuria, proteinuria, frequently with nephrotic syndrome, hypertension, hypocomplementemia, elevated anti-dsDNA titres, elevated serum creatinine
CLASS V (MEMBRANOUS GLOMERULONEPHRITIS)	Diffuse thickening of glomerular capillary wall, diffuse membrane thickening, subepithelial deposits under electron microscope	Signs of nephrotic syndrome; microscopic haematuria, hypertension; may lead to thrombotic complications
CLASS VI (ADVANCED SCLEROSING LUPUS NEPHRITIS)	Global sclerosis involving > 90% of glomeruli	Slowly progressive kidney dysfunction

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

osms.it/membrano-golmerulonephritis

PATHOLOGY & CAUSES

- Type of nephrotic syndrome; inflammation of glomerular basement membrane, mesangium → decreased kidney function, proteinuria
- Immune complex/complement deposits trigger immune reactions
  - Activates complement system → enzyme cascade → membrane attack complex → damage to podocytes, mesangial cells
  - Recruits inflammatory cells → proteases, oxidants release → basement membrane damage → proteins leak into urine → nephrotic syndrome

TYPES

- Appearance under light microscopy
  - Type I, II, II
  - All three can present as nephrotic, nephritic syndrome
- *Immunofluorescence:* immune complex-mediated MPGN, complement-mediated MPGN

CAUSES

Type I

- Chronic infection (e.g. hepatitis B, hepatitis C)
  - Antigens released → bind antibodies in blood → immune complexes deposit in glomerular basement membrane → activate classical complement pathway → complement protein + immune complex deposits
- Inappropriate activation of alternative pathway of complement
  - Mutation in proteins that regulate pathway
  - Presence of autoantibodies against proteins that regulate pathway
- Nephritic factor (C3NeF)
  - IgG antibody, binds to C3 convertase → C3 convertase more stable, active longer
  - Only complement deposits, no immune complex deposits
  - *Autoimmune diseases:* systemic lupus erythematosus, scleroderma, Sjögren syndrome, sarcoidosis
  - *Cancer:* leukemia, lymphoma

Type II

- Nephritic factor (C3NeF)
  - IgG antibody binds to C3 convertase → C3 convertase more stable, active longer

Type III

- Idiopathic

RISK FACTORS

- Dysregulation of complement system

COMPLICATIONS

- Chronic renal failure, hypertension

SIGNS & SYMPTOMS

- Nephrotic syndrome
  - Proteinuria, peripheral edema, foamy urine, hyperlipidemia, lipiduria
- Nephritic syndrome (more common)
  - Hematuria, oliguria (low production of urine), hypertension

DIAGNOSIS

LAB RESULTS

Kidney biopsy

Electron microscopy

- Type I
  - Subendothelial deposits
  - Thickening of basement membrane
  - Mesangial interposition: mesangial cells reach cytoplasmic arms through thick basement membrane, split lengthwise → duplicate basement membrane → "tram-track" appearance
- Type II
  - Complement deposits along basement membrane of glomeruli, tubules, Bowman's capsule
- Type III
  - Subepithelial deposits in mesangium, subendothelial space

TREATMENT

MEDICATIONS

- Treatment of underlying cause (e.g. antiviral therapy for hepatitis B virus)
- If underlying cause ruled out/nephrotic range proteinuria
  - Immunosuppressive therapy (steroids)

MEMBRANOUS GLOMERULONEPHRITIS

osms.it/membranous-glomerulonephritis

PATHOLOGY & CAUSES

- Inflammation of glomerular basement membrane triggered by immune complex deposits → increased permeability, proteinuria → nephrotic syndrome
- Glomerular basement membrane damaged by immune complex deposits; sandwiched between epithelial cells of podocytes, glomerular basement membrane (subendothelial deposits)
- Autoantibodies target glomerular basement membrane
  - *Two major antigen targets on podocytes:* M-type phospholipase A2 receptor, neural endopeptidase
- Complexes outside kidney, carried through blood, deposit in basement membrane
  - *Possible antigens:* cationic bovine serum albumin (cow's milk, beef protein)
- Immune complex deposits → immune reactions
  - Activates complement system → enzyme cascade → membrane attack complex → damage to podocytes, mesangial cells
  - Recruits inflammatory cells → proteases, oxidants release → basement membrane damage → proteins leak into urine → nephrotic syndrome
- Often benign
  - *Spontaneous complete remission:* 5–30% at five years
  - *Spontaneous partial remission:* 25–40% at five years

CAUSES

Primary

- Mostly idiopathic
- Associated with human leukocyte antigen (HLA) alleles (e.g. HLA-DQA1)

Secondary

- Auto-antibodies generated in response to underlying conditions
- Infections
  - Hepatitis B virus, hepatitis C virus, syphilis
- Medications
  - NSAIDs, penicillamine, gold
- Autoimmune
  - Systemic lupus erythematosus
- Malignancy

RISK FACTORS

- White people of European descent
- Increase risk of end-stage renal disease
  - Older age at onset (> 50 years), individuals who are biologically male, nephrotic-range proteinuria (> 8–10g/day), increased serum creatinine

COMPLICATIONS

- Chronic kidney failure, if untreated + nephrotic range proteinuria

SIGNS & SYMPTOMS

- Often asymptomatic, discovered incidentally
- Proteinuria, hypoalbuminemia, edema, hyperlipidemia, lipiduria, hypercoagulability; develop gradually over months

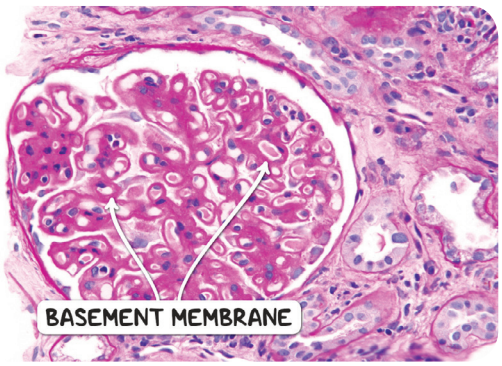

Figure 118.5 Histological appearance of membranous glomerulonephritis. The basement membrane of the glomerulus is markedly thickened.

DIAGNOSIS

LAB RESULTS

- Proteinuria

Renal biopsy

- Light microscopy
  - Diffuse thickening of glomerular basement membrane
- Electron microscopy
  - "Spike and dome" appearance due to glomerular basement matrix on top of subepithelial deposits; effacement of podocytes
- Immunofluorescence
  - Deposits appear granular throughout glomerular basement membrane
- If kidney biopsy not an option
  - *Serum:* assayed for antibodies associated with membranous glomerulonephritis (anti-PLA2R antibody)

TREATMENT

MEDICATIONS

Primary cause

- Diuretics (furosemide), ACE inhibitors, heparin, antibacterial drugs
  - Symptomatic therapy
- Close observation, no immunosuppression
  - If at low risk of end-stage renal disorder (i.e. proteinuria < 3.5g/day)
- Prednisone + calcineurin inhibitor (e.g. tacrolimus, cyclosporine)/cytotoxic agent (e.g. cyclophosphamide)
  - If at moderate/high risk of end-stage renal disorder
- Rituximab

Secondary cause

- Treat underlying condition

OTHER INTERVENTIONS

- Lifestyle changes
  - Medical nutrition therapy, reduce cholesterol, saturated fat intake

MINIMAL CHANGE DISEASE

osms.it/minimal-change-disease

PATHOLOGY & CAUSES

- Type of glomerulonephritis; podocytes in glomeruli damaged by T cells cytokines
- Foot processes of podocytes damaged, flattened (AKA effacement) → lose function as barrier → albumin permeates, bigger proteins cannot get through (selective proteinuria)

CAUSES

- Unknown; T cells release cytokines, may cause effacement of podocytes

RISK FACTORS

- Recent infection; immunization; immune stimulus; medications: nonsteroidal anti-inflammatory drugs (NSAIDs)
- Hematologic malignancies (e.g. Hodgkin's lymphoma)
- Most common nephrotic syndrome in children

COMPLICATIONS

- Relatively benign, does not affect kidney function

SIGNS & SYMPTOMS

- Proteinuria, hypoalbuminemia, edema, hyperlipidemia, lipiduria, hypercoagulability
- Onset more rapid (days to weeks) than other nephrotic syndromes

DIAGNOSIS

LAB RESULTS

- Protein in urine > 3.5g/day

Kidney biopsy

- Corticosteroid resistant patients
- Light microscopy
  - Glomeruli appear normal, hence "minimal change disease"
- Electron microscopy
  - Effacement of foot processes.
- Immunofluorescence
  - Negative (no immune complex deposition)

TREATMENT

MEDICATIONS

- Prednisone therapy
  - Excellent response, more quickly in children than adults; potential relapse

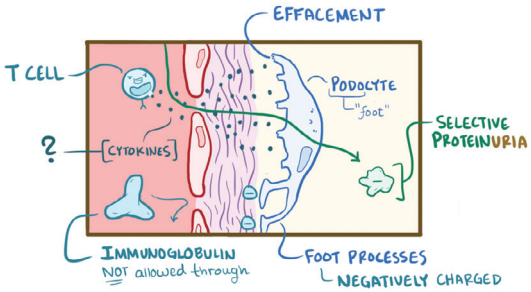

Figure 118.6 An illustration demonstrating the pathophysiology of minimal change disease.