Kidney diseases – the context
Each year in the US >100,000 people are diagnosed with end stage renal disease
CDC estimates that >10% of adults in the US (>20 million people) may have chronic kidney disease, of varying levels and seriousness.
Causes of kidney failure: - prerenal, - intrarenal, - postrenal. Glomerular diseases fit into a much bigger category of intra renal diseases and are actually much less common than diabetes and hypertension. However, their evaluation via biopsy plays a major role in the selection of therapies.

Hematuria = blood in urine. Blood in the urine can originate at any point along the urinary tract and both gross and microscopic hematuria may represent serious underlying disease. Hematuria can be divided into glomerular and extraglomerular (nephrologic and urologic) diseases. On microscopy, dysmorphic red cells and red blood cell (RBC) casts are consistent with a glomerular source of bleeding (“active” urinary sediment).

Hematuria is the hallmark of nephritic syndrome. Nephritic syndrome is a clinical entity defined as being usually of acute onset, characterized by (i) hematuria with dysmorphic cells and red blood cell casts in the urine, (ii) some degree of oliguria and azotemia and (iii) hypertension.

Acute nephritic syndrome can be associated with a primary glomerular disease such as acute poststreptococcal glomerulonephritis or may be produced by systemic disorders such as systemic lupus erythematosus; IgA nephropathy and hereditary nephritis are typically associated with a variable degree of hematuria and some of the features of nephritic syndrome. In some patients, renal failure associated with hematuria may be clinically associated with a rapid decline in renal function and this condition is termed Rapidly Progressive Glomerulonephritis (RPGN) – discussed in the second part of this lecture.

Although IgG is the main immunoglobulin in serum and extravascular spaces, other immunoglobulins, most notably IgA, can also be involved in the formation of immune complexes and their deposition in tissues. Moreover, genetic defects can be involved in the pathogenesis of glomerular diseases through their involvement in the modulation of the immunologic response or by causing structural defects in glomeruli, leading to the development of hereditary nephritis.

Glomerulonephritis may be caused by deposition of circulating immune-complexes within glomeruli because of physico-chemical properties and hemodynamic factors peculiar to the glomerulus. The antibodies are directed against the infectious agent and have NO immunological specificity for glomerular constituents. The immune complexes elicit an inflammatory reaction in the glomerulus, which is the site of their deposition via complement and leukocyte-mediated pathways.

Glomerulonephritis caused by circulating immune complexes can be either acute or chronic. An example of the former is postinfectious glomerulonephritis, where the antigen is exogenous and an antibody response leads to the elimination of the antigen - a “one-shot” exposure. In chronic circulating immune complex glomerulonephritis, the antigen is endogenous and elicits
autoimmune antibodies, which persist (unless controlled by medication) and lead to chronic
disease (see systemic lupus erythematosus).

Acute postinfectious glomerulonephritis
1. Typical presentation: in children – acute nephritic syndrome with hematuria, edema,
hypertension and renal failure while in adults acute nephritic syndrome is less common.
2. Epidemiology: typically children 6-10 years old, rarer in adults; can be sporadic or
endemic
3. Etiology/pathogenesis: glomerulonephritis develops 1-4 weeks after recovery from
pharyngeal infection by streptococci (or other bacteria or even viruses) or following skin
infection (impetigo)
4. Pathology: proliferative glomerulonephritis with obliteration of capillaries and
neutrophilic influx, deposition of IgG and complement immune complexes detectable by
immunofluorescence and electron dense deposits by electron microscopy. While there
are mesangial as well as subendothelial deposits (which elicit inflammatory response)
there are also peculiar “hump-like” subepithelial deposits which are very characteristic of
postinfectious glomerulonephritis and therefore diagnostically useful.
5. Laboratory tests: urinalysis disclosing tea-color (smoky or coca-cola-like) urine with
hematuria and mild proteinuria. Anti-streptolysin O (ASO) may be elevated while
complement is typically low.
6. Prognosis: in children excellent with recovery and resolution of pathology in >95% of
patients. In adults there is slow progression to chronic glomerulonephritis with 15-50%
of adults developing end stage kidney disease. In a small subset of patients, both children
and adults, a very aggressive form of glomerulonephritis may develop with rapidly
progressive renal failure (to be discussed in the second part of this lecture – see rapidly
progressive glomerulonephritis type II).
7. Treatment is largely supportive.

The classic case of poststreptococcal glomerulonephritis is a prototype of circulating immune
complex glomerulonephritis. However, its exact pathogenesis has not been fully understood.

The following facts have been known:
1. there is a relationship between the infection and subsequent development of
glomerulonephritis
2. this disease is an example of immune complex disease with similarities with serum sickness
model
It has been thus postulated that circulating immune complexes have a propensity to deposit in the
subendothelium and mesangium. These deposits, which are in contact with the circulation,
activate complement and drive the influx of inflammatory cells essential for the initiation of
glomerulonephritis with its endocapillary proliferation.
But this is not all the story…:
apparently immune complexes are formed in the circulation and also in-situ… the latter by
binding of antibodies to bacterial antigens “planted” in the glomerular basement membrane.
Cationic nephritogenic antigens (for example SpeB - streptococcal exotoxin B, streptococcal GAPDH) have propensity to traverse the anionic glomerular basement membrane to subepithelial location ("humps"). This free antigen deposition probably occurs early in the course of disease followed by in situ antibody binding. Several cationic antigens unique to nephritogenic strains of streptococci can be found in affected glomeruli.

[GAPDH (GlycerAldehyde 3-Phosphate DeHydrogenase) is a highly conserved glycolytic enzyme found in all living cells.]

Thus, in postinfectious glomerulonephritis, the large subepithelial deposits, “humps” are very characteristic and diagnostically useful. However, there are also subendothelial, as well as mesangial, deposits and it is the activation of complement on the subendothelial and mesangial deposits, which are in contact with the circulation, that drives the influx of inflammatory cells essential for the initiation of glomerulonephritis with its endocapillary proliferation.

**Postinfectious glomerulonephritis typical presentation:**


Pathology: mesangial and endothelial proliferation, leukocytic infiltration within the tuft with narrowing of the glomerular capillaries. The deposited immune complexes are detectable in the glomeruli by immunofluorescence studies. The typical pattern is “lumpy-bumpy stain for IgG and C3 in the mesangium and glomerular capillary wall. By electron microscopy the immune complexes are electron dense. The deposits are in the mesangium and under the endothelium; the latter elicit the “inflammatory” response. However, there are also sparse large subepithelial deposits, which are “hump-like” and characteristic of postinfectious glomerulonephritis; they are useful in making this diagnosis. (Robbins pp 529-530)

Laboratory tests that are useful in linking glomerulonephritis with a poststreptococcal etiology include the ASO (anti-streptolysin O antibody) titer. In the acute phase, during immune complex formation, complement levels are transiently lowered. Also, the urine is “smoky” in appearance and there may be red cell casts. The immune complexes are subsequently degraded by neutrophils, monocytes/macrophages, as well as mesangial cells and a healing phase ensues.

Postinfectious glomerulonephritis = prototypic disease of proliferative glomerulonephritis
Postinfectious glomerulonephritis = acute (1 shot) immune complex disease
Acute versus chronic immune complex diseases
SLE – systemic lupus erythematosus = chronic autoimmune disease, multisystem, kidney involvement. Lecture III, also separate lectures, etc
IgA

IgA is the second most common serum immunoglobulin and is the main immunoglobulin in mucosal secretions. IgA can be involved in immune complex formation and deposition in tissues and is involved in the pathogenesis of IgA glomerulonephritis. (Robbins, pages 530-531).

IgA nephropathy:
1. Typical presentation: recurrent gross hematuria with episodes of gross hematuria within 1-2 days of a nonspecific upper respiratory tract infection; alternatively after gastrointestinal or even urinary tract infection. Hematuria lasts for a few days with recurrence every few months.
2. Epidemiology: IgA nephropathy is the most common glomerular disease worldwide affecting mostly children and young adults.
3. Etiology/pathogenesis: abnormally glycosylated IgA1 (galactose-deficient IgA1) is thought to play a central role. There may be either genetic or acquired abnormalities of immune regulation (such as in celiac disease), increased IgA synthesis (after respiratory or gastrointestinal exposure to viruses, bacteria, food products), abnormalities in clearance of IgA, antibodies against abnormally glycosylated IgA; complement activation is via alternative pathway and formation of IgA containing immune complexes.
4. Pathology: mesangial proliferation with IgA-complement immune complexes in the mesangium which are diagnostic; electron dense deposits are seen by electron microscopy.
5. Laboratory tests disclose hematuria; there may be also a mild proteinuria. Complement levels are normal.
6. Prognosis is variable depending on the severity of glomerular pathology. While many patients have a relatively indolent course, renal failure ultimately develops. A small subset of patients may succumb to aggressive disease (discussed in the second part of this lecture – see rapidly progressive glomerulonephritis type II).
7. Treatment - supportive

The hallmark of this disease is deposition of IgA-containing immune complexes in the mesangium. IgA is a poor activator of the complement system. In IgA nephropathy, complement involvement is via the alternative (“tickover” rather than classic) complement pathway. Consequently complement levels are continuously replenished by the liver and usually not decreased.

IgA nephropathy occurs with increased frequency in patients with celiac and liver disease where intestinal mucosal defects or clearance of IgA, respectively, are seen.

IgA nephropathy – typical case:
• 32 yo male initially presented 4 months ago with gross hematuria after a respiratory tract infection
• Hematuria lasted for several days and then subsided
• Now he is presenting with gross hematuria again…
UA: hematuria, trace protein

Clinical diagnosis: nephritic syndrome NOS (not otherwise specified). Hence a kidney biopsy is needed for a more specific diagnosis.
Pathology: predominantly mesangial proliferation, no IgG deposits, while IgA and C3 deposits are present, mesangial deposits by electron microscopy
Pathologic diagnosis: IgA nephropathy (Berger disease)

The term “IgA nephropathy” refers to disease with deposits of IgA limited to kidney. However, deposits of IgA may be also systemic and involve kidneys with hematuria as well as skin with purpuric skin lesions, gastrointestinal tract with bleeding and abdominal pain and arthralgia. This disease is termed “Henoch-Schoenlein purpura”[HSP]. It typically affects children 3-8yo. Deposits consisting of IgA and C3 are detectable not only in the kidney (predominantly in the mesangium) but also in the affected sites in systemic diseases – i.e. skin affected by purpura (see also lecture on vasculitis).

**Hereditary nephritis** refers to a group of hereditary glomerular diseases caused by mutations in genes encoding glomerular basement membrane proteins. The best-studied entity is Alport syndrome which involves: (i) nephritis, (ii) nerve deafness and (iii) various eye disorders.

Hereditary nephritis:
1. Typical clinical presentation: gross or microscopic hematuria, hearing and ocular abnormalities
2. Epidemiology: 5-20 years at presentation with overt renal failure between 20-50 years of age.
3. Etiology/pathogenesis: inheritance most commonly X-linked
4. Pathology: no diagnostic abnormalities in paraffin sections and no immune complex deposits but electron microscopy discloses diagnostic alterations in the lamina densa of the glomerular basement membrane in the form of splitting and/or basket weaving.
5. Laboratory tests: hematuria; genetic testing
6. Prognosis: overt renal failure between 20-50 years of age

Treatment: supportive, transplantation, counseling, family testing. Molecular genetic testing of the type IV collagen gene (*COL4A5*) implicated in X-linked Alport syndrome and the type IV collagen gene (*COL4A3* and *COL4A4*) implicated in autosomal recessive Alport syndrome is available on a clinical basis (detection of mutation >60%)
Prenatal testing is available for X-linked Alport syndrome.

**Hereditary nephritis – typical case**

A 20 year old male was diagnosed with hematuria; his serum creatinine was elevated. Several members of his family, mostly males, developed chronic renal failure by age 50 years. The affected individuals also were diagnosed with hearing problems and had various eye disorders, including lens dislocation.
Clinical diagnosis: hematuria, familial
Pathology: light microscopy with occasional globally-sclerosed glomeruli, interstitial foam cells, immunofluorescence negative. Electron microscopy showed splitting and layering of the lamina densa.
Diagnosis: Hereditary nephritis associated with Alport syndrome.

**Nephritic syndrome – summary:**
- **Hematuria, oliguria with azotemia, hypertension, mild proteinuria**
- The most common causes of glomerular injury = immunologically mediated; lesions are characterized by proliferative changes and leukocyte infiltration
- Acute postinfectious glomerulonephritis typically occurs after streptococcal infection in children and young adults but may occur following infection with many other organisms; it is caused by deposition of immune complexes (with diagnostic large sub-epithelial deposits “humps”), with abundant neutrophils (“exudative component”) and proliferation of endocapillary cells. Most affected children recover, prognosis in adults is worse
- IgA nephropathy, characterized by mesangial deposits of IgA-containing immune complexes, is the most common cause of nephritic syndrome worldwide; it is also a common cause of recurrent hematuria; it commonly affects children and young adults and has a variable course.
- Hereditary nephritis (Alport syndrome) is caused by mutation of genes encoding glomerular basement membrane collagen; it manifests as hematuria and slowly progressing proteinuria and declining renal function; glomeruli appear normal by light microscopy until late in the disease course. Immunofluorescence is negative, electron microscopic studies showing splitting of the lamina densa of the glomerular basement membrane are diagnostic.

**Rapidly progressive glomerulonephritis (RPGN)** is a clinical syndrome characterized by a rapid and progressive loss of renal function, often with severe oliguria, and laboratory findings typical of the nephritic syndrome. The characteristic pathologic finding associated with RPGN is the presence of crescents.

Crescents are formed by proliferation of the parietal epithelial cells, shaped into a crescent-like structure, as they fill the Bowman’s space. The proliferation of parietal cells is in response to severe injury of the glomerular basement membrane resulting in necrosis and breaks with leakage of blood and fibrin to the urinary space. Crescents obliterate the urinary space and compress the tuft, with shutting-off of blood circulation and filtration; rapid renal failure ensues. Evaluation of crescents is important for prognosis: their size (small versus circumferential), % (focal versus diffuse), composition (cellular in early stage to fibrous at the later stages).

Crescents are a hallmark of various forms of glomerulonephritis with severe injury of the glomerular basement membrane. This injury may occur due to different mechanisms including anti-glomerular basement membrane antibody mediated glomerulonephritis (RPGN type I), severe immune-complex glomerulonephritis (RPGN type II), or pauci-immune/ANCA associated glomerular injury (RPGN type III).
RPGN type I is caused by anti-glomerular basement membrane antibody. Frequently, this antibody also binds to pulmonary alveolar basement membrane to produce a clinical picture of pulmonary hemorrhage associated with renal failure; this is termed Goodpasture syndrome. Diagnosis is based on the demonstration of a linear stain for IgG along the glomerular basement membrane. Anti-glomerular basement membrane antibodies are also present in the serum and their detection is helpful in the diagnosis of RPGN type I.

1. Typical presentation: gross hematuria/hemoptysis, drop in urinary output (acute renal failure)
2. Epidemiology: young MEN, rare, 12% of crescentic glomerulonephritis
3. Etiology/pathogenesis: anti-glomerular basement membrane antibodies following exposure to viruses, hydrocarbon solvents (paints, dyes), drugs, also smoking; genetic predisposition to autoimmunity
4. Pathology: crescents, linear stain for IgG
5. Laboratory tests: anti-glomerular basement membrane antibodies in serum; levels may be low in active disease due to rapid binding to the kidney
6. Prognosis: renal, pulmonary failure
7. Treatment: plasmapharesis - removal of pathogenic antibodies from the circulation

RPGN type I – typical presentation
A 22 yo college student while working during the summer in a car garage developed hemoptysis. He also noted that his urinary output dropped. UA showed red blood cell casts, his serum creatinine was elevated to 5.0 MG/DL [n=0.7-1.5]. Chest X-ray showed bilateral pulmonary opacities…

RPGN type II involves a subset of patients with immune complex glomerulonephritis (<1% of postinfectious glomerulonephritis, IgA nephropathy, some patients with lupus nephritis), where exuberant damage to glomerular basement membrane occurs, with necrosis, breaks and leakage of blood and fibrin into the glomerular urinary space, and proliferation of the parietal epithelial cells with formation of crescents. Except for the severity and the presence crescents, the other diagnostic pathology remains the same as in the corresponding forms of glomerulonephritis not complicated by crescents, i.e. granular deposits containing immune complexes of IgG-C3 in postinfectious glomerulonephritis and IgA-C3 complexes in IgA nephropathy.

1. Typical clinical presentation: gross hematuria, drop in urinary output (acute renal failure)
2. Epidemiology: rare (1% of postinfectious, small subset of IgA), children, young adults (10-40 yo)
3. Etiology/pathogenesis: severe immune complex formation with necrosis and breaks in glomerular basement membrane
4. Pathology: crescents, immune complexes
5. Laboratory tests: depending on etiology
6. Prognosis: chronic renal failure
7. Treatment: immunosuppression
RPGN type III is defined by the lack of anti-glomerular basement membrane antibodies or the presence of immune complex deposition, detectable by routine immunofluorescence, hence termed “pauci-immune”. This type of RPGN is caused by antineutrophil cytoplasmic autoantibodies (ANCA), which react with neutrophil cytoplasmic antigen and are typically found in the serum. ANCA autoantibodies do not form circulating immune complexes. ANCAs are involved in type III RPGN and in some vasculitides (see lecture on vasculitis).

ANCAs are antibodies against constituents (mainly enzymes) of neutrophiles primary granules. ANCAs are a highly sensitive diagnostic marker of pauci-immune glomerulonephritis/systemic vasculitis. ANCAs play a role as a direct cause of pauci-immune glomerulonephritis/systemic vasculitis by inducing premature degranulation and activation of neutrophiles with release of lytic enzymes

1. Typical clinical presentation: drop in urinary output (acute renal failure), gross hematuria; frequently (75% of patients) have also systemic small vessel vasculitis manifestations at the time of initial presentation: hemoptysis, shortness of breath
2. Epidemiology: older patients
3. Etiology/pathogenesis: anti-neutrophil antibodies (ANCA)
4. Pathology: crescents, no deposits (“pauci-immune”)
5. Laboratory tests: ANCA
6. Prognosis: renal, pulmonary failure
7. Treatment: immunosuppression

In 75% of patients, RPGN type III may be a component of systemic vasculitis such as:
   a. microscopic polyangiitis
   b. pulmonary angitis and granulomatosis (aka Wegener granulomatosis) where vasculitis may involve upper respiratory tract (Ear/nose/throat), Lung and Kidney (ELK) synchronously or in turns.
   c. Churg-Strauss syndrome (allergic granulomatosis and angiitis), small vessel vasculitis associated with peripheral eosinophilia and eosinophilia associated symptoms (asthma, allergic rhinitis, lung infiltrates) (more during future lectures on vasculitis and pulmonary diseases)

RPGN type III – typical presentation:
A 75 yo female developed malaise, cough with blood tinged sputum
   • PMH: recurrent “sinusitis”
   • UA: RBCs, protein <1GM
   • serum creatinine 3.5MG/DL [n=0.7-1.5]
   • Lungs: bilateral opacities
Clinical diagnosis: nephritic features with rapidly developing renal failure = RPGN

RPGN summary: Robbins pp 531-533
- RPGN is a clinical entity with features of nephritic syndrome and rapid loss of renal function with severe oliguria (“severe nephritic syndrome”)
- RPGN is associated with severe glomerular injury with necrosis of glomerular basement membrane with breaks and subsequent proliferation of parietal epithelium (crescents)
- RPGN may be
  - antibody mediated, when autoantibodies develop to the glomerular basement membrane in anti-glomerular basement membrane antibody disease (RPGN type I)
  - consequent to severe glomerular basement membrane injury in the course of immune complex diseases (RPGN type II)
  - pauci-immune, associated with antineutrophil cytoplasmic antibodies (RPGN type III).

Lecture I summary:

Glomerular diseases associated with

1. nephritic syndrome/hematuria: postinfectious, IgA nephropathy, hereditary
2. severe nephritic syndrome and rapidly progressive renal failure types I, II, III

VOCABULARY

Glomerular diseases usually have the “glomerulo” prefix: see postinfectious glomerulonephritis etc

Glomerulonephritis is used preferentially in reference to glomerular diseases with inflammatory/proliferative response

Glomerular pathologies without inflammatory response may be referred to as “nephropathy” or “glomerulopathy”
- see membranous nephropathy (glomerulopathy)

Nephrosis is meant to indicate a non-inflammatory nephropathy which is associated with nephrotic syndrome
“nephritis” can also be attached/used in connection with other kidney diseases, such as “pyelonephritis”

Sclerosis:

Glomerular sclerosis: increased collagenous extracellular matrix that is expanding the mesangium, obliterating capillary lumens, or forming adhesions to Bowman’s capsule

Vascular sclerosis:

Hyaline arteriolosclerosis: hyaline deposits with thickening of the wall and narrowing of lumen

Arteriosclerosis: “hardening of the arteries”, wall thickening and loss of elasticity

Nephrosclerosis: hardening of the kidney due to renovascular disease