Nephrology CPC

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December 9, 2005
Case

Mrs. Y is a 53 y/o white female referred to nephrology for acute deterioration of renal function.

Patient has a 3 month h/o malaise, 20 lb weight loss, questionable peptic ulcer, erratic vomiting, some LE edema, and intermittent low-grade fevers.
Case

Because of these concerns, she underwent a cholecystectomy 2 months prior, showing cholecystitis and gall stones, but her sxs did not improve.
Case

- The patient’s serum creatinine in Oct 2003 was 0.9. In Oct 2004, at the time she began having these problems, her creatinine had risen to 1.9. Couple of weeks later, before her referral, her creatinine had risen into the 6’s.
Case

- **ROS:**
  - Changes in vision with flashes of light
  - BP has become low and she is off of her BP meds now
  - Polyuria and nocturia
  - Mild constipation
  - Erratic joint pain for several months, but with no true major inflammation
  - Anxiety and difficulty sleeping
Case

- **PMH:**
  - HTN for 3-4 yrs medicated with HCTZ
  - Hyperlipidemia, not treated
  - Mild chronic venous insufficiency
  - Recurrent skin lesions on neck/leg with previous bx of a nasal lesion at outside institution with uncertain dx
Case

- **Past Surg Hx:**
  - Cholecystectomy with hernia repair 2 months prior
  - Tonsillectomy age 9
  - Tubal ligation age 39

- **Medications:**
  - Prilosec 20 mg QD
  - HCTZ stopped 6 wks prior to evaluation
  - Occasional NSAID (Aleve, Ibuprofen, ASA) use – less than 1-2 per wk
Case

- **Soc Hx:**
  - Single, worked as a business assistant at A&M University
  - H/o smoking, but quit 20+ yrs ago
  - No alcohol or drug use

- **FHx:**
  - Father – died age 81 with pneumonia
  - Mother – died age 75 with PE
  - Brother – diabetes
  - Aunt – breast ca
  - Uncle – colon ca
Physical Exam

- Vitals: BP 150/80 with no orthostasis, P 68 regular, 5’7 wt 244 lbs, Afebrile
- Gen: AA, oriented, NAD, obese
- HEENT: nml eye exam
- Neck: No JVD, LAD, or carotid bruits
- CV: Reg rhythm without m/r/g
- Resp: Diminished breath sounds at bases, otherwise clear
- Abd: obese limited exam with no mass or tenderness
- Ext: good pulses
- Neuro: no focal deficits, CN intact
- Skin: chronic venous stasis of LE with 1+ edema; several large erythematous flaking lesions on R knee
Labs

- 3 days prior to admission:
  - UA (done by nephrology): few granular and hyaline casts present, few epithelial cells, 1+ protein, NO WBCs, NO RBCs
  - Bun 57, Creat 6.5, Na 136, K 3.3, Cl 98, Bicarb 22,
  - Hgb 9.4, Hct 28.0, Plt 153,000
  - PT/PTT nml
  - C3/C4 nml, ANA neg
  - Renal US: Unremarkable except for some questionable minor cysts
  - CXR: nml
Case

- Patient was admitted for further studies and diagnostic intervention.
Problem List

- Rapidly progressing renal failure
- Proteinuria
- Recurrent skin lesions
- Changes in vision
- Erratic joint pain
- Intermittent low-grade fevers
- Polyuria
- Nocturia
- 20 lb weight loss
- GI sx/vomiting
- HTN
- Hyperlipidemia
- Mild chronic venous insufficiency
- Hypokalemia
- Anemia
Rapidly Progressive Renal Failure

- Glomerular Filtration Rate (GFR) – sum of filtration rates in all of functioning nephrons
- When GFR halves – creatinine doubles in a steady state; Problem – given the rapid deterioration of renal function, this is not a steady state
Rapidly Progressive Renal Failure – Cockcroft Gault Method

- Serum creat, wt, age, gender
- GFR 10/03 -126.2 ccs/min
- Creat 10/03 – 0.9
- GFR 10/04 – 59.8 ccs/min
- Creat 10/04 – 1.9
- GFR 2 wk later – 17.5 ccs/min
- Creat 2 wk later – 6.5
Outline

- Basic etiologies for renal failure
  - Prerenal
  - Postrenal
  - Intrinsic renal
    - Diseases of glomeruli
    - Tubulointerstitial diseases
    - Renovascular obstruction
    - Intratubular deposition and obstruction
CAUSES OF ACUTE RENAL FAILURE

1. Prerenal
   Sudden and severe drop in blood pressure (shock) or interruption of blood flow to the kidneys from severe injury or illness

2. Intrarenal
   Direct damage to the kidneys by inflammation, toxins, drugs, infection, or reduced blood supply

3. Postrenal
   Sudden obstruction of urine flow due to enlarged prostate, kidney stones, bladder tumor, or injury
Prerenal

- Hypovolemia – hemorrhage/dehydration
- Low cardiac output
- Systemic vasodilation – sepsis
- Alteration in intrarenal hemodynamics – ace inh/ NSAIDS
- Hyperviscosity syndrome – multiple myeloma, polycythemia
Not Prerenal in this case

- BUN/Creat not 20/1
- No orthostatic changes
- No exam findings to suggest
Postrenal

- Obstruction –
  - Bilateral ureteric – calculi, mass
  - Bladder neck – neurogenic bladder
  - Urethra - stricture
Not Postrenal in this case

- No hydronephrosis seen on US
- No abdominal/flank pain
- No exam findings to suggest
Intrinsic Renal

I. **Renovascular obstruction** (bilateral or unilateral in the setting of one functioning kidney)
   A. **Renal artery obstruction**: atherosclerotic plaque, thrombosis, embolism, dissecting aneurysm, vasculitis
   B. **Renal vein obstruction**: thrombosis, compression
Intrinsic Renal (cont)

II. Disease of glomeruli or renal microvasculature
   A. Glomerulonephritis and vasculitis
   B. Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, toxemia of pregnancy, accelerated hypertension, radiation nephritis, systemic lupus erythematosus, scleroderma
III. Acute tubular necrosis

A. Ischemia: as for prerenal ARF (hypovolemia, low cardiac output, renal vasoconstriction, systemic vasodilatation), obstetric complications (abruptio placentae, postpartum hemorrhage)

B. Toxins
   1. Exogenous: radiocontrast, cyclosporine, antibiotics (e.g., aminoglycosides), chemotherapy (e.g., cisplatin), organic solvents (e.g., ethylene glycol), acetaminophen, illegal abortifacients
   2. Endogenous: rhabdomyolysis, hemolysis, uric acid, oxalate, plasma cell dyscrasia (e.g., myeloma)
Intrinsic Renal (cont)

IV. Interstitial nephritis

- Acute
- Chronic
Intrinsic Renal (cont)

V. Intratubular deposition and obstruction
   - Myeloma proteins, uric acid, oxalate

VI. Renal allograft rejection
Intrinsic Renal narrowed to

- Diseases of Glomeruli or microvasculature –
  - Glomerular – Nephritic and Nephrotic
  - vasculitis
- Tubulointerstitial diseases
- Intratubular deposition and obstruction – multiple myeloma
- Renovascular Obstruction – atheroembolism
Glomerular diseases

- **Primary** – pathology confined to kidney
  - Acute nephritic syndrome
  - Rapidly progressive glomerulonephritis
  - Nephrotic syndrome
  - Asymptomatic abnormalities of urinary sediment – hematuria/proteinuria
  - Chronic glomerulonephritis
Glomerular diseases

- Secondary - associated with multisystem diseases
  - Diabetic nephropathy
  - Immunologically mediated diseases –
    - Polyarteritis nodosa–RBC in urine
    - ANCA / small vessel vasculitis–RBC in urine
    - Essential mixed cryoglobulinemia–RBC in urine
    - SLE - +ANA (95-99%), low C3/C4 (75-90%)
    - RA – exam findings
    - Sjogren’s syndrome – history, exam
    - Poly/dermatomyositis – history, exam
Glomerular diseases (cont)

- Drug induced
  - NSAIDS/HCTZ

- Glomerular deposition diseases
  - Amyloidosis – usually presents as nephrotic syndrome
  - Multiple Myeloma
  - Waldenstrom’s macroglobulinemia – no h/o bleeding
Glomerular diseases (cont)

- Infectious diseases
- **Neoplasm** – solid tumors (lung, GI, breast, kidney, ovary)
- **Hereditary diseases** –
  - Alport’s syndrome
  - Fabry’s disease
  - Lipodystrophy
Nephritic syndrome

Clinical syndrome

Pathogenic category

Anti-GBM disease

Pauci-immune GN

Immune complex GN

Some mimickers

Serologic marker

Anti-GBM antibody (negative ANCA, normal C3)

ANCA (anti-GBM negative, normal C3)

Low C3 (anti-GBM negative, ANCA negative)

Normal C3 (anti-GBM negative, ANCA negative)

Normal C3 Anti-GBM negative, ANCA negative

Immunofluorescence microscopy

Linear Ig and C3

Sparse or absent Ig/C3

Granular Ig and C3

Granular Ig and C3

Sparse or absent Ig/C3

Differential diagnosis

Anti-GBM disease

Good-pasture's syndrome

Wegener's granulomatosis

Microscopic polyarteritis nodosa

Renal-limited crescentic GN

Idiopathic proliferative GN, crescentic GN, and MPGN

Postinfectious GN (ASO, ADNase)

Lupus nephritis (ANA, anti-dsDNA)

Cryoglobulinemia (cryocrit, HCV)

Bacterial endocarditis (echo, blood cultures)

Shunt nephritis (history, blood cultures)

IgA nephropathy†

HSP

Fibrillar GN†

Visceral abscess

Malignant hypertension

HUS/TTP

Interstitial nephritis

Scleroderma crisis

Toxemia

Atheroemboli‡
Nephrotic syndrome

- **Membranous nephropathy** – most common; infection, drugs, neoplasm, autoimmune diseases
- **Minimal change disease** – majority are idiopathic; drugs, assoc with lymphoma
- **Focal and segmental glomerulosclerosis** - assoc with systemic dz/drugs – HIV; as consequence of sustained glomerular capillary HTN
- **Membranoproliferative glomerulonephritis** – idiopathic, infections, leukemia/lymph, liver dz
- **Diabetic nephropathy**
- **Amyloidosis**
Nephrotic syndrome
Our Case

- Given the bland urine with no active sediment (RBCs) – rule out nephritic syndromes
- Given only 1+ proteinuria (though we are not given a volume – the presence of hyaline casts are observed with small volumes of concentrated urine) with no lipiduria along with little edema noted on exam – doubt nephrotic syndrome
Intrinsic Renal narrowed to

- Rapidly progressive renal failure with proteinuria and bland urine:
  - Tubulointerstitial disease –
    - Acute
    - Chronic
  - Intratubular deposition and obstruction – multiple myeloma
  - Renovascular Obstruction – atheroembolism
Tubulointerstitial Disease

- **Acute Interstitial Nephritis**
  - **Drugs** - Antibiotics, Nonsteroidal anti-inflammatory drugs, Diuretics (thiazides, furosemide, triamterene), Anticonvulsants, Miscellaneous (captopril, H₂ receptor blockers, omeprazole, mesalazine, indinavir, allopurinol)
  - **Infection** - Bacteria (Streptococcus, Staphylococcus, Legionella, Salmonella, Brucella, Yersinia, Corynebacterium diphtheriae), Viruses (Epstein-Barr virus, cytomegalovirus, Hantavirus, HIV), Miscellaneous (Leptospira, Rickettsia, Mycoplasma)
Tubulointerstitial Disease (cont)

- **Acute Interstitial Nephritis**
  - Idiopathic Tubulointerstitial nephritis-uveitis syndrome (TINU)
  - Anti-tubule basement membrane disease
  - Sarcoidosis
Tubulointerstitial Disease (cont)

- Chronic Tubulointerstitial Diseases
  - Hereditary renal diseases
    - Polycystic kidney disease, Medullary cystic disease, Medullary sponge kidney
Tubulointerstitial Disease (cont)

- **Chronic Tubulointerstitial Diseases**
  - Exogenous toxins
    - Analgesic nephropathy, Lead nephropathy, Miscellaneous nephrotoxins (e.g. lithium, cyclosporine, heavy metals, slimming regimens with Chinese herbs)
  - Metabolic toxins
    - Hyperuricemia, Hypercalcemia, Miscellaneous metabolic toxins (e.g., hypokalemia, hyperoxaluria, cystinosis, Fabry's disease)
Tubulointerstitial Disease (cont)

- **Chronic Tubulointerstitial Diseases**
  - Autoimmune disorders
    - Sjogren's syndrome, Scleroderma
  - Neoplastic disorders
    - Leukemia, Lymphoma, Multiple Myeloma
  - Miscellaneous disorders
    - Chronic pyelonephritis, Chronic urinary tract obstruction, Vesicoureteral reflux, Radiation nephritis, Tubulointerstitial disease secondary to glomerular and vascular disease
Tubulointerstitial Diseases

- **Pertinent to our patient:**
  - Drugs – NSAIDs, thiazide diuretics
  - Infection – bacterial, viral
  - Tubulointerstitial nephritis and uveitis syndrome (TINU)
  - Sarcoidosis
  - Multiple Myeloma
  - Vascular - Scleroderma renal crisis
  - Vascular – renal atheroemboli
Drugs (NSAIDs, HCTZ)

- Most common cause of acute interstitial nephritis; see an abrupt rise in creat. related to administration of the offending drug
- Most common drugs – NSAIDs, PCN, cephalosporins, rifampin, sulfonamides
- Sxs – allergic-type rx – rash, fever, eosinophilia, N/V, malaise, no sx
- Cases (bx proven AIN) spontaneously improved with discontinuation of drug
Acute Interstitial Nephritis
Infection

Most common – legionella, leptospirosis, CMV, streptococci, mycobacterium TB

Not much in history or PE to suggest – No WBCs in urine, no travel history or exposure history
Tubulointerstitial nephritis and uveitis syndrome (TINU)

- First described 1975 – approx 140 cases now reported (ophtho/peds lit)
- Pathogenesis – not well understood; delayed-type hypersensitivity and suppressed cell-mediated immunity
- Epidemiology – adolescents/young women; median age 15
- Associations – drugs (abx, NSAIDs), infections (EBV, chlamydia), autoimmune dz (RA)
- Systemic sxs – fever, wt loss, fatigue, anorexia, abdominal/flank pain, arthralgias/myalgias, polyuria/nocturia
Tubulointerstitial nephritis and uveitis syndrome (TINU) (cont)

- Uveitis – predominantly anterior; pain or redness +/- decreased visual acuity
  - Most cases present after the onset of renal dz and is recurrent
- Renal – typical for AIN, may see hematuria, sterile pyuria, or just subnephrotic proteinuria; US can demonstrate marked swelling of kidneys; usually self-limited and spontaneously resolves in most patients
- Lab – eosinophilia, anemia, abn LFTs, elevated ESR, glucosuria, phosphaturia
Tubulointerstitial nephritis and uveitis syndrome (TINU) (cont)

- Pathology – tubulointerstitial edema and infiltration of inflammatory cells composed mainly of mononuclear cells (lymphocytes, plasma cells, histiocytes); glomerular and vascular structures usually spared
Sarcoidosis

- Typically a multisystem granulomatous disorder of unknown etiology; most frequently involves the lung
- Generally presents with 1 or more: bilateral hilar adenopathy, pulmonary infiltrates, skin/eye lesions
- Typically 3-4x more common in African Americans
Extrapulmonary Sarcoidosis

- Derm – 20% pts
  - maculopapular eruption – nares, lips, eyelids, forehead, neck
  - Waxy, pink nodular lesions – face, trunk, arms/legs
  - Plaque-like lesions – cheeks, chin, ears, nose
  - Erythema nodosum
  - Atypical – psoriasiform, hypopigmented, follicular, rosacea-like, angiolupoid lesions
Erythema nodosum
Extrapulmonary Sarcoidosis (cont)

- Ophthalmologic – 20% pts
  - uveitis (ant/post)
  - Retinal vasculitis
  - Keratoconjunctivitis
- Musculoskeletal 10% pts, arthritis/myositis
- GI – 1% pts; stomach most commonly affected; postprandial abd pain, heartburn, n/v, wt loss
Extrapulmonary Sarcoidosis (cont)

- Reticuloendothelial system – LAD
- Exocrine glands – swelling of salivary glands
- Cardiovascular – ventricular septum
- Neurologic – meningitis
- Reproductive system – endometrium
- Thyroid - goiter
Sarcoidosis - Renal

- Interstitial nephritis with granuloma formation is common but development of renal insufficiency is unusual.
- Most pts have clear evidence of diffuse active sarcoidosis but some can present with isolated elevated creat and none/minimal extra-renal manifestations.
- Urine typically nml or with mild proteinuria.
Sarcoidosis – Renal (cont)

- Can get hypercalcemia/hypercalciuria due to extra-renal production of calcitriol by activated sarcoid macrophages – lead to polyuria, nephrolithiasis, and nephrocalcinosis, and renal insufficiency – though most pts remain asymptomatic.
Sarcoidosis – Renal (cont)

- Pathology - reveals nml glomeruli, interstitial infiltration mostly with mononuclear cells, noncaseating granulomas in the interstitium, tubular injury, and with more chronic dz – interstitial fibrosis
Sarcoidosis – Renal
Renal Sarcoidosis - Cases

- 7 reported cases out of London with granulomatous interstitial nephritis with no features of extrarenal sarcoid:
  - Age 35-72, mild proteinuria, 5 with nml Calcium, 4 with nml ACE levels
  - Treated with steroids – 5/7 improved renal function
Renal Sarcoidosis - Cases

- 6 reported cases out of Germany with granulomatous interstitial nephritis; 3 of which had no features of extrarenal sarcoid:
  - Age 48-74, 3 with mild proteinuria, 3 with nml Calcium, 3 with nml ACE levels
  - Treated with steroids – 3 improved renal function
Multiple Myeloma

- Neoplastic proliferation of single clone of plasma cells – monoclonal immunoglobulin
- Etiology – unknown
- Epidemiology – 1% of all malignant dz, and 10+% of hematologic malignancies in US
- Median age about 66 yrs
- Sxs – bone pain (back/chest), weakness, fatigue, anemia, fever, hypercalcemia, renal insufficiency (elevated creat in approx 50% pts at dx)
Multiple Myeloma (cont)

2 major mechanisms of renal insufficiency:

- Hypercalcemia
- Cast nephropathy (myeloma kidney) – large, waxy, laminated casts in distal and collecting tubules mainly composed of precipitated monoclonal light chains which are thought to interact with Tamm-Horsfall mucoprotein
Myeloma Kidney

- Suspect in older pt who presents with otherwise unexplained acute/subacute renal failure, bland urine sediment, and neg/mild proteinuria
Myeloma Kidney (cont)

- Factors thought to promote cast formation
  - High rate of light chain excretion
  - Biochemical characteristics of some light chains (nephrotoxic)
  - Volume depletion – by slowing flow within tubules
Myeloma Kidney
Scleroderma

- Greek “scleros” to describe thickened, hardened skin
- Divided into systemic sclerosis, localized scleroderma, and scleroderma-like d/o
- Age onset 30-50 yrs
- Skin induration + dysphagia, acute onset HTN, renal insufficiency, DOE with associated interstitial pulmonary findings on CXR support dx + autoantibodies (Scl70)
Systemic sclerosis

Further divided: on extent of skin involved

- Diffuse cutaneous systemic sclerosis (DcSSc)
- Limited cutaneous systemic sclerosis (LcSSc)
DcSSc

- 60-80% pts have pathologic evidence of kidney damage
- 50% pts have proteinuria, elevated creat, +/- HTN
- 10-15% pts develop scleroderma renal crisis with acute onset renal failure, mild proteinuria with bland urine sediment, +/- HTN
- Case – incidence of severe renal dz 12.4%
Scleroderma Renal Crisis

- Usually occurs w/in first 5 yrs of dz
- Most pts have Raynaud’s even without skin findings
- Pathology - primary histologic changes in kidney are in the arcuate and interlobular arteries and the glomeruli (similar to changes seen with malignant HTN)
- End stage renal dz can develop in 1-2 months
Scleroderma Renal Crisis
Renal ateroemboli

- Also called cholesterol crystal emboli affect older pts with diffuse erosive atherosclerosis
- Risk factors: manipulation of aorta or spontaneous, also suggested with trmt with anticoagulation (coumadin) thought to interfere with healing of ulcerated atheromatous plaques
- Age 60-70 yr
- Rare 0.7-1%
Renal atheroemboli (cont)

- Also see findings compatible with embolization to other sites – blue toe syndrome, livedo reticularis, abd pain
- Produce incomplete occlusion with secondary ischemic atrophy rather than infarction like you might see with clot emboli
- Active phase – see eosinophilia and hypocomplementemia
- Over time – get intimal proliferation, giant cell formation, and further narrowing of lumen
Blue toe syndrome
Renal atheroemboli (cont)

- Urine is typically bland with few cells/casts; mild proteinuria; nephrotic proteinuria indicative of more chronic dz
- Pathology – needle-shaped clefts w/in occluded vessel often accompanied by a perivascular inflammatory rx
Renal atheroemboli
Tubulointerstitial Diseases

- Pertinent to our patient:
  - Drugs – NSAIDs, thiazide diuretics
  - Infection – bacterial, viral
  - Tubulointerstitial nephritis and uveitis syndrome (TINU)
  - Renal Sarcoidosis
  - Myeloma kidney
  - Vascular - Scleroderma renal crisis
  - Vascular – renal atheroemboli
Diagnostic Study

- Renal biopsy
  - Indicated in this situation for an unexplained acute/subacute renal failure
Final Diagnosis:

Renal Sarcoidosis
References:

- Up To Date. 2005.

[Image 36x36 to 576x756]
ST case
• Endocapillary proliferation
• Most glomeruli involved
• No global sclerosis
• Minimal tubular atrophy
• Mild interstitial inflammation
Focal necrosis, neutrophilic infiltrate and nuclear debris
Crescent formation

Thickened membranes, spikes
Mild interstitial fibrosis, focal synechiae between Bowman’s capsule and tuft
Foot process fusion

Subendothelial deposit

Subepithelial deposits

?
Tubuloreticular body
Diagnosis

- Lupus Nephritis, combined class 4 and 5
- Activity index 10 of 24
- Chronicity index 1-2 of 12
BY case
Immunofluorescence and EM

- Focal 1+ staining for C3 in Bowman’s membrane and BM of some tubules
- Focal 1+ staining for fibrinogen in granulomas
- EM essentially normal
Diagnosis

- Granulomatous interstitial nephritis, suggestive of sarcoidosis
- Cannot rule out infectious or drug etiology
- Mild interstitial fibrosis and tubular atrophy
KB case
• Lobular glomeruli
• Mesangial hypercellularity
• No inflammation or crescents
• All glomeruli affected
“tram tracking”
Foot process fusion

Microvillous transformation

Basement membrane duplication, mesangial interpositioning
Immunofluorescence

- Patchy, 2+ mesangial and membranous IgM
- C3 deposition, 2+ in membranes
- C4 strongly positive, membranous pattern
- C1q positive in characteristic lobular pattern
Diagnosis:
Type 1 membranoproliferative glomerulonephritis
The End

- Proceed to the post test
- Print the post test
- Complete the post test
- Return the post test to:
  - Dr. Sandra Oliver
  - 407c TAMU II
Post test

- Differentiate Nephritic from Nephrotic syndrome by completing the sentences
  1. Nephritic syndrome is characterized by:
  2. Nephrotic syndrome is characterized by: