DISEASES OF THE TUBULES AND INTERSTITIUM

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Mechanisms of Tubulointerstitial Disease

- 2 general categories:
  - Ischemic/toxic (non-inflammatory)
    - Acute tubular necrosis
  - Inflammatory
    - Tubulointerstitial nephritis
    - Infection, allergic/drug-induced, systemic disease (i.e. Sarcoid, Sjogren’s), etc
Case 1

A 58 year old W M with a history of ETOH abuse, but normal renal function on ER visit 2 months ago, is admitted to the hospital in a stuporous condition having been found by his friend in his room to be unarousable. The friend states that they had been drinking 3 days ago and when he now called for his drinking buddy there was an empty bottle of Jack Daniels next to him.

PE: BP 100/60 mm Hg, P 110, R12, Temp 101, Cor -, Chest rales at R base, Abd-, Ext swelling and tender R and L legs below the knee.
Lab: BUN 48 mg/dl, Creatinine 6.2 mg dl, CBC – wbc 15,000, with increased polys, Cxray RLL infiltrate.
U/A tr prot, 4+ heme, no rbc or wbc.
Pt is hydrated with 1 L Saline and BP 135/82. Given 150 mg Gentamicin and 1g Ampicillin.
Over the next 2 days pt makes little urine and creatinine rises to 8.4 mg/dl.

Case 1

Should a kidney biopsy be done?
Is the renal failure acute or chronic? How do you know? How can you prove it?
What is the likely etiology of the renal failure (hypotension, rhabdomyolysis, gentamicin, leptospirosis )
What lab tests might confirm the diagnosis?

Acute renal Failure

- Prerenal azotemia
- Post-renal azotemia
- Acute tubular necrosis
- Acute interstitial nephritis
- Acute glomerulonephritis
- Vascular ARF
**Acute Tubular Necrosis**

- Predisposition of tubular epithelial cell
  - High metabolic activity/O2 requirements
  - Prone to ischemic/hypoxic injury
  - Role in concentrating/reabsorbing filtrate
  - Increased exposure to toxins
- Two subtypes of ATN
  - Ischemic ATN
  - Nephrotoxic ATN

**Ischemic ATN**

- Occurs in setting of decreased renal blood flow / hypotension, i.e. trauma/severe blood loss, CHF, septic shock
- Pathology
  - Gross: P & S
  - Degenerative changes
  - Subsequent regenerative changes
  - Most severe changes in proximal tub and mTAL

**Clinical Phases of ATN**

- Initiation
  - first 36 hours, dominated by initial event
- Maintenance
  - up to 3 weeks, oliguric, dialysis required
- Recovery ("diuretic phase")
  - Increasing urine output – often substantial, electrolyte abnormalities
- Prognosis: > 90% recovery if survive initiating event
Many toxins implicated
- Heavy metals: Hg, Pb, gold, arsenic...
- Organic solvents: CCl₄, ethylene glycol
- Therapeutics
  - Antibiotics: gentamicin
  - Antifungals: amphotericin B
  - Chemotherapeutic agents: cisplatin
  - Blasphosphonates: zoledronate
  - Radiation & radiocontrast
  - Pigments: Hgb, Mgb
  - Abnormal levels of physiologic substances
  - Osmotic agents: mannitol

Nephrotoxic ATN

Similar pathology to ischemic ATN
Additional, toxin-specific findings:
- Ethylene glycol
- Osmotic agents/radiocontrast
- Light chains
- Hemoglobin/Myoglobin
Case 2

- 65 y o retired Ob-Gyn MD refer by NYC nephrologist for presumed RPGN
- Past Hx: HBP x 40 yrs controlled on meds, arrhythmia → verapamil, hypothyroidism
- Some urinary urgency 1 wk PTA ¬ Urologic check (U/A neg); Urticarial rash on legs several days PTA disappeared.
- 1 wk PTA gave blood and played golf.
- Not feeling well, thirsty. Check chem7

Case 2

- BUN 94, creat 4.4 mg/dl
- Friend nephrologist - BUN 91 creat. 4.9 mg/dl K+ 6.7, alb 4.1 WBC 8.4, Hct 36, Plts 441, U/A some rbc, no casts, ANA-, ASLO 33, UIF normal pattern, Ccr 32 cc/min
- Meds calan SR, PPI, zoloft, synthroid, cozaar - given Kayexolate ¬ CPMC 7 BX
- Px BP 170/90, P82, Cor-Chest-Abd- neg, no edema, fine maculo-papular rash on chest and upper arms.
- BUN 96 creat 5.1 U/A tr prot, 2+ heme, no casts

Case 2

- What is the differential Dx of the acute renal failure?
- What labs help or hurt each diagnosis?
- Would you biopsy now? Wait and then consider biopsy if no recovery? Treat and then biopsy if no recovery? (What therapy if treating?)
Drug-Induced Interstitial Nephritis

- Pathogenesis: cell-mediated hypersensitivity reaction (T’s)
- Pathology
  - Interstitial inflammation & edema
  - EOSINOPHILS
  - Tubulitis
  - +/- granulomas

Clinical Features Penicillin-Related AIN

- Rash = > 40%
- Fever = > 75%
- Eosinophilia = > 80%
- Hypersensitivity Triad = 30% (R + F + E)

Urinary Findings in Penicillin-Related AIN

- Mild proteinuria
- Hematuria in over 90% (Gross hematuria in over 30%)
- Sterile pyuria
- Eosinophiluria
Medication Associated AIN

- Beta-Lactam Antibiotics
- Other Antibiotics - Sulfonamides
- TM-SMX
- Rifampin
- Quinolones
- Diuretics
- NSAIDS
- Other Drugs – Cimetidine, Dilantin, Sulfinpyrazone, Allopurinal
- Proton Pump Inhibitors

Course Patient 2

- D/C all meds – use alts for HBP and ulcer disease
- Prednisone 120 mg QOD x 6 wks
- Plasma creatinine decreased from 5.1 to 1.8 mg/dl
- Stable RFTs 4 yr later

Case 3

- A 64 yo BF has had diabetes and mild HBP for 6 yrs. Her BS has recently been poorly controlled and and she has had polyuria and nocturia. Recently she noticed dysuria and frequency as well.
- She develops fever, chills, and left flank pain which increases over 24 hrs. She calls her MD who send her to the ER immediately.

Case 3

- In the ER her BP is 110/72, P 100, Temp 102, R14. She has marked L CVA tenderess.
- BUN 35 mg/dl, Creatinine 1.4 mg/dl
- WBC – 16,500, Hct 39%, platelets nl.
- U/A shows 3+gluc, 2+ heme, tr alb, 10-15 rbc, wbc – TNTC, and wbc casts.
- Urinary Na+ is 42 mEq/L. FENa+ is 1.8.
- USG shows no hydronephrosis (obstruction) but a stone in L kidney.
- She is treated with hydration, amp, gent.
- Over the next 24 hours her BP incr to 145/82, temp 100, and urine output remains copious.
- BUN decrease to 14 mg/dl and creatinine to 0.7 mg/dl.
Acute Pyelonephritis

- Acute suppurative infection of kidney
- Clinical: back pain, fever, pyuria, +/- RI
- Urine cultures: confirmation / Ab sensitivity
- Route of infection
  - ascending > hematogenous
  - ascending starts in bladder as UTI (F>M)
  - hematog: septic emboli, bacteremia (F=M)
- Organisms
  - 85% gram negative bacilli (#1 E. coli)
  - fecal flora

Acute Pyelonephritis

- Increased risk of ascending infection in three clinical settings
  - Obstruction: BPH, tumors, pregnancy, neurogenic bladder (DM)
  - Instrumentation
  - Vesicoureteral reflux
    - 50% UTI’s in 1st year of life
    - congenital anomaly: intravesical portion of ureter lacks normal oblique course that prevents reflux
**Acute Pyelonephritis**

- **Gross:** normal size, +/- coalescent abscesses
- **Micro:** severe inflammation, PMN's
- **Microabscesses**
- **PMN casts & tubulitis**
- **Distribution:**
  - Ascending: originates near medulla
  - Hematogenous: cortical

**Chronic Pyelonephritis**

- **Definition:** chronic renal disorder with scarring, inflammation, and deformity of calyces/pelvis (ascending*)
- **Gross:** shrunken
  - Irregular, asymmetric broad/flattened scars (U*)
  - Papillary blunting and calyceal deformity
- **Micro:**
  - Disproportionate tubulo-interstitial scarring
  - Atrophic tubules with colloid casts (*"thyroidization")
  - Chronic inflammation (not PMN's)

**Chronic Pyelonephritis**

- **Clinical**
  - Insidious onset of RI
  - +/- HTN, mild proteinuria, decreased urinary concentration, culture neg
  - Rarely follows "usual" acute pyelo
  - More common with persistent obstruction or VUR
  - +/- awareness of acute episodes
  - Rx: relieve obstruction / correct VUR, antibiotics as indicated
Case 4

- A 52 yo F has had rheumatoid arthritis for 20 yrs and has been taking aspirin, tylenol, and NSAID’s daily but no other medications for her disease. She develops R flank pain, but no fever, chills, or dysuria. Physical examination shows marked deformities of her joints but no edema.
- Labs: U/A tr protein, few rbc and many wbc. BUN 32 mg/dl, P creatinine 2.4 mg/dl, 24 hr prtoein 0.4 g/d, and negative or normal tests for complement, anti-DNA antibody, HBV, BS, HCV, etc. Urine culture is “no growth” after 2 days.
- An Intravenous Urogram is performed.
Case 4

- Is bacterial pyelonephritis the cause of this patient's back pain?
- What are other possible causes?
- What other diseases could cause this picture?

Analgesic Nephropathy

An international disease (Australia, Switzerland, Scandinavia, USA)
Abusers and Users – Headaches and Arthritis
Female:Male 6:1
Large amounts over prolonged time periods
Renal abnormalities
- sterile pyuria
- only mild proteinuria and hypertension
- Decreased concentration ability
- Decreased net acid excretion
- Salt wasting
- Papillary necrosis
Patients can recover function if they stop analgesic use

Causes of Papillary Necrosis

- Obstructive pyelonephritis
- Sickle Cell Anemia
  - medulla leads to sickling
  - sickling leads to medullary ischemia
- Analgesic abuse (phenacetin*)
  - increased risk with combinations
  - direct toxicity and ASA-induced PG deficiency
- Diabetes Mellitus

NSAIDs

- Multiple patterns of renal disease
- Acute interstitial nephritis
- Acute tubular necrosis
  - Loss of PG vasodilation / precip ATN in the setting of volume depletion
- Minimal change disease (rarely MG)
- Papillary necrosis
- Same nephrotoxicity for COX-2 inhibitors