2) Glomerulopathy, Interstitial Nephritis & Polycystic dis. - Dr. Rasul

Pathogenesis of glomerular injury

- Antibody mediated injury
- In situ immune complex deposition
  - Fixed intrinsic tissue antigens
  - NC1 domain of collagen type 4 antigen [anti GBM-nephritis]
  - Heymann antigen [membranous nephropathy]
  - Mesangial antigens
- Circulating immune complex deposition
  - Endogenous antigen [DNA, Nuclear proteins, immunoglobulins, IgA]
  - Exogenous antigen [infectious agents, drugs]
- Cytotoxic antibodies
- Cell mediated immune injury
- Activation of alternative complement pathway

Clinical manifestation of glomerular injury

- Asymptomatic
- Macrscopic hematuria
- Nephrotic Syndrome
- Nephritic syndrome
- Rapidly Progressive glomerular nephritis
- Chronic Nephritic Syndrome

Glomerular diseases with primary haematuria

- IgA Nephropathy (Berger’s Disease]
- Most common primary glomerular disease. Mostly adolescents and young adults
  1. gross hematuria occurring coincidentally with or immediately following (24-48 hours), a viral upper respiratory infection, flu-like illness, gastrointestinal syndrome
  2. Episodes of gross hematuria,
  3. Microscopic hematuria.
    - Focal and segmental glomerular mesangial proliferation, with IgA deposits.
    - Increased serum IgA. Normal C3 complement.
    - Prognosis – Generally benign
    - 20% progress to renal insufficiency in 10 years.
    - Recurs after renal transplantation.

Membrano proliferative glomerulonephritis (MPGN)

Mesangiocapillary

- 5-30 years. Immune complex disease
- Associated conditions: Chronic infections (especially hepatitis C), cancer, heroin abuse, SLE, etc
- Usually nephrotic syndrome, less often acute nephritic syndrome. Recent history of URI in many patients. Hypertension and/or renal insufficiency may occur.
- Decreased serum complement levels. Hepatitis C serology should be obtained
- Glomerular hypercellularity with capillary basement membrane thickening and splitting [TRAM-TRACKING]. Subendothelial deposits of C3 complement and sometimes IgG
- Prognosis Progressive deterioration of renal function;
- Many patients develop end-stage renal insufficiency within 10 years.
Glomerular disease presenting as RPGN

- Goodpasture’s syndrome
- Vasculitis
  - Wegner’s granulomatosis
  - Microscopic polyangitis (MPA)
  - Pauci immune crescentic glomerulonephritis
- Immune complex disease
  - SLE
  - Post steptococcal glomerulo nephritis
  - IgA nephropathy/Henoch –Schonlein purpura
- Endocarditis

Diabetic Glomerulosclerosis

*(Kimmelstiel-Wilson Syndrome)*

- Most common glomerular disease.
- Multifactorial.
- >20%-40% - type I diabetes mellitus in approximately 20 years. 20%-30% - type II DM
- proteinuria
- full-blown nephrotic syndrome
- Microscopic hematuria and hypertension
- Hypertension and retinopathy
- Microalbuminuria is an early sign of diabetic nephropathy, usually about 10 years after onset of disease.
- initially diffuse diabetic glomerulosclerosis later becomes nodular diabetic glomerulosclerosis, Kimmelstiel-Wilson kidney
- Prognosis – Gradual progression to ESRD. Commonly recurs after renal transplantation.

Acute Interstitial nephritis

- Term first used by Councilman in 1898
- Noted the histopathologic changes in autopsy specimens of patients with diptheria and scarlet fever
- Immune-mediated cause of acute renal failure
- Characterized by presence of an inflammatory cell infiltrate in the renal interstitium and tubules
- There is a paucity of data in the literature regarding optimal management of the condition

Clinical Presentation

**AIN of any cause**

- Nausea
- Vomiting
- Malaise

**Drug-Induced AIN**

- Rash 15%
- Fever 27%
- Eosinophilia 23%
- Triad 10%

**TUBULOINTERSTITIAL DISEASES**

- Primary tubulointerstitial disease of the kidney characterized by histologic and functional abnormalities that involve the tubules and interstitium to a greater degree than glomeruli and renal vasculature
- Acute tubular necrosis
- Acute interstitial nephritis
- Chronic interstitial nephritis
CHRONIC INTERSTITIAL NEPHRITIS

CAUSES

- KIDNEYS MACROSCOPICALLY NORMAL
- Drugs [lithim, cyclosporine, tacrolimus, indinavir, cisplatin]
- Metabolic [hyperuricemia, hypokalemia, hypercalcemia, hyperoxaluria, cystinosis]
- Heavy metals [lead, cadmium, arsenic, mercury, gold, uranium]
- Radiation
- Balkan nephropathy
- Immune mediated [SLE, Sjogren’s syndrome, sarcoidosis, Wegner’s granulomatosis, other vasculitis]
- Vascular diseases [atherosclerotic kidney disease]
- Hematologic disturbances [multiple myeloma, light chain deposition disease, lymphoma, Sickl.C.D, PNH]
- Progressive glomerular disease of all etiologies [glomerulonephritis, diabetes, hypertension]
- Idiopathic

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<tr>
<th>Diagnostic group</th>
<th>Common</th>
<th>Uncommon</th>
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<tr>
<td>Systemic infection</td>
<td>Diphtheria Streptococci</td>
<td>Leprosy Rickettsia legionella Syphilis Leptospira Toxoplasma Brucella Mycoplasma Measles virus Epstein-Barr virus</td>
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<td>Antibiotics</td>
<td>Methicillin Penicillin Ampicillin Cephalosporins Sulfonamides Rifampin Phenindione Nonsteroids</td>
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<td>Immune or immune-like inflammation</td>
<td>Sarcoidosis</td>
<td>Anti-TBM disease Sjögren’s syndrome TINU syndrome</td>
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Noninvasive diagnostic procedure: eosinophiluria

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<td>1</td>
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<td>Patients without AIN</td>
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<td>27</td>
<td>12</td>
<td>15</td>
<td>10</td>
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<td>29</td>
<td>69</td>
<td>160</td>
<td>174</td>
<td>432 (87%)</td>
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TINU syndrome: tubulointerstitial nephritis and uveitis
Lab: biopsy

- Inflammation of renal interstitium
  - Microscopically
    - Multifocal cellular infiltration and edema
    - Mononuclear cells (lymphocytes and macrophages) usually are the predominant types
    - Drug reaction
      - Mononuclear cells, typically T cells (CD4>CD8)
  - Glomerular and vascular sparing

Pathophysiology – drug induced AIN

- Drug-induced AIN is secondary to immune reaction
  - AIN occurs only in a small percentage of individuals taking the drug
  - AIN is not dose-dependent
  - Association with extrarenal manifestations of hypersensitivity
  - Recurrences after re-exposure to the drug
- Experimental models
  - Suggest that drugs responsible for AIN induce an immune reaction directed against endogenous renal antigens

Involvement of Drug-Specific T cells in Acute Drug-Induced Interstitial Nephritis

- Role of drug-specific responses in patients with a histologic diagnosis of DIN (Drug-Induced Nephritis)
- Identified drug-specific T cells.

Treatment

- Therapy aimed at modulating the immune response has been the main treatment for AIN
- Several small retrospective studies have suggested that corticosteroid therapy improves clinical outcome; however, no prospective studies exist.

Why no benefit?

- Significant proportion of pts had NSAID-associated AIN, which is less likely to respond to steroid tx

Interferences with the interstitium: broad spectrum

- Infection:
  - direct (acute pyelonephritis),
  - indirect (βStreptococci)
- Immunologic
  - Allergic: drug – induced
  - Auto-immune: Sjögren syndrome
  - Alloimmune: acute cellular allograft rejection
  - Unknown: IgG4- associated acute interstitial nephritis
- Toxic: Pb poisoning, cadmium poisoning, Balkan endemic nephropathy
- Metabolic: oxalosis secondary to malabsorption, gout
- Obstruction: ureteral - pelvic junction stenosis:
- Radiation: radiation interstitial nephritis
- Idiopathic: sarcoidosis
Importance of interstitial cells

- Interstitial fibroblasts:
  o Fibrogenesis
  o Production of erythropoietin (they lose this function during the process of fibrogenesis)
  o Can transform into myofibroblasts (expression of SMA)
  o Changes in the interstitial area play an important negative predictive value on the long term follow up of the primary kidney disease. Important and determining factors are interstitial volume (=fibrosis) and inflammation

Acute interstitial nephritis

- Most common etiologies are:
  a) those related to the use of medications: 85%
  b) those related to infectious agents: 10%
  c) those associated to systemic disease or glomerular diseases: 1%
  d) idiopathic disease: 4%

Acute interstitial nephritis: drugs

- Etiology: (penicillins and cephalosporins, methicillin), diuretics, NSAID’s, chinese herbs, lithium
- Pathogenesis:
  o T cell mediated allergic - immune reaction on drug or drug-self protein conjugate (hapten) later followed by accumulation of lymphocytes, plasmocytes and histiocytes
- Histology:
  o Early signs: oedema, lymphocytes focally
  o Later: eosinophils, lymphocytes, plasmocytes and histiocytes with granuloma formation(with giant cells) in 30 %, Tubulitis (distal tubules): with breaks of Tubu Base M, necrosis of tubular cells and atrophy and loss of tubules.
  o Tamm Horsfall may find its way to the interstitium (obstruction of nephron).

Outcome of drug-induced interstitial nephritis

**Recovery?**
- Drug withdrawal: 60-90% in 1 to 12 mths
- Irreversible with analgesics, NSAIDs, longterm use

**Adverse prognostic features**
- Marked interstitial inflammation
- Granuloma (50% irreversible)
- Tubular atrophy
- Fibrosis

Acute pyelonephritis

- Etiology: ascending infection from the pyelon
- Pathogenesis: microbial release of degradative enzymes and toxic molecules, direct contact or penetration of the host cell by the infectious agent and the inflammatory response mediated by antibodies, T cells
- Histology: Tubules are damaged by neutrophils (Congored)

Acute interstitial nephritis: systemic

- Association with: Goodpasture syndrome, lupus nephritis, mixed cryoglobulinemia, membranoproliferative glomerulonephritis
Xanthogranulomatous pyelonephritis

- Etiology: chronic ascending infection: lithiasis, pyelal or ureteral tumors, ureter stenosis. The infective organisms are E. Coli, Proteus sp, Klebsiella, Pseudomonas, Enterococcus
- Histology:
  - accumulation of histiocytes in the interstitum containing PAS/Diastase resistant granules in the cytoplasm
  - fibrosis
  - chronic inflammatory cells

Granulomatous interstitial nephritis

- Sarcoidosis: naked granulomas in cortex with Langhans giant cells: 29%
- Drug induced interstitial nephritis: 45%
- Infection: TB, fungal infections
- Gout: urate granuloma
- Cholesterol granuloma

Balkan endemic nephropathy

- Where?: Croatia, Bosnia, Serbia, Bulgaria, Romania with prevalence between 2% and 10%
- Pathogenesis: unknown: genetic predisposition, role played by coronavirus, heavy metals, ochratoxin, mycotoxins

Tubular disease

Acute tubular damage:

- Ischemia: vasoconstriction with endothelial activation will determine the extent of the tubular cell loss: cellular, geographic, focal
- Toxins:
  - Myoglobinuria
  - Heavy metal exposure (Pb, Cd)
  - Oxalate crystal deposits: ethylene glycol toxicity
  - Calcineurin inhibitors: megamitochondria, isometric vacuolisation

Analgesic abuse nephropathy

- Chronic interstitial nephritis
- Result from excessive consumption (Phenacetin & Aspirin)
- Dose dependent (at least 1 kg)
- Being responsible for 1% to 3% of ESRD cases

Laboratory Manifestations

- Acute rise in plasma creatinine concentration
- Eosinophilia and eosinophiluria
- Urine sediment: wbcs, rbcs, white cell casts
- Proteinuria (< 1 g/day)
- Signs of tubulointerstitial damage
Features of acquired cystic kidney disease

- Multiple
- Bilateral
- Usually < 0.5 cm
- “Positive” u/s or CT: both kidneys w/ >/= 4 cysts
- No Family H ADPKD, small/normal sized kidneys, smooth contour, cysts are only in the kidney
- Increased incidence w/ increasing time on dialysis; ~ 35-50% of dialysis patients overall
- Men and blacks are at much higher risk

Alport Syndrome

Diagnosis

- Historical information (family history, hearing loss, visual disturbances, gross hematuria)
- Tissue biopsy often reveals ultrastructural abnormalities and confirm diagnosis.
- Skin biopsy is less invasive than renal biopsy and should be obtained first.
- Molecular genetic testing in equivocal biopsy cases, patients in whom biopsy is contraindicated and prenatal testing.

Treatment – Renal Transplant

- For unclear reasons, certain patients are at very low risk for developing post-transplant anti-GBM nephritis, including patients with normal hearing, patients with late progression to ESRD, or females with XLAlportSyndrome.
- Unlike de novo anti-GBM nephritis, pulmonary hemorrhage is never observed because the patient's lung tissue does not contain the antigen.
- Treatment with plasmapheresis and cyclophosphamide is usually unsuccessful, and most patients lose the allograft.
- Retransplantation in most patients results in recurrence of anti-GBM nephritis despite the absence of detectable circulating anti-GBM antibodies before transplantation.

Ocular Findings – Anterior Lenticonus

- Conical protrusion of the central portion of the lens into the anterior chamber.
- Occurs in approximately 15-20% of AlportSyn patients.

Hearing Deficits

- Bilateral sensorineural hearing loss is a characteristic feature observed frequently, but not universally.
- About 50% of male patients with XLAS show sensorineural deafness by age 25 years, and about 90% are deaf by age 40 years.

ESRD – Female Carriers

- Prognosis in females carriers with XLAS is usually benign, and they develop ESRD at much lower rates.
- Reported probability of developing ESRD in female carriers is 12% by age 40 yrs & 30% by age 60 yrs.
Non-Genetic Renal Cystic Disease

- Multicystic Dysplastic Kidney
- Benign Multilocular Cyst (Cystic Nephroma)
- Simple Cysts
- Medullary Sponge Kidney
- Sporadic Glomerulocystic Kidney Disease
- Acquired Renal Cystic Disease
- Calyceal Diverticulum
- Cystic Renal Cell Carcinoma

Polycystic Kidney Disease (PKD)

- ADPKD (adults) and ARPKD (infantile) are the 2 main types of PKD; ARPKD occurs in association with congenital hepatic fibrosis & causes death from renal failure within the first year of life
- ADPKD is the most common hereditary disease in the USA, affecting >500,000 people: the most common genotype (ADPKD 1) is located on chromosome 16 but other forms exist
- Complete penetrance of the gene is expected to occur by age 90

Autosomal Dominant Polycystic Kidney Disease

- Common cause of ESRD (7-15%)
- May present in newborn but most common presentation 30-50 years
- Two genes identified – PKD1, PKD2
  - PKD1 (Chr 16) – more hypertension, infections – younger age at presentation, onset of renal failure
  - PKD2 (Chr 4) – older at presentation

PKD Genetics

- Incidence
  - Autosomal Dominant 1:500-1,000 live births
  - Autosomal Recessive 1:6,000-40,000 live births

Diagnosis

- Imaging tests the gold standard
- At present, asymptomatic screen not recommended
- Ultrasound: false negative rate 16-18% before age 30
- CT, MR: probably more sensitive

ADPKD – Evaluation

- Diagnosis (in absence of positive family history)
  - Presence of bilateral cysts with at least 2 of:
    - Bilateral renal enlargement
    - 3 or more hepatic cysts
    - Cerebral artery aneurysm
    - Cysts of arachnoid, pineal, pancreas, spleen
Renal Complications

1. Hypertension  60-100%
2. Gross hematuria  50%
3. Infection  common
4. Nephrolithiasis  20-25%
5. Renal failure 50% by age 60 (PKD1)

ADPKD - Treatment

- Role of genetic counselling
- Role of hypertension management
- Risk of infection
- Avoid nephrotoxins
- Management of pain – medical vs surgical
  - Role for unroofing cysts

Medullary Cystic Disease

- Presentation
  - Polydipsia / polyuria in > 80% (not to the degree of patients with DI) resistant to vasopressin
  - Polyuria due to inability to conserve sodium – so salt restriction not indicated in these patients
  - Salt losing nephropathy
  - Associated with retinal disorders (retinitis pigmentosa), skeletal abnormalities, hepatic fibrosis

Medullary Sponge Kidney

- Noninheritable condition – usually incidental finding
- Due to dilated collecting ducts – “blush” in papillae on IV contrast studies
- Increased risk of
  - Nephrolithiasis (50-60%)
    - Hypercalciuria (at least 33%)
  - Urinary tract Infection (20-33%)
  - Hematuria (0-18%)

von Hippel Lindau Disease

- Cerebral and retinal hemangioblastoma – major cause of morbidity and mortality
- Cysts
  - Pancreas
  - Kidney – 76%
  - Epididymis
- Epididymal cystadenoma
- Pheochromocystoma – 10-17%
- Renal cell carcinoma -in 50%
Wegener granulomatosis (WG)

- It is a complex, immune-mediated disorder, which along with microscopic polyangiitis and Churg-Strauss syndrome, comprises a category of small vessel vasculitis related to antineutrophil cytoplasmic antibodies (ANCAs), characterized by a paucity of immune deposits.

- Clinical Features
  - Weight loss
  - Malaise
  - Fever
  - Arthralgia
  - Myalgia
  - Upper respiratory tract disease
  - Mouth ulcers
  - CNS manifestation
  - Glomerulonephritis progressing to renal failure: 70-80% with WG
  - Lung involvement: pulmonary hemorrhage, granulomas

Anti-Neutrophil Cytoplasmic Antibodies

- ANCAs are directed against antigens (ANCA), (P-ANCA)) present within the primary granules of neutrophils and monocytes; these antibodies produce tissue damage via interactions with primed neutrophils and endothelial cells.

The Problem with Changing

- Multiple ANCA+ diseases:
  - microscopic polyangiitis (MPA)
  - "renal-limited" vasculitis (pauci-immune glomerulonephritis without evidence of extrarenal disease)
  - Churg-Strauss syndrome (CSS)
  - Drug-induced vasculitis
  - Goodpasture’s
  - Rheumatic disorders
  - Autoimmune GI disorders

- Diagnostic Criteria primarily clinical

Classic Symptoms

- Upper respiratory tract
  - Sinuses
  - Nose
  - Ears
- Trachea
- Lungs
- Kidneys

Eye

- Scleritis
- Uveitis
- Orbital pseudotumor /proptosis
Upper Respiratory Tract

Nose
- Nasal crusting
- Frequent nosebleeds
- Erosion and perforation of the nasal septum. The bridge of the nose can collapse resulting in a “saddle-nose deformity”.

Lungs
- Nodules (which may cavitate)
- Alveolar opacities
- Pleural opacities
- Diffuse hazy opacities (which may reflect alveolar hemorrhage)

Kidney
- Glomerulonephritis w/ associated hematuria and proteinuria
- Can lead to renal failure if not treated aggressively
- Renal masses (rare)
- Active urine sediment: red blood cell casts

Skin
- “palpable purpura” most common
- Raynaud’s phenomenon—due to inadequate blood flow to fingers and toes
- Ulcers

Diagnosis

Criteria for Classification
- Nasal or oral inflammation
  - Development of painful or painless oral ulcers or purulent or bloody nasal discharge
- Abnormal chest radiograph
  - Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities
- Abnormal urinary sediment
  - Microhematuria (>5 red blood cells per high power field) or red cell casts in urine sediment
- Granulomatous inflammation on biopsy
  - Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole)
- Biopsy specimens showing the triad of vasculitis, granulomata, and large areas of necrosis
  - Sinuses
  - Nose
  - Skin--leukocytoclastic vasculitis with little or no complement and immunoglobulin on immunofluorescence
  - Kidney--segmental necrotizing glomerulonephritis that is usually pauci-immune on immunofluorescence / EM
  - Lung--vasculitis and granulomatous inflammation
    - (Only large sections of lung tissue obtained via thoracoscopic or open lung biopsy are likely to show all of the histologic features)
- Seropositivity for C-ANCAs
Treatment

- Prednisone (initiated at 1 mg/kg daily for 1 to 2 months, then tapered)
- Cyclophosphamide (2 mg/kg daily for at least 12 months)
- >90% improve and 75% remit. However, 50% in remission relapse
- AND daily cyclophos is very toxic
- pancytopenia,
- infection,
- hemorrhagic cystitis
- bladder cancer (increased 33-fold)
- lymphoma (increased 11-fold)

Vasculidities

- Large vessel vasculitis
  - Takayasu arteritis
  - Giant cell arteritis
- Medium sized vessel vasculitis
  - Polyarteritis nodosa
  - Isolated central nervous system vasculitis
- Small vessel vasculitis
  - Churg-Strauss arteritis
  - Wegener's granulomatosis
  - Microscopic polyarteritis
  - Henoch-Schönlein purpura
  - Essential cryoglobulinemic vasculitis
  - Hypersensitivity vasculitis
  - Vasculitis secondary to connective tissue disorders -- SLE, rheumatoid arthritis, relapsing polychondritis, Behcet's disease
  - Vasculitis secondary to viral infection —hepatitis B and C, HIV, CytomegV, EBV, Parvo B19