Nephritic Syndrome:

Summary

Nephritic syndrome is characterized by glomerular capillary damage leading to hematuria, pyuria, water retention, and subsequent hypertension and edema. It can be caused by a variety of conditions including autoimmune, hereditary, and infectious diseases. Nephritic diseases can manifest with varying degrees of severity, ranging from asymptomatic hematuria to systemic involvement, as in rapidly progressive glomerulonephritis. The urine sediment is typically characterized by red blood cell casts, mild to moderate proteinuria (< 3.5 g/day), and sterile pyuria. Diagnosis of the underlying disease is often based on presentation and laboratory values, although renal biopsy may be indicated for confirmation.

Definition

Nephritic syndrome is an inflammatory process that is defined as the presence of one or more of the following: [1]

- **Hematuria** with acanthocytes
- **RBC casts in urine**
- **Proteinuria (< 3.5 g/24 h)**
- **Hypertension**
- Mild to moderate edema
- Sterile pyuria
- Oliguria
- Azotemia — An increase in the level of nitrogenous waste (both urea and creatinine) due to renal insufficiency.

Nephr**I**tic syndrome indicates glomerular **I**nflammation.

Pathophysiology

- **General pathophysiology**
  - Inflammation → cytokine release → **glomerular capillary damage**
    - Porous glomerular basement membrane → leakage of proteins and RBCs → nephritic sediment (all blood components are detectable on urinalysis)
      - **Proteinuria** (< 3.5 g/24h): leakage of proteins
      - **Hematuria**: leakage of RBCs, which stick together and form red blood cell casts in the renal tubules
    - **Oliguria**: inflammatory infiltrates reduce fluid movement across the membrane (↓ GFR)
    - **Azotemia**: inflammation prevents sufficient filtering and excretion of urea
    - **Salt retention** → intravascular volume expansion → hypertension and edema
- **Membranoproliferative glomerulonephritis**: characterized by deposition of antibodies between podocytes and the basal membrane
  - **Membranoproliferative glomerulonephritis type 1**: subendothelial immune complex deposits → activation of the classical complement pathway → cell injury, mesangial proliferation, and matrix expansion
  - **Membranoproliferative glomerulonephritis type 2** (dense deposit disease): intramembranous deposition of complement C3 (**C3 nephritic factor**, an IgG autoantibody that stabilizes C3 convertase and continuously activates C3, leading to its depletion) → activation of the alternative complement pathway

FEEDBACK

Clinical features

- Intermittent gross hematuria (red or brown urine, i.e., **cola-colored urine**)
- **Hypertension**
- Pitting **edema**
- In ↓ GFR: **oliguria** and uremic symptoms (see "Uremia")
- For a comparison of nephrotic and nephritic syndrome see "Nephrotic vs. nephritic syndrome"

FEEDBACK

Disease associated with nephritic syndrome:

First: Poststreptococcus Glomerulonehritis

Diseases associated with nephritic syndrome			
	Epidemiology	**Clinical features**	**Diagnostics**
Poststreptococcal glomerulonephritis	• Usually affects **children** 3–12 years of age and elderly patients [2]	• Occurs weeks **after group A β-hemolytic streptococcal infections** ◦ Pharyngitis/tonsillitis (most common): 1–2 weeks after infection ◦ Skin infections: 3–4 weeks after infection • Periorbital and peripheral edema • Hypertension • Tea- or cola-colored urine • Usually **self-limiting** in children • May lead to rapidly progressive glomerulonephritis (RPGN) → renal insufficiency in adults	• **Positive antistreptococcal antibodies** (ASO, ADB) • ↓ **Serum C3** complement levels (due to consumption) • Type III hypersensitivity reaction • LM: glomeruli appear enlarged and hypercellular • IF ◦ Granular subepithelial immune complex **depositions (IgG, IgM, C3)** along the GBM and the mesangium ◦ So-called "lumpy bumpy" or "starry sky" appearance • Electron microscopy (EM): dome-shaped, subepithelial immune complex deposits **(humps)**

a. **Epidemiology. PSGN** is the **most common form of acute glomerulonephritis** that occurs in school-age children. (Note that some of the other less common causes of postinfectious glomerulonephritis include malaria, HIV, hepatitis B and C, and congenital syphilis.) PSGN is rare before 2 years of age.

b. **Clinical features**

1. PSGN typically develops **8–14 days after an infection of the skin or pharynx** with a **nephritogenic strain of group A β-hemolytic streptococcus.** The latency period after impetigo may be as long as 21–28 days.
2. **Hematuria** (often gross hematuria), **proteinuria** (rarely of nephrotic proportion), and **hypertension** with signs of fluid overload (e.g., edema) are common clinical features.
3. **Low serum complement** (C3) is present but transient and normalizes within 8–12 weeks.
4. The degree of impairment of renal function is variable and usually normalizes within 6–8 weeks. Severe renal failure is rare.

c. **Diagnosis.** Diagnosis is on the basis of clinical features and laboratory findings, including evidence of prior streptococcal infection.

An antibody used as a marker for recent skin and/or throat infection by group A beta-hemolytic streptococci (GAS). Increased anti-DNase B antibody titers can be used to identify recent GAS skin infection, particularly if ASO titers are falsely negative.

1. **Detection of prior streptococcal infection**
   a. **ASO titer** is positive in 90% of children after streptococcal pharyngitis, but is positive in only 50% of patients with impetigo.
   b. **ADB titer** is reliably positive after respiratory or skin infections with streptococcus.
2. **Other diagnostic tests** should include urinalysis, serum complement levels, renal ultrasound, tests of renal function, serum albumin, and serum cholesterol if the serum albumin is depressed.
3. **Renal biopsy** is indicated only if the patient has significant renal impairment or nephrotic syndrome, or if the serum complement fails to normalize within 12 weeks. **Biopsy** typically shows mesangial cell proliferation and increased mesangial matrix, as well as very large subepithelial deposits (humps) on electron microscopy, and C3 and IgG deposits on immunofluorescent microscopy.

d. **Management.** Treatment is supportive in most cases and includes fluid restriction, antihypertensive medications, and dietary restriction of protein, sodium, potassium, and phosphorus, as dictated by the level of renal functional impairment.

e. **Prognosis** is excellent with complete recovery in most patients.

f. **Prompt antibiotic treatment of infections with nephritogenic strains of group A β-hemolytic streptococcus does not reduce the risk of PSGN, although it will reduce the risk of rheumatic fever** (see Chapter 16, section VI and Chapter 7, section IX.A.5.f).

2nd:IgA nephropathy:

IgA nephropathy (Berger disease)	• Most common type of idiopathic glomerulonephritis worldwide • Incidence: ♂ > ♀ [3] • Peak incidence: 2nd to 3rd decade of life [4]	• Asymptomatic microhematuria with intermittent gross hematuria during or directly after one or more of the following: ◦ Upper respiratory tract infections ◦ Gastrointestinal infections ◦ Strenuous exercise • 25–30% of patients progress to end-stage renal disease (ESRD) within 20 years of diagnosis. [5]	• ↑ Serum IgA • Normal C3 complement levels • Renal pathology findings of IgA vasculitis (IgA vasculitis) ◦ LM: mesangial proliferation ◦ IF: mesangial IgA immune complex deposits ◦ EM: mesangial immune complex deposits

a. **Epidemiology**
   1. IgA nephropathy is the **most common type of chronic glomerulonephritis worldwide.** It typically presents in the second or third decade of life.
   2. It is more prevalent in **Asia** and **Australia** and in **Native Americans**, and it is rare in African Americans.

b. **Etiology.** The cause is poorly understood but may relate to abnormal clearance and formation of IgA immune complexes containing IgA molecules that are abnormally glycosylated.

c. **Clinical features.** Clinical findings classically include **recurrent bouts of gross hematuria associated with respiratory infections.** However, not all patients experience gross hematuria. Transient acute renal failure may occur in some patients. Microscopic hematuria is present in between the bouts of gross hematuria. The presence of heavy proteinuria and elevated serum creatinine are poor prognostic signs.

d. **Diagnosis. Renal biopsy,** which shows mesangial proliferation and increased mesangial matrix on light microscopy, is the basis of diagnosis. Immunofluorescent microscopy reveals mesangial deposition of IgA as the dominant immunoglobulin. Approximately 50% of patients have elevated serum levels of IgA. In more advanced cases there may be crescents, glomerular scarring, and tubular atrophy.

e. **Management.** Treatment is supportive and includes regular follow-up for the development of hypertension. Hypertension may eventually worsen proteinuria and renal function. Medications (angiotensin-converting enzyme [ACE] inhibitors, steroids, and immunosuppressants such as mycophenolate mofetil) are usually recommended for patients with associated pathologic proteinuria, renal insufficiency, or more significant glomerular inflammation on renal biopsy.

f. **Prognosis** is variable. Twenty to forty percent of patients eventually develop end-stage renal disease (ESRD).

	IgA nephropathy	Postinfectious glomerulonephritis
Clinical presentation	• Usually within 5 days of upper respiratory tract infection (**synpharyngitic**) • More common in young adult men (age 20-30) • Recurrent gross hematuria	• Usually 10-21 days after upper respiratory tract infection (post-pharyngitic) • More common in children (age 6-10), but can occur in adults • Gross hematuria • Adults can be asymptomatic or develop acute nephritic syndrome
Diagnosis	• Normal serum complements • Mesangial IgA deposits seen in kidney biopsy	• Low C3 complement • Elevated anti-streptolysin O &/or anti-DNAse B • Kidney biopsy with subepithelial humps consisting of C3 complement
Prognosis	• Usually benign • Possible rapidly progressive glomerulonephritis or nephrotic syndrome with worse prognosis	• Children have good prognosis • Possible chronic kidney disease in adults

3rd:Goodpasture syndrome)

Goodpasture syndrome (anti–GBM antibody disease)	• Two peaks of occurrence [9] ◦ 20–30 years (♂ > ♀) ◦ 60–70 years (♀ > ♂)	• Pulmonary infiltrates on chest x-ray • Pulmonary hemorrhage and hemoptysis • Usually presents as RPGN type 1 • Anti-GBM glomerulonephritis: glomerulonephritis in the presence of anti-GBM antibodies without lung involvement	• Caused by antibodies against type IV collagen • Type II hypersensitivity reaction • Hemosiderin-filled macrophages in sputum • Iron deficiency anemia • IF: linear deposition of immunoglobulin (IgG) along the glomerular basement membrane (and the alveolar basement membrane in the lung)

- Goodpasture syndrome (GP) is an idiopathic disorder of renal and lung disease characterized by a unique antibasement membrane antibody formation.
- The underlying cause is formation of antibodies to the alpha-3 chain of type IV collagen, a protein expressed most strongly in the glomerular and alveolar basement membranes.
- Goodpasture's disease affects the lungs (causing cough, dyspnea, and hemoptysis) and kidneys (causing nephritic range proteinuria, acute renal failure, and dysmorphic red cells/red cell casts on urinalysis).
- Unlike Wegener or Churg-Strauss, GP does not affect multiple organs or sites in the body besides the lung and kidney. Signs of systemic vasculitis are absent. There is no skin, joint, GI, eye, or neurological involvement.
- Unlike Wegener granulomatosis (WG), there is no upper respiratory tract involvement.
- Diagnostic Tests/Treatment:

- The best initial test is anti-glomerular basement membrane antibodies.
- The most accurate test is a lung or kidney biopsy.
- Renal biopsy demonstrating linear IgG deposition along the glomerular basement membrane on immunofluorescence is diagnostic.
- Anemia is often present from chronic blood loss from hemoptysis. The chest x-ray will be abnormal but is insufficient to confirm the diagnosis.
- Treat with plasmapheresis and steroids. Cyclophosphamide can be helpful.

4th: small vessels vasculitis

Small vessel vasculitis	**Granulomatosis with polyangiitis**	• Slightly more common in men • Peak incidence: 65–74 years [6]	• Pulmonary and nasopharyngeal involvement is common • May manifest with hemoptysis and nasal ulcers. • Can cause pauci-immune RPGN	• **c-ANCA/PR3-ANCA** • Type IV hypersensitivity reaction • Renal biopsy: segmental necrotizing glomerulonephritis
	Microscopic polyangiitis	• Slightly more common in men • Peak incidence: 50–60 years [7]	• Usually only mild respiratory symptoms • Can cause pauci-immune RPGN	• **p-ANCA/MPO-ANCA**
	Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	• Least common type of small vessel vasculitides • Peak incidence: 38–54 years [8]	• Asthma • Allergic rhinitis • Purpura • Peripheral neuropathy • Can cause pauci-immune RPGN	• p-ANCA/MPO-ANCA • **Peripheral eosinophilia** • Focal segmental necrotizing glomerulonephritis

Wegener granulomatosis (granulomatosis with polyangiitis)

- Wegener granulomatosis (WG) is characterized by systemic vasculitis that most often involves the kidney, lung, and upper respiratory tract such as the sinuses or middle ear. It can also involve the skin (50%), joints, eyes (50%), and GI tract. Neuropathy may be a symptom.
- Prominent upper respiratory tract involvement (otitis, sinusitis).
- If a patient with chronic upper and lower respiratory illness does not respond to antibiotics, consider WG.
- All vasculitides are associated with fever, weight loss, and malaise.
- The best initial test specific is the antiproteinase-3 antibody (or cytoplasmic antineutrophil cytoplasmic antibody [C-ANCA]).
- The most accurate test is a biopsy of the kidney, nasal septum, or lung, looking for granulomas.
- Treatment for WG is steroids and cyclophosphamide.

Summary

Granulomatosis with polyangiitis (GPA; previously referred to as Wegener granulomatosis) is a systemic vasculitis that affects both small and medium-sized vessels. Patients typically initially present with a limited form that consists of constitutional symptoms and localized manifestations, such as chronic sinusitis, rhinitis, otitis media, ocular involvement, and/or skin lesions. More serious manifestations may develop in later stages, including pulmonary complications and glomerulonephritis; the heart may also be involved. Testing modalities include laboratory studies, imaging, and biopsy. Diagnosis is confirmed by biopsy findings of necrotizing granulomatous inflammation. Pharmacotherapy consists of immunosuppressive drugs, typically glucocorticoids combined with methotrexate, cyclophosphamide, or rituximab. Relapses are common.

Pathophysiology

- The following processes play a key role in the pathophysiology of GPA:
  - Aberrant epigenetic expression of proteinase-3 on the cell membrane of neutrophils
  - Formation of antibodies against proteinase-3 (PR3-ANCA)
- Binding of PR3-ANCA to PR3 activates neutrophils → release of neutrophilic inflammatory mediators, formation of neutrophil extracellular traps, complement activation → damage to endothelial cells of small blood vessels

Clinical features

- **Constitutional symptoms**: fever, night sweats, weight loss, arthralgias
- **ENT involvement**: often the first clinical manifestation
  - **Chronic rhinitis/sinusitis**: nasopharyngeal ulcerations → nasal septum perforation → **saddle nose deformity** (depression of the nasal dorsum)
  - Chronic otitis and/or mastoiditis
  - In some cases, thick, purulent discharge, sometimes containing blood
  - Oral ulcers
  - **Strawberry gingivitis**: a characteristic feature of granulomatosis with polyangiitis characterized by painful, erythematous, gingival inflammation with petechiae that results in the appearance of the surface of a strawberry [5][6]
- **Lower respiratory tract**: potentially life-threatening
  - Treatment-resistant, pneumonia-like symptoms with **cough**, **dyspnea**, **hemoptysis**, wheezing, hoarseness, and/or pleuritic pain
  - Clinical features of pulmonary fibrosis, pulmonary hypertension, and/or pulmonary hemorrhage may occur.
- **Renal involvement**: potentially life-threatening
  - **Pauci-immune** glomerulonephritis (Pauci-immune indicates that there is little evidence of immune complex/antibody deposits.) → rapidly progressive (crescentic) **glomerulonephritis** (**RPGN**) with possible pulmonary-renal syndrome
  - Typically causes hematuria and red cell casts
- **Skin lesions**
  - Papules, vesicles, ulcers
  - Purpura of the lower extremities
  - May lead to necrotizing vasculitis of small vessels → dry gangrene of digits
- **Ocular involvement**
  - Conjunctivitis, episcleritis, retinal vasculitis
  - Corneal ulcerations
- **Cardiac involvement**: potentially life-threatening
  - Pericarditis, myocarditis
  - Vasculitis of the coronary arteries; may lead to myocardial infarction and death
  - Rarely: cardiomyopathy

Upper respiratory manifestations (i.e., purulent, sometimes bloody discharge, chronic nasopharyngeal infections, saddle nose deformity) are the most common chief complaints.

Classic GPA **triad**: necrotizing vasculitis of small arteries, upper/lower respiratory tract manifestations, and glomerulonephritis

Induction of remission

Indication: patients with active disease

- **Nonsevere disease**
  - **Glucocorticoids**
  - **PLUS** a glucocorticoid-sparing agent, e.g., **methotrexate** (preferred) or azathioprine
- **Severe disease** (i.e., organ- or life-threatening)
  - **Glucocorticoids**
  - **PLUS** a glucocorticoid-sparing agent, e.g., rituximab (preferred) or **cyclophosphamide** [1]

Microscopic polyangiitis

- Less upper respiratory tract involvement than Wegener although it is a systemic vasculitis as well.
- No granulomas.
- Anti-myeloperoxidase positive (p-ANCA).

Summary

Microscopic polyangiitis (MPA) is an ANCA-associated small-vessel vasculitis. Typical clinical features include pulmonary vasculitis, pauci-immune glomerulonephritis, and palpable purpura. ANCAs (most commonly MPO-ANCAs) are present in up to 75% of patients with MPA. CT chest is indicated in all patients with pulmonary symptoms and often reveals ground-glass opacifications or nodular lesions. Biopsy is required to confirm the diagnosis; histopathology findings include fibrinoid necrosis without granulomas. Management involves immunosuppressive agents (e.g., glucocorticoids plus a glucocorticoid-sparing agent such as rituximab or methotrexate). Plasmapheresis may be considered for patients with severe disease.

Clinical features

- Constitutional symptoms
- Renal (~ 90%): **pauci-immune glomerulonephritis** with hypertension [3][4]
- Lungs (~ 50%): pulmonary vasculitis → diffuse alveolar hemorrhage → **hemoptysis**
- Skin (~ 40%): **palpable purpura**, nodules, necrosis
- Gastrointestinal: abdominal pain (~ 50%), GI bleeding (~ 25%)
- Neurological (~ 70%): mononeuritis multiplex, distal symmetric polyneuropathy

> Clinical features are very similar to those of granulomatosis with polyangiitis (GPA), but MPA spares the vessels in the upper respiratory tract (no sinusitis or rhinitis). [4]

- **Induction of remission**: for patients with active disease
  - Nonsevere disease
    - Oral glucocorticoids: e.g., prednisone
    - PLUS a glucocorticoid-sparing agent: e.g., methotrexate (preferred), cyclophosphamide, rituximab, OR azathioprine
  - Severe disease
    - High-dose glucocorticoids: e.g., methylprednisolone pulses OR prednisone
    - PLUS a glucocorticoid-sparing agent: e.g., rituximab (preferred) OR cyclophosphamide

Churg Strauss Syndrome (allergic angiitis)

- Churg-Strauss syndrome (CS) is a vasculitis similar to Wegener granulomatosis, and also characterized by chronic lung involvement, neuropathy, skin lesions, GI, cardiac, and renal involvement.
- CS is characterized by a history of asthma, eosinophilia, and other atopic diseases.
  - Diagnosis requires elevated eosinophils and positive P-ANCA.
  - The most accurate test is a lung biopsy showing the granulomas and eosinophils.
  - Treatment is cyclophosphamide and glucocorticoids.

Summary

Eosinophilic granulomatosis with polyangiitis (EGPA) is an ANCA-associated vasculitis of small vessels characterized by necrotizing granulomatous vasculitis with eosinophilia. It most commonly involves the lungs and skin. Clinical features are often divided into three phases: a prodromal phase (i.e., severe allergic asthma attacks, allergic rhinitis/sinusitis), an eosinophilic phase (e.g., pericarditis, gastrointestinal involvement), and a vasculitic phase (e.g., cutaneous nodules, palpable purpura, mononeuritis multiplex); constitutional symptoms are often also present. Laboratory studies typically reveal peripheral blood eosinophilia, MPO-ANCAs, and increased IgE levels. High-resolution CT chest and echocardiogram are required to assess for pulmonary and cardiac involvement. Biopsy of the affected tissue is required to confirm the diagnosis; findings include necrotizing vasculitis (eosinophilic infiltration with fibrinoid necrosis). Management typically involves immunosuppressive agents (e.g., glucocorticoids). Plasmapheresis may be indicated in patients with rapidly progressive renal failure or pulmonary hemorrhage.

Clinical features

- **Prodromal phase** [3]
  - Severe allergic **asthma attacks** (chief concern) [3]
  - **Allergic rhinitis/sinusitis**
- **Eosinophilic phase**
  - Lung disease
  - Pericarditis
  - Gastrointestinal involvement: bleeding, ischemia, perforation [4]
- **Vasculitic phase**
  - **Skin nodules**, palpable purpura
  - Mononeuritis multiplex (loss of motor and sensory function with wrist or foot drop), symmetric or asymmetric polyneuropathy
  - Pauci-immune glomerulonephritis

Constitutional symptoms are often present in all phases. Features from all three phases may be present at the same time and do not necessarily follow a specific order. [3]

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome): pANCA and polyneuropathy (foot or wrist drop), allergic rhinitis/sinusitis/asthma, vasculitis, eosinophilia, and skin nodules

- **Induction of remission**: for patients with active disease
  - Nonsevere disease
    - Oral glucocorticoids: e.g., prednisone [5]
    - PLUS a glucocorticoid-sparing agent: e.g., mepolizumab (preferred), methotrexate, OR mycophenolate mofetil
  - Severe disease
    - High-dose glucocorticoids: e.g., methylprednisolone pulses OR prednisone
    - PLUS a glucocorticoid-sparing agent: e.g., rituximab (preferred) OR cyclophosphamide

5th:Alport Syndrome

Alport syndrome	• 85% of cases X-linked dominant (♂ > ♀), ~ 15% autosomal recessive [11] • Severe disease typically manifests during adolescence	• Most common type of hereditary nephritis (but rare) • Mutation in gene encoding **type IV collagen** • Associated with sensorineural **hearing loss** • And **abnormalities of the eye** (anterior lenticonus, retinopathy) • Often leads to ESRD	• Persistent microhematuria with intermittent gross hematuria • EM: splitting and alternating thickening and thinning of the glomerular basement membrane (lamellated and basket-weave appearance)

1. **Definition.** Alport syndrome is a form of **progressive hereditary nephritis** that is secondary to defects in the side chains of **type IV collagen** within the glomerular basement membrane.
2. **Etiology. Inheritance** is usually **X-linked dominant,** although autosomal dominant and autosomal recessive variants exist.
3. **Clinical features**
    a. **Renal manifestations** initially include hematuria, often gross hematuria, and sometimes hypertension. ESRD often occurs in males with X-linked Alport syndrome as early as adolescence, but the age of onset of ESRD differs between kindreds. Women who carry the gene are less likely to develop ESRD, but it may occur. Autosomal dominant and autosomal recessive Alport syndrome may also lead to ESRD.
    b. **Hearing loss** typically begins in childhood and progresses; approximately 50% of adults have some loss of hearing, ranging from mild to severe.
    c. **Ocular abnormalities** involving the lens and retina occur in 25–40% of patients.
4. **Management.** Therapy includes treatment of hypertension, use of ACE inhibitors (even in patients who have proteinuria without hypertension), sometimes with the addition of an angiotensin receptor blocker to slow the progression of renal disease, and eventually renal transplantation.

6th:Diffuse proliferative glomerulonephritis (DPGN:

Diffuse proliferative glomerulonephritis (DPGN)	• Most common and severe manifestation of lupus nephritis in systemic lupus erythematosus (SLE) • Also seen with IgA nephropathy and with other inflammatory, autoimmune, or infectious diseases	• Can also be nephritic with nephrotic-range proteinuria (nephritic-nephrotic syndrome) • Can lead to immune complex RPGN	• ↓ Serum **C3 complement** levels • ANA, anti-dsDNA antibodies • LM ◦ Thickening of glomerular capillaries (appear as wire loops) ◦ Characterized by increased glomerular cellularity in more than half of the glomeruli • IM: granular appearance • EM ◦ Most commonly subendothelial immune deposits (IgG immune complexes, C3, and C1q) ◦ Less commonly subepithelial or intramembranous deposits

7th:Rapidly progressive glomerulonephritis

Rapidly progressive glomerulonephritis (RPGN)	• Occurrence: ♂ = ♀ • Peak incidence: 60–85 years [12]	• Renal function declines rapidly over days to weeks • Not a disease entity itself but a possible manifestation of glomerulonephritis • Poor prognosis: can progress to ESRD within weeks to months	• LM, IF, EM ◦ **Crescent formation** (moon-shaped) made of plasma proteins (e.g., C3b) and fibrin ◦ Monocytes, macrophages, glomerular parietal cells • Can be caused by a variety of diseases categorized in three groups according to their IM pattern ◦ **Linear**: Goodpasture syndrome (anti-GBM disease) ◦ **Granular** (immune complex RPGN) ▪ Poststreptococcal glomerulonephritis ▪ Diffuse proliferative glomerulonephritis (most common with SLE) ◦ **Negative** (pauci-immune RPGN) ▪ Granulomatosis with polyangiitis ▪ Microscopic polyangiitis ▪ Eosinophilic granulomatosis with polyangiitis

Summary

Rapidly progressive glomerulonephritis (RPGN) is an inflammatory disease of the kidneys characterized by rapid destruction of the renal glomeruli that often leads to end-stage renal disease. There are three different pathophysiological mechanisms that can result in RPGN: anti-glomerular basement membrane disease (Goodpasture syndrome), immune complex glomerulonephritis (e.g., lupus nephritis), and glomerulonephritis associated with vasculitis (e.g., granulomatosis with polyangiitis). Patients may present with mild symptoms such as flank pain, edema, and decreased urine output. Laboratory tests show a sudden rise in serum BUN and creatinine as well as RBC casts and dysmorphic red blood cells on urinalysis. If the patient presents with hemoptysis, pulmonary-renal syndrome should be suspected. RPGN requires rapid diagnosis and immediate initiation of immunosuppressive therapy to prevent irreversible kidney damage.

Etiology

- **Anti-glomerular basement membrane (GBM) glomerulonephritis**: anti-glomerular basement membrane antibody disease (Goodpasture syndrome)
- **Immune complex-mediated glomerulonephritis**
  - IgA nephropathy
  - IgA vasculitis
  - Lupus nephritis
  - Poststreptococcal glomerulonephritis (PSGN)
- **Pauci-immune glomerulonephritis**: ANCA-associated vasculitides
  - Granulomatosis with polyangiitis
  - Microscopic polyangiitis
  - Eosinophilic granulomatosis with polyangiitis

Clinical features

- **Nephritic syndrome**
- Decrease in urine output within days to weeks → possibly **anuria**
- Fatigue
- Pulmonary symptoms (e.g., hemoptysis) may occur (see "Differential diagnosis of pulmonary-renal syndromes").

Treatment

- Glucocorticoids and cyclophosphamide
- Goodpasture syndrome: plasmapheresis in addition to immunosuppression
- RPGN due to ANCA-associated vasculitis (granulomatosis with polyangiitis, microscopic polyangiitis): combination therapy with glucocorticoids and rituximab is an effective alternative
- If therapy is initiated early: full recovery of renal function in > 50% of cases
- Without proper treatment, the prognosis is unfavorable: rapid progression to end-stage renal disease and high mortality

(12) Rapid progressive GN :- its progression to other dz and lead to AKI ...

* Types of RPGN :- 1. type I :- Anti GBM Ab.. [so it's progression from Good pasture ✓]..
and the progression to AKI occur within days - months.

2. Type II :- due to immune complexes as SLE or Cryoglobinemia or IgA nephropathy...

3. Type III :- called OC immune so we should take Biopsy → we not see any immune complexes..
↳ as :- wegner granulomatosis - Churg strauss dz - microscopic cholangitis...
... Ab ✓ تنظر ✓ [intra cellular] ANCA Ab بين بتكون Ab

* In RPGN there is changes in the glomeruli → which form crescant shape so called crescentric glomerulonephritis...

* There is rapid deterioration in the kidney fx within days - weeks → indicate RPGN..

→ The crescent shape formed due to :-
fibrin deposition - immune cell infiltration - IS damage ... etc

* The cases of low complement level :-
1. post infectious GN...
2. lupus nephritis...
3. Cryoglobinemia...
4. membrano palifrative GN...

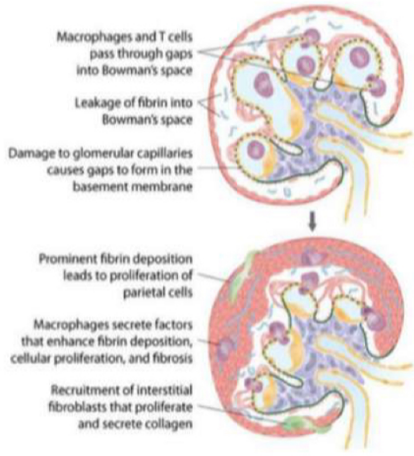
* The cases of normal complement level :-
1. IgA nephropathy...
2. Anti GBM dz...
3. wegner dz...
4. HSP...
5. PAN...

Rapidly Progressive Glomerulonephritis

- Rapidly progressive glomerulonephritis (RPGN) is not a separate disease.
- RPGN refers to the most severe and rapidly progressive form of the diseases described in this section. The terms RPGN and "crescentic glomerulonephritis" are essentially interchangeable.
- Some diseases like Goodpasture (anti-GBM disease) frequently become rapidly progressive. Some, like PSGN, rarely become progressive.

>50% crescents + >50% decline in GFR in 3 months = RPGN

- Diagnostic Tests/Treatment:
  - Biopsy is the most accurate Diagnostic test.
  - The best initial therapy is high-dose corticosteroids, often with cyclophosphamide and plasmapheresis.



❖ Complement Levels:

- Complement levels can help somewhat in establishing a diagnosis.
- In terms of SLE, they can be used to assess the presence of an acute exacerbation or worsening of disease.
- Interpretation of Complement Levels:

Low complement levels	Normal complement levels
• Post-infectious glomerulonephritis • Lupus nephritis • Cryoglobulinemia • Membranoproliferative Glomerulonephritis	• IgA nephropathy • Anti-GBM disease • PAN • Wegener • Henoch-Schönlein

8th:Membranoproliferative glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN)	• Primary disease occurs mainly in children	• Most commonly nephritic, but severe forms can also be nephrotic • Immunoglobulin (IG)-mediated membranoproliferative glomerulonephritis (type 1 MPGN) ◦ Associated with SLE, monoclonal gammopathy ◦ Can also be idiopathic • Complement-mediated membranoproliferative glomerulonephritis (type 2 MPGN: associated with dense deposit disease (IgG antibodies that stabilize C3 convertase, i.e., C3 nephritic factor, cause a persistent complement activation, leading to a depletion of C3) • Both associated with HBV, HCV, and cryoglobulinemia ◦ Hereditary diseases (e.g., sickle cell disease, α1-antitrypsin deficiency) [13] ◦ Drugs (e.g., heroin, α-interferon) ◦ Tumors (e.g., lymphoma) ◦ Autoimmune diseases (e.g., SLE) • May manifest with concomitant nephrotic-range proteinuria (nephritic-nephrotic syndrome)	• IG-mediated (type 1) ◦ IF: subendothelial and mesangial IgG immune complex deposits with granular appearance ◦ ↓ Serum **C3 complement** levels • Complement-mediated (type 2) ◦ Intramembranous C3 deposits (dense deposit disease) on basement membrane ◦ ↓ Serum **C3 complement** levels • Both types: LM with H&E or PAS stain shows mesangial ingrowth, which leads to thickening and splitting of the glomerular basement membrane (**tram-track** appearance)

a. **Definition.** MPGN is a term used for three forms of histologically distinct glomerulonephritis that share similar features. MPGN is characterized by lobular mesangial hypercellularity and thickening of the glomerular basement membrane.

b. **Clinical features**

1. Patients typically present with acute nephritic syndrome or with nephrotic syndrome accompanied by microscopic or gross hematuria.
2. Hypertension is common.
3. Seventy-five percent of patients have low serum complement levels.
4. Clinical course is variable, although most patients ultimately develop ESRD.

c. **Management.** There is no standardized treatment for MPGN, although some patients may respond to corticosteroids or mycophenolate mofetil. ACE inhibitors may slow disease progression.

- This condition is unique among glomerulopathies, because it is caused by IgG antibodies (termed C3 nephritic factor) directed against C3 convertase of the alternative complement pathway. These antibodies reacting with C3 convertase lead to persistent complement activation and kidney damage.
- Associated with chronic hepatitis and low serum complement levels.
- Treat the underlying disease, especially infections such as hepatitis C. Otherwise, trials of prednisone, cyclophosphamide, and cyclosporine will work in about half of cases.

9th:polyarteritis Nodosa:

Summary

Polyarteritis nodosa (PAN) is a systemic vasculitis of medium-sized vessels that most commonly affects the skin, peripheral nerves, muscles, joints, gastrointestinal tract, and kidneys, but usually spares the lungs. Most cases are idiopathic, but PAN is associated with certain viral infections, most commonly hepatitis B virus (HBV) infection. Patients typically present with constitutional symptoms (e.g., fever, weight loss, muscle and joint pain); additional symptoms vary based on the organ of involvement (e.g., acute kidney injury, myocardial infarction, rash). ANCAs and cryoglobulins are typically negative on laboratory studies. The diagnosis is confirmed via biopsy or visceral angiography of the affected organs. Management typically involves immunosuppressive agents (e.g., glucocorticoids). For patients with HBV-associated PAN, antiviral therapy and, in selected cases, plasmapheresis, are also indicated.

- Definition:
- Polyarteritis nodosa (PAN) is a systemic vasculitis of small and medium-sized arteries that most commonly affects the kidney.
- Virtually every organ in the body can be affected, but it tends to spare the lung.
- Although it is of unknown etiology, it can be associated with hepatitis B (10-30%) and all patients with PAN should be tested.

- Presentation:
- Besides the presentation of glomerulonephritis, PAN presents with nonspecific symptoms of fever, malaise, weight loss, myalgias, and arthralgia developing over weeks to months as does almost every type of vasculitis.
- The most common organ systems involved are:
  - Gastrointestinal: Abdominal pain, bleeding, nausea, and vomiting occur. Pain can be worsened by eating because of mesenteric vasculitis.
  - PAN spares the lungs.
  - Neurologic: Vasculitis damages the blood vessels surrounding larger peripheral nerves such as the peroneal, ulnar, radial, and brachial nerves. When more than one large peripheral nerve is involved, it is called "mononeuritis multiplex". When presented with stroke in a young person, you should look for vasculitis.
  - Damage to small blood vessels around nerves starves them into neuropathy.
  - Skin: Vasculitis of any cause leads to purpura (large) and petechiae (small). PAN also gives ulcers, digital gangrene, and livedo reticularis.
  - Cardiac disease is present in about one-third of patients.
- Stroke or MI in a young person suggests PAN.

- PAN is nonspecific. There is no single finding that allows you to answer the "most likely diagnosis" question.

- Diagnostic Tests:
- There is no blood test to confirm PAN.

- Blood tests will show:
  - Anemia and leukocytosis.
  - Elevated ESR and C-reactive protein.
  - ANCA: not present in most cases.
- Angiography of the renal, mesenteric, or hepatic artery showing aneurysmal dilation in association with new-onset hypertension and characteristic symptoms is the best initial test that has specificity for PAN. Angiography is a clear answer as a diagnostic test when the most involved organ is not easily accessible for a biopsy (such as the kidney).
- The most accurate diagnostic test is a biopsy of a symptomatic site such as skin, nerves, or muscles.

- Treatment:
- Prednisone and cyclophosphamide are the standard of care and they lower mortality.
- Treat hepatitis B when it is found.

* The Diagnostic tests:- Not specific...
- The Angiography is the Best initial diagnostic test [we find aneurysm]...
- The most accurate test is Biopsy...
  [done for any accesable affected organs]...
- we do HBV serology...

10th:cryoglobulinemia:

Summary

Cryoglobulinemic vasculitis is a type of small-vessel vasculitis characterized by the deposition of cryoglobulins. It is most commonly caused by type II and III cryoglobulinemia. Patients typically present with fatigue and other constitutional symptoms, along with palpable purpura, arthralgia, myalgias, and glomerulonephritis. Diagnosis is based on clinical features and laboratory findings, e.g., cryoglobulinemia; additional studies should be requested based on suspected organ involvement (e.g., kidney biopsy) and the underlying etiology (e.g., hepatitis C diagnostics). Management includes specific treatment of the underlying etiology (e.g., direct-acting antivirals for HCV infection), in addition to management of cryoglobulinemic vasculitis, which usually involves immunosuppressive agents (e.g., glucocorticoids plus rituximab) and is guided by disease severity. Plasmapheresis may also be considered in patients with life-threatening disease.

① Cryoglobulinemia:- Circulating immune globulin in the BV which formed in cold temp. and dissolved in warm T.
- 3 Types of Cryoglobulinemia:
  1- mono Clonal Ab...
  2- mono clonal + poly clonal Ab...
  3- poly clonal Ab...

- Cryoglobulinemia is associated with chronic hepatitis C and sometimes hepatitis B.
- In addition to renal involvement, Cryoglobulinemia is an immune complex disorder (IgM against anti-hepatitis C virus IgG) most commonly due to chronic hepatitis C.
- Patients may develop vasculitis involving the skin, kidney, nerves, or joints:
  - Joint pain.
  - Skin lesions.
  - Hepatosplenomegaly.
- The best initial tests are a cryoglobulin level and a rheumatoid factor and low serum complement levels.
- The best initial therapy is to control the hepatitis with interferon and ribavirin. For cryoglobulins not caused by hepatitis C, use plasmapheresis, steroids, and rituximab.

Cold agglutinins = hemolysis, Cryoglobulins = glomerulonephritis

① Type I:- mono clonal Ab due to → multiple myloma or waldenstrom macroglobulinemia... mono clonal gammopathy of uncertin significance... (MGUS [uncommon])
called lymphoplasmocytic lymphoma...
[so the mono clonal Ab plasma cell dyscrasis]
② Type II and III :- called mixed cryoglobulinemia...
due to:- HBV - HCV - SLE - RA...
* The mono clonal or polyclonal Ab maybe IgG - IgA - IgM...
- The presentation of cryoglobulinemia :- [SKIN]
① Skin manifestation :- levido reticularis - purpura - Raynaud phenomenon [in type I]...
② Kidney disease:- membranoproliferative GN called mesangio capillary GN...
③ Intra articular manifestation [joints]:- joint pain - arthralgia...

④ Neuropathy :- peripheral neuropathy...
→ The cryoglobinemia pt may present with hepatosplenomegaly...
due to HBV - HCV - waldenstrom macroglobulinemia
* Diagnostic tests:-
1- Blood sample then put it in cold media to see if there is precipitation of Ab or not...
2- RF : +ve in mixed cryoglobinemia...
3- low serum complement → in mixed cryoglobinemia...
* Treatment:- 1- treat the underlying cause...
2- steroid or steroid sparing agent...
3- plasmapharesis...

11th:Henoch-Schonlein purpura (HSP)/ IgA vasculitis

Summary

IgA vasculitis (IgAV), previously referred to as Henoch-Schonlein purpura (HSP), is an acute immune complex-mediated small vessel vasculitis that most commonly occurs in children. Onset is often preceded by an upper respiratory tract or gastrointestinal infection; IgAV in adults may be idiopathic. Affected individuals typically develop palpable purpura, arthritis and/or arthralgia, and abdominal pain. Renal involvement (i.e., IgAV nephritis) is more common and usually more severe in adults than in children, typically manifesting with hematuria. While IgAV is a clinical diagnosis, laboratory studies are used to identify organ involvement and exclude differential diagnoses, and skin biopsy can confirm the diagnosis in patients with atypical presentations. IgAV is usually self-limited; treatment is generally supportive. Systemic glucocorticoids may be required depending on severity of manifestations (e.g., in IgAV nephritis, orchitis). IgAV has an excellent prognosis in children, usually resolving within one month when not complicated by IgAV nephritis. Adults often manifest with more severe features and have lower remission rates. All patients require follow-up assessments to rule out the development of chronic renal disease.

⑥ Henoch-Schonlein purpura:-

- small vessel vasculitis...
- associated with IgA nephropathy [specific]...
- multisystem disease so the pt may presented with:-

1- kidney:- IgA nephropathy → AKI and may lead to glomerulonephritis...

2- GIT [most important]:- abdominal pain. diarrhea. GI Bleeding due to IgA vasculitis in the mesentric vesseles so may lead to mesentric Ischemia...

3- joints :- arthralgia...

4- skin:- purpura in 90% of cases...

* The diagnostic criteria of HSP :- ① pt < 12 y/o...
② purpura...
③ abdominal anginal [pain - Bleeding]...
④ neutrophil + IgA infiltration in the Biopsy...

...HSP تشخيص لـ 4 من 2 على تعاني

* we test the IgA level may be elevated or not [however there in IgA infiltration in the Biopsy].
* The most accuret test is Biopsy...
* The ttt of HSP :- 1- The HSP is self limited dz [no need for ttt] as sarcidosis...
[has excellent prognosis...
2- Symptomatic ttt...
3- steroid or steroid sparing agent in specific cases:- if there is kidney or neurological affection...
4- anti HTN drug :- make nephritic ← IgA nephropathy يؤدي HSP إلى nephritic syndrome → 2ry HTN
ACEI the best anti HTN drug in kidney dz...
[has antiproteinuric effect [nephritic لأنه يقلل proteinuria].

Henoch-Schönlein Purpura — more in children...

- Henoch-Schönlein purpura (HSP) is an immunoglobulin A (IgA)-mediated vasculitis of the small vessels in multiple tissues that is most common in children, Classic manifestations include:
  - Gastrointestinal (abdominal pain, diarrhea, bleeding).
  - Joint pain/arthralgia.
  - Skin (purpura, petechiae), more on the lower extremities.
  - Renal (glomerulonephritis).
- The most accurate test is a biopsy. IgA levels are not useful.
- No treatment is usually necessary since resolution is spontaneous. If proteinuria is present, the answer is ACE inhibitors (or ARBs). If "progressive renal ailure" is described, the answer is trial of steroids.

12th:Lupus Nephritis:

⑩ The lupus nephritis:- pt has SLE which lead to damage in the kidney → AKI, CKD, end stage renal dz, glomerular dz.
...nephrotic $
...nephritic $

* There is 6 classes of lupus nephritis:-
- class I : minimal mesingeal GN...
- class II : mesingeo proliferative GN...
- class III : focal proliferative GN...
- class IV : diffuse proliferative GN...
  - the most common and most severe form of lupus nephritis...
- class V : diffuse membranous GN...
- class VI : advanced sclerosis... → not has ttt just follow up [irreversable - slowely progressive]...

*any pt has SLE then presented with renal symptom we should do Biopsy to determine the class of lupus nephritis...

Lupus Nephritis

- SLE can give any degree of renal involvement. The kidneys in SLE can be normal or present with mild, asymptomatic proteinuria. Severe disease presents with membranous glomerulonephritis. Long-standing SLE may simply "scar" the kidneys and biopsy will show glomerulosclerosis, which has no active inflammatory component but may lead to such damage as to require dialysis.
- Double-stranded DNA levels go up and complement levels go down as a marker of severity in flare-ups of the disease.
- Biopsy is the most accurate test of lupus nephritis.
- Biopsy is not performed to diagnose lupus, but rather to guide intensity of therapy.
- Biopsy is indispensable in determining therapy based on the stage:
  - Mild inflammatory changes may respond to glucocorticoids.
  - Severe, proliferative disease such as membranous nephropathy is treated with glucocorticoids combined with either cyclophosphamide or mycophenolate.
  - Treatment is not needed for sclerosis; it is simply scarring of the kidney

13th:Thin basement membrane nephropathy

Thin basement membrane nephropathy (benign familial hematuria)	• Estimated to affect 5–10% of the general population [10]	• Hereditary disorder • Persistent microhematuria and episodic gross hematuria (e.g., following an upper respiratory tract infection or exercise) • Good prognosis	• Abnormalities of type IV collagen • EM: diffuse thinning of glomerular basement membrane

Summary

Thin basement membrane nephropathy is a primary glomerulonephritis caused by abnormalities of type IV collagen and thinning of the glomerular basement membrane. Patients typically present with episodes of intermittent gross hematuria and flank pain, often triggered by upper respiratory tract (URT) infections or exercise. Urinalysis shows persistent microhematuria and sometimes proteinuria. Kidney biopsy is required for diagnosis, showing diffuse thinning of the glomerular basement membrane. While the disease generally has an excellent prognosis and often does not require treatment, patients with proteinuria should be treated with ACE inhibitors to slow progression.

By:Deema Muhanna