Tubulointerstitial Diseases

Mark D. Baldwin D.O., FACOI, FASN

Professor and Chair Department of Internal Medicine

Pacific Northwest University

Yakima, Washington

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Disclosures

- None, just working for The Man

Case

- A 49 y.o. WF presents for follow up on a new patient visit. She has a hx of HTN for which she takes valsartan 160 mg daily and GERD for which she takes omeprazole 20 mg. BID. She is a non smoker and drinks rarely.
- Her exam is unremarkable BP 132/82 and mild obesity was noted.
- LAB: Na 133, K 3.4, Cl 100, bicarb 21, BUN 33, creatinine 2.9, glucose, LFTs, CBC, lipids were WNL
- UA SG 1.014, +leukocyte esterase, no blood, protein or nitrite, micro 4-10 WBCs, 02 RBCs no bacteria and C&S neg.

Features of Tubulointerstitial Disease

1. Proteinuria- usually less than 1 Gm/da
2. Anemia-due to low level of Erythropoietin
3. Acidosis-RTA's are common
4. Hypertension-common
5. Urinalysis-WBC's and WBC casts seen
6. Electrolyte Abnormalities-Na and K

Many of the above features are seen at relatively mild elevations of Serum Creatinine

Features of Glomerular Disease

1. Proteinuria->3 Gm/da
2. Anemia-uncommon until late
3. Acidosis-uncommon until late
4. Hypertension-may occur at any time
5. Urinalysis-may see Oval Fat Bodies
6. Electrolytes-May see low Na

Unlike Tubulointerstitial Disease, many of these feature do not occur until late in the course of the underlying disease.

Types of Tubulointerstitial Disease

1. Acute Interstitial Nephritis
2. Chronic Interstitial Nephritis
3. Acute Tubular Necrosis
4. Renal Tubular Acidosis
5. Multiple Myeloma

Chronic Interstitial Nephritis (CIN)

- A chronic condition involving fibrosis of the interstitium and tubular destruction
- Chronic low grade inflammation leads to tubular injury and fibrosis
- Macroscopically normal kidneys
- The final common pathway of most chronic renal diseases

Causes of Chronic Interstitial Nephritis

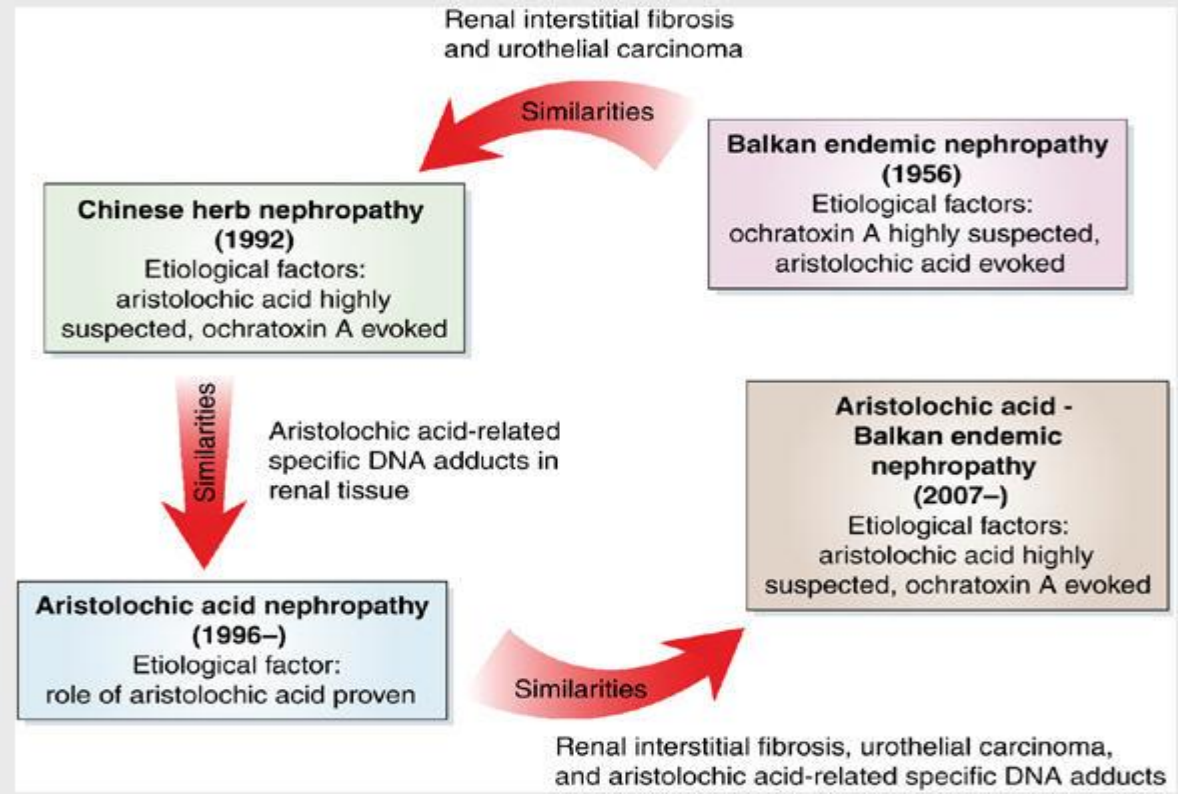
- Mechanical: ureteral reflux, obstruction, stones, infection, neurogenic bladder, medullary cystic disease, Alport's
- Drugs: NSAIDs, Lithium, PPI's, cyclosporine, tacrolimus, indinavir, cisplatin
- Heavy Metals: Hg, Pb, Cd, arsenic, gold, uranium, too much Ozzy
- Metabolic: hyperuricemia, hypercalcemia, hypokalemia, hyperoxaluria, cytinosis
- Radiation
- Immune mediated: ANCA, SLA, Sjorgren's, sarcoid
- Vascular: atherosclerotic renal disease
- Heme/Onc: myeloma, amyloid, lymphoma, sickle cell, PNH
- Late glomerular disease
- Aristolochic acid: Balkan nephropathy, Chinese herb nephropathy

Aristolochic acid

- Acute exposure: Chinese herb nephropathy-AKI, rapid decline in renal function
- Chronic exposure: Balkan endemic nephropathy-CIN/CKD slow decline over years from chronic exposure

Debelle *Kidney Int* 2008;74: 158-169

Aristolochic acid Nephrotoxicity

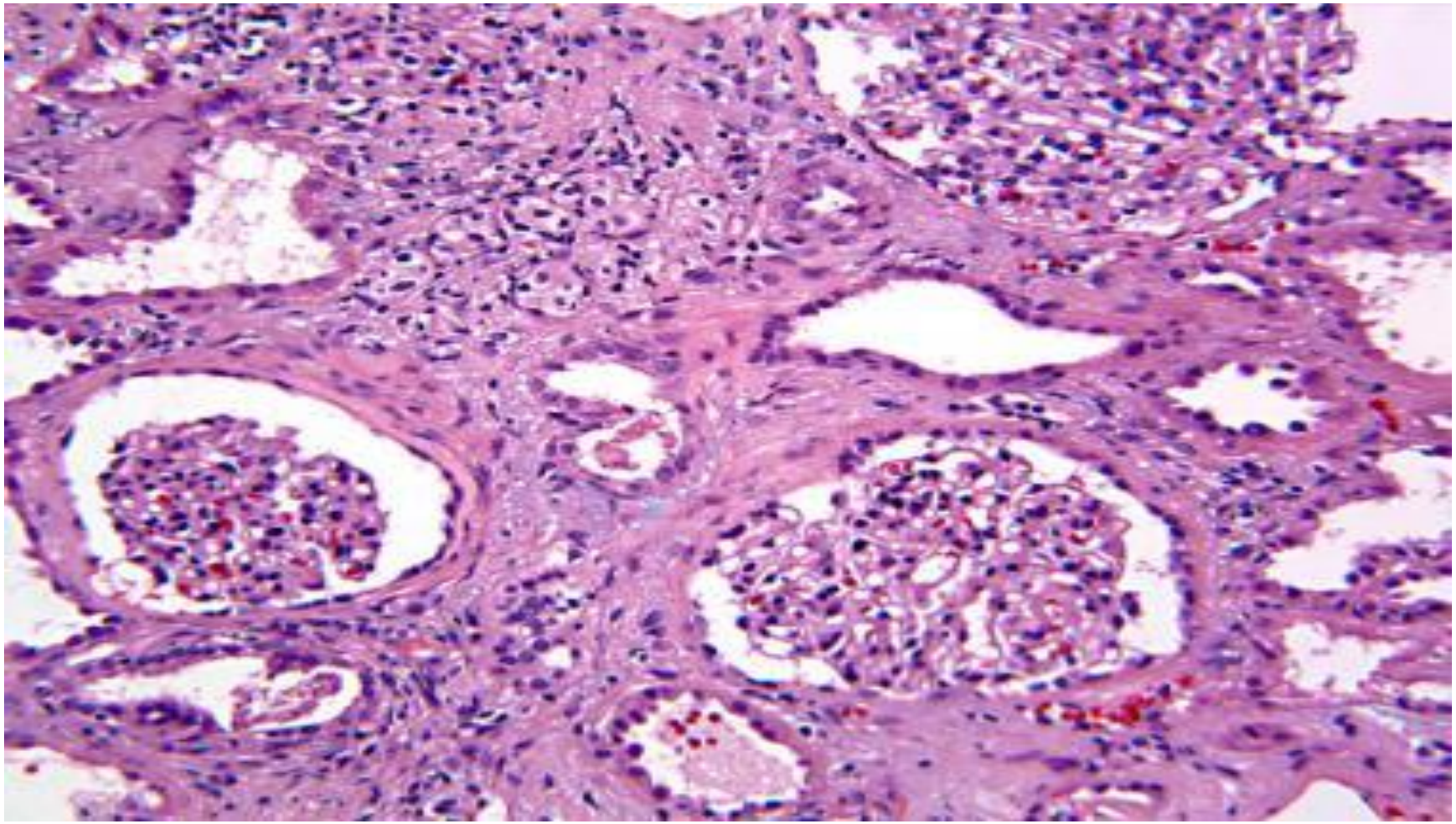


Debelle *Kidney Int* 2008;74: 158-169

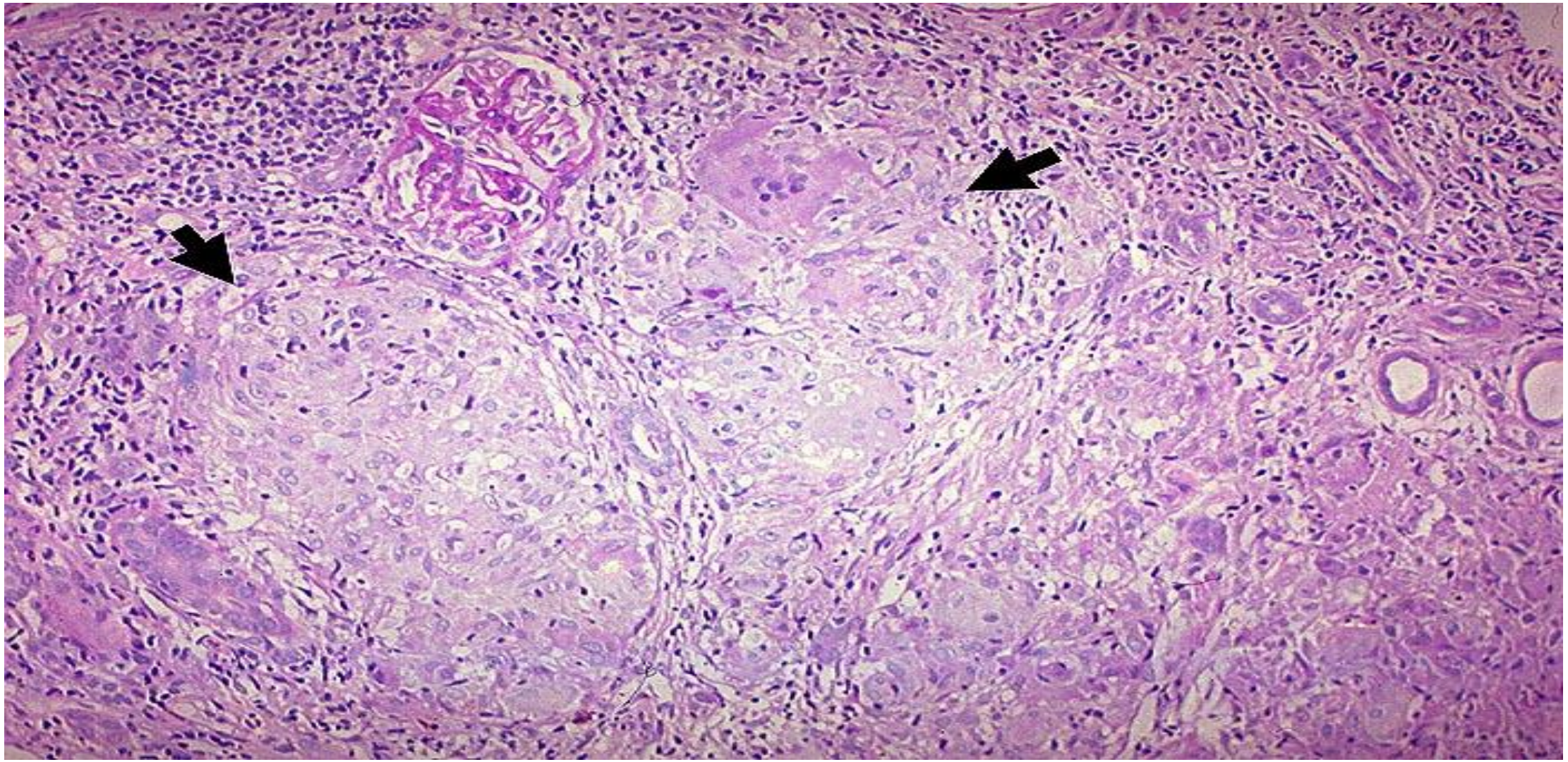
Clinical Features of CIN

- Usually Asymptomatic
- STERILE PYURIA-The Hallmark of CIN
- Anemia
- Acidosis-Renal Tubular Acidosis
- Hypo or hyperkalemia
- Minimal Proteinuria
- Hypertension

Chronic Interstitial Nephritis



Chronic Interstitial Nephritis



Treatment of CIN

- Do NOT give antibiotics for pyuria unless there is bacteria present-this is a chronic inflammatory condition, NOT an infection
- BP control-The MOST important treatment
- ACE-I or ARBs-The drugs of choice
- Anemia control
- Acidosis control
- Phosphorus control

Renal Tubular Acidosis (RTA)

- Distal Type I RTA -associated with Chronic Urinary Tract Obstruction, Bicarb<15*NAG, hypokalemia, urine pH>5.5
- Proximal Type II RTA -associated with Fanconi's Syndrome Bicarb 15-21*NAG, hypokalemia, urine pH>5.5
- Distal Type IV RTA- Most common RTA, Seen w/ DM and CKD, NAG, Hyperkalemia urine pH<5.5
- All RTA have +UAG

* Point of differentiation, NAG non anion gap acidosis

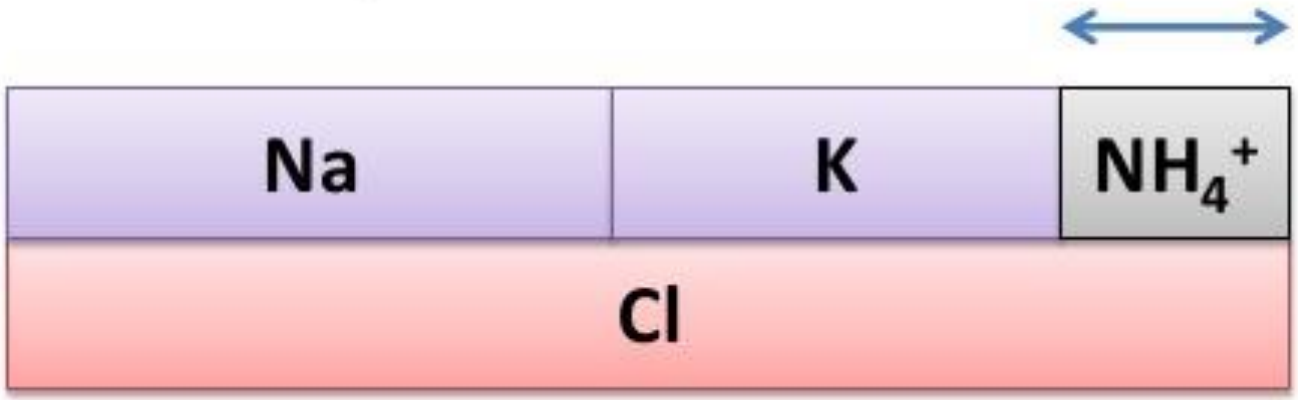
URINE ANION GAP

$U_{Na+} + U_{K+}$ + Unmeasured cations = U_{Cl-} + Unmeasured anions

Or, Unmeasured anions – Unmeasured cations = $(U_{Na+} + U_{K+}) - U_{Cl-}$

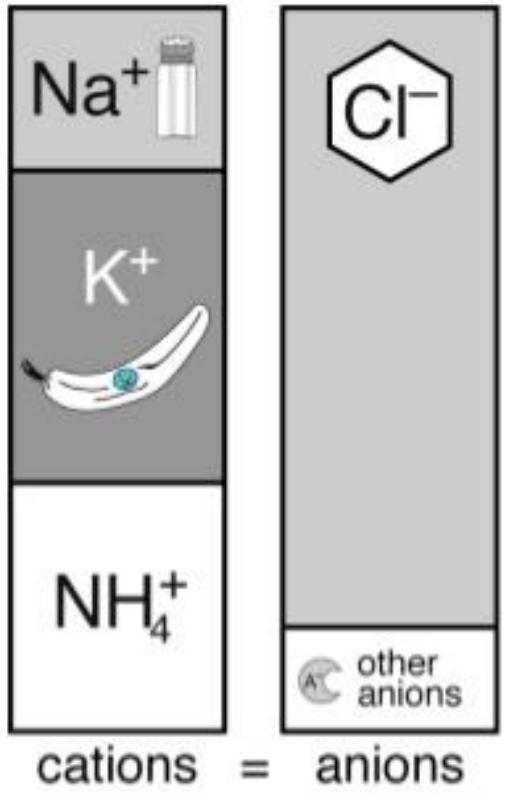
Urine Anion Gap (UAG) = $(U_{Na+} + U_{K+}) - U_{Cl-}$

- **NH_4^+** is the primary unmeasured cation which is not balanced by anions.
- **UAG as indirect assay for renal NH4+ excretion**



Urinary anion gap: $(Na^+ + K^+) - Cl^-$
Urinary ammonium detector

- In the presence of ammonium the chloride will be larger than the sum of Na and K.
- So a negative anion gap means ammonium in the urine.
- Ammonium in the urine means effective renal acid secretion
- Ammonium in the urine usually rules out RTA



Myeloma and the Kidney

- 10% of all hematological malignancies
- Plasma cell clone of Immunoglobulins usually IgG
- Renal, Cardiac and Liver are the most common organs involved
- Renal impairment-acute or chronic- is commonly seen ~50% of cases with severe involvement in 15-20% of cases
- Proteinuria-globulin or albuminuria is seen in >80% of cases
- Myeloma can involve the vascular, glomerular or tubular/interstitial segments of the kidney
- Frequent cause of mortality and morbidity

Pathophysiology

- Plasma cell clones leading to IgG light chains, heavy chains can be seen
- Can see clonal IgA, D, M or E variants of myeloma
- Light chain or fragments deposited in a tissues
- Kappa or lambda light chains
- Amyloid (AL) can be deposited
- Tubular obstruction
- Tubular dysfunction- Fanconi’s Syndrome & Proximal Type 2 RTA
- AKI of multiple etiologies

Renal Effects

- Glomerular: Amyloid light chain (AL) or heavy chain (AH) amyloidosis, Light Chain Deposition Disease (LCDD) or Heavy Chain Deposition Disease (HCDD) plasma cell infiltration

- Tubular: Cast nephropathy “Myeloma kidney”, tubular dysfunction, hypercalcemia, hyperuricemia, contrast induced AKI

- Interstitial: Plasma cell infiltration, pyelonephritis

Amyloid MM v LCDD

- Amyloid myeloma (AL):
- lambda>kappa, +congo red, +fibrils on EM

- Light chain deposition disease(LCDD): kappa>lambda, -congo red, -fibrils on EM

Cast Nephropathy

- Most common cause of renal failure in myeloma
- Globulin light chains are filtered at the glomerulus
- Can exceed 10-20 grams/day and are toxic to the tubular cells, negative dipstick d/t globulins not albumin
- Light chain are partially reabsorbed damaging to proximal tubular cells and delivered distally, combing with Tamm-Horsfell protein produced in the thick ascending limb occluding the tubule
- Obstructing casts lead to inflammation, fibrosis and tubular rupture

Presentation

- >50 years old
- Males>females
- African Americans >other groups
- Long history of back pain or “arthritic” pain
- Pathological fractures
- Fatigue
- Anemia
- Infection
- Renal failure

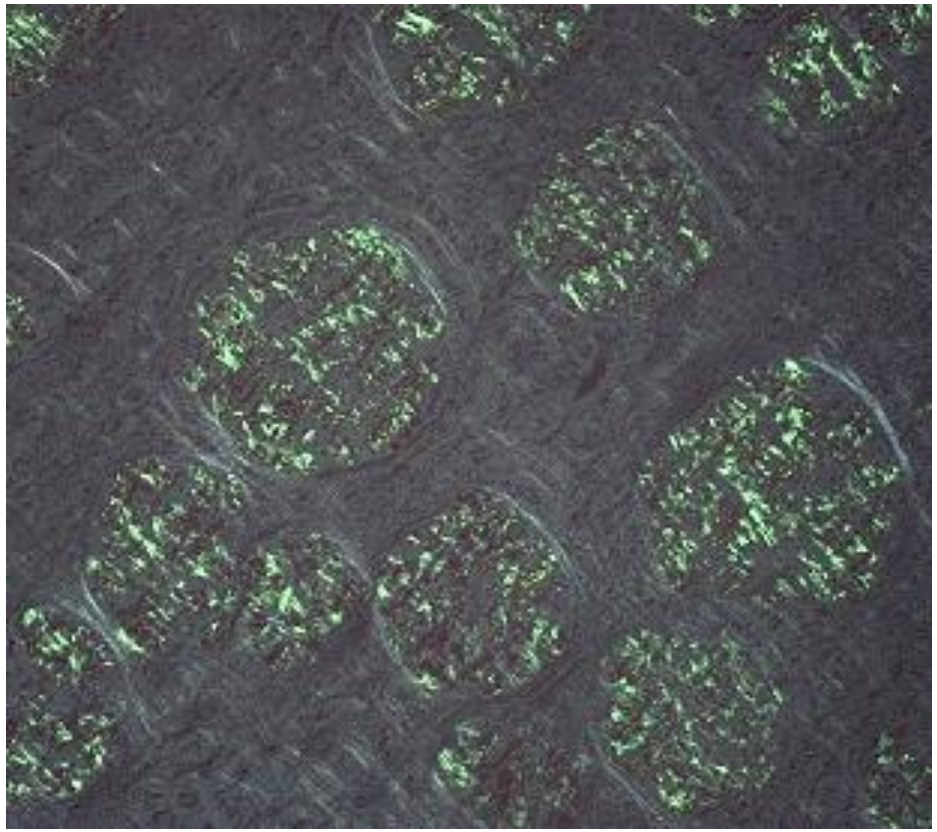
Multiple Myeloma Laboratory Findings

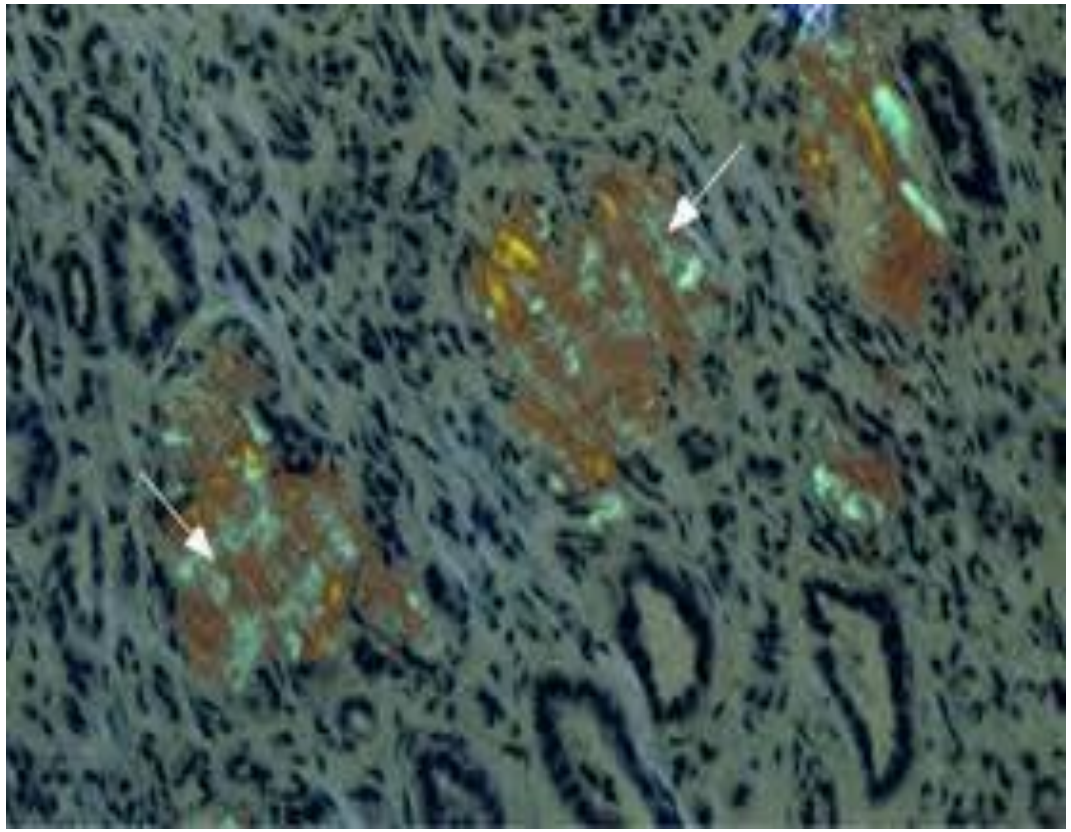
- Elevated BUN and Creatinine
- Hypercalcemia
- Hyperuricemia
- Normocytic Normochromic Anemia, Rouleaux formation
- Serum Protein Electrophoresis/ Urine Protein Electectrophoresis positive for elevations in the Gamma fraction-M spike
- Low Anion Gap
- Urinalysis may show NO Protein, unless Sulfa salicylic Acid test is done, which will be positive.

Serology

- Serum protein electrophoresis/urine protein electrophoresis
- Free light chain assay
- Immunofixation: quantifies IgA, IgD, IgE, IgM, IgG
- Cytogenic analysis: karyotyping
- Flow cytometry

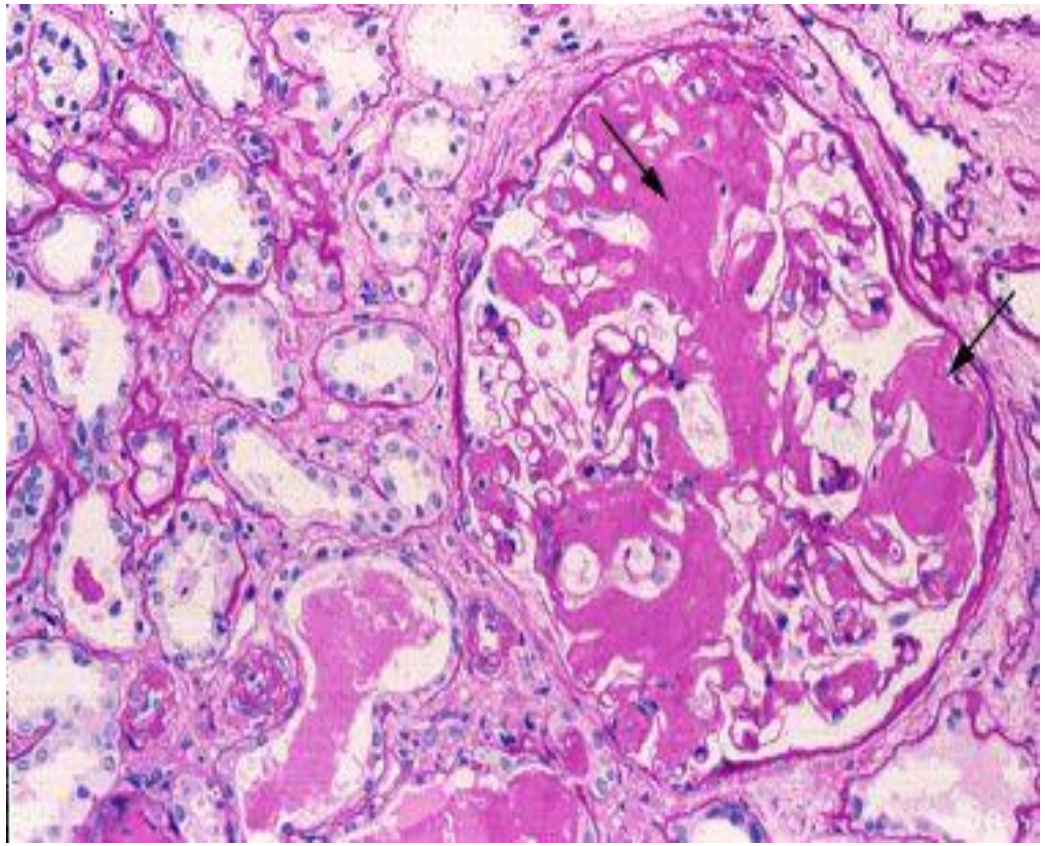
Congo Red “Apple green birefringence”



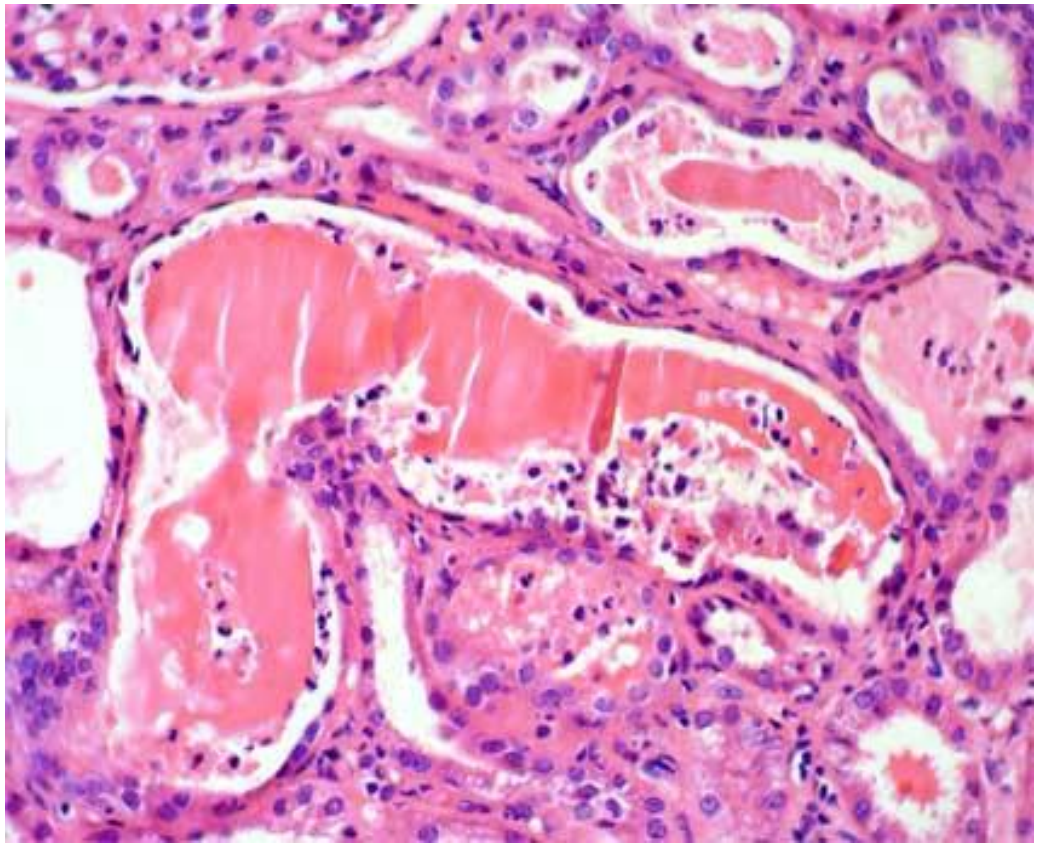


Renal Myeloma

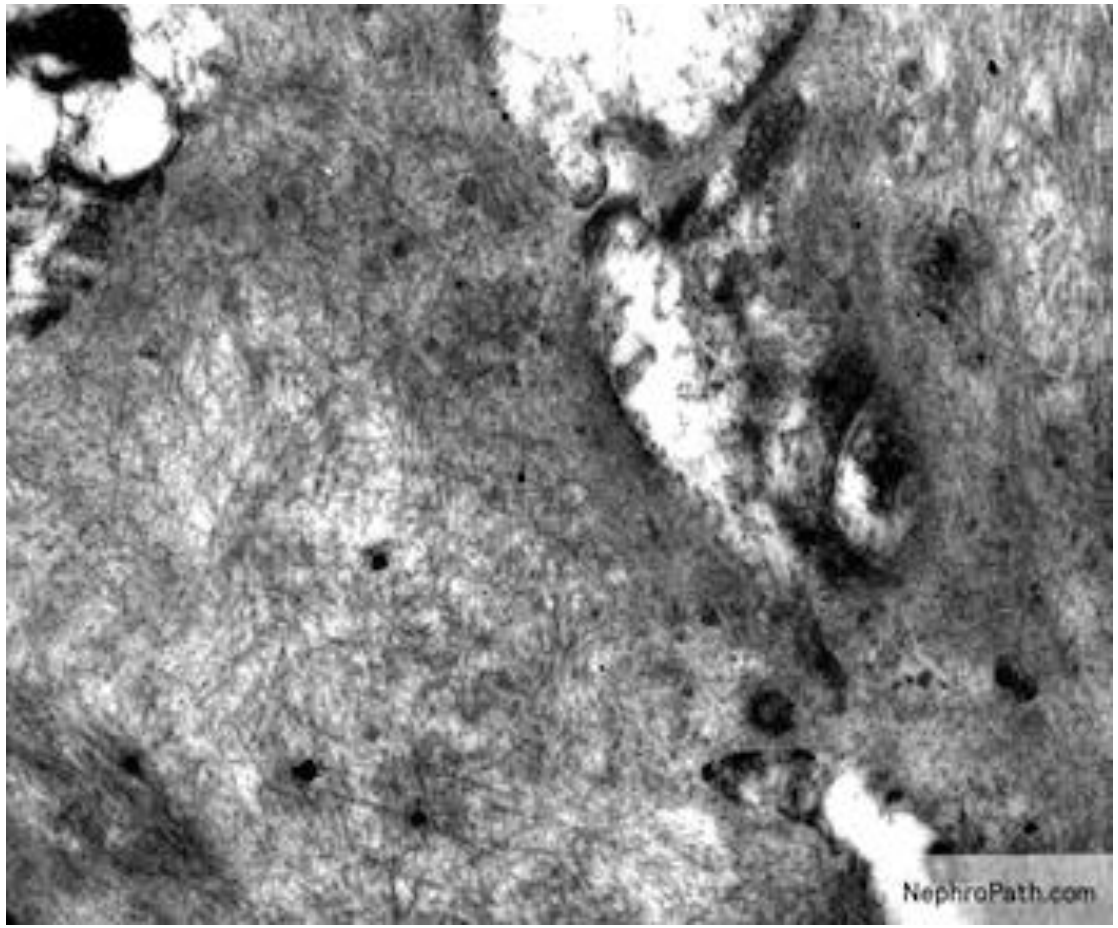
Glomerular Amyloid

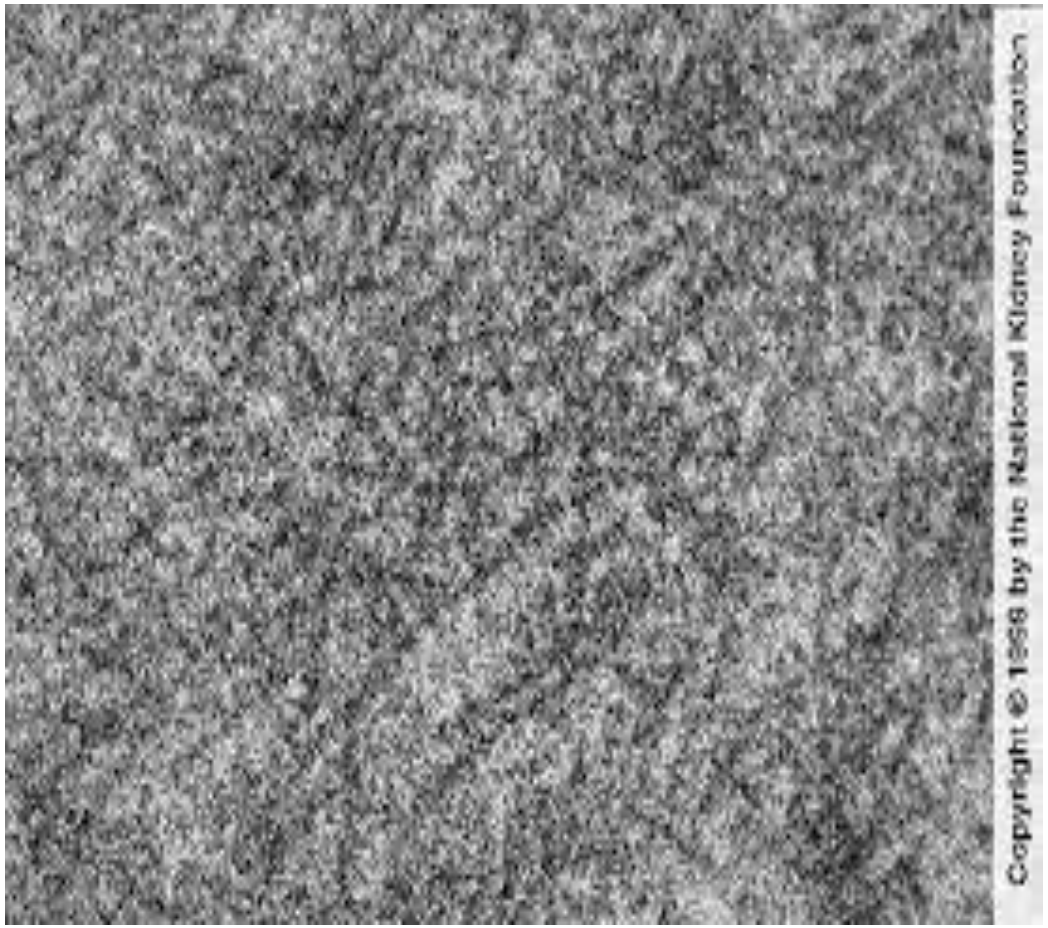


Cast Nephropathy

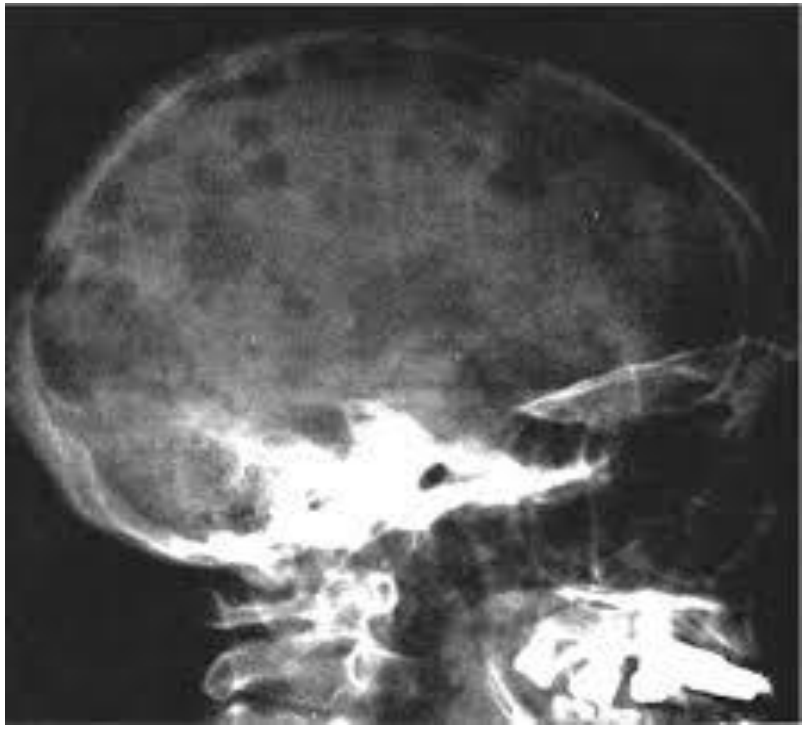


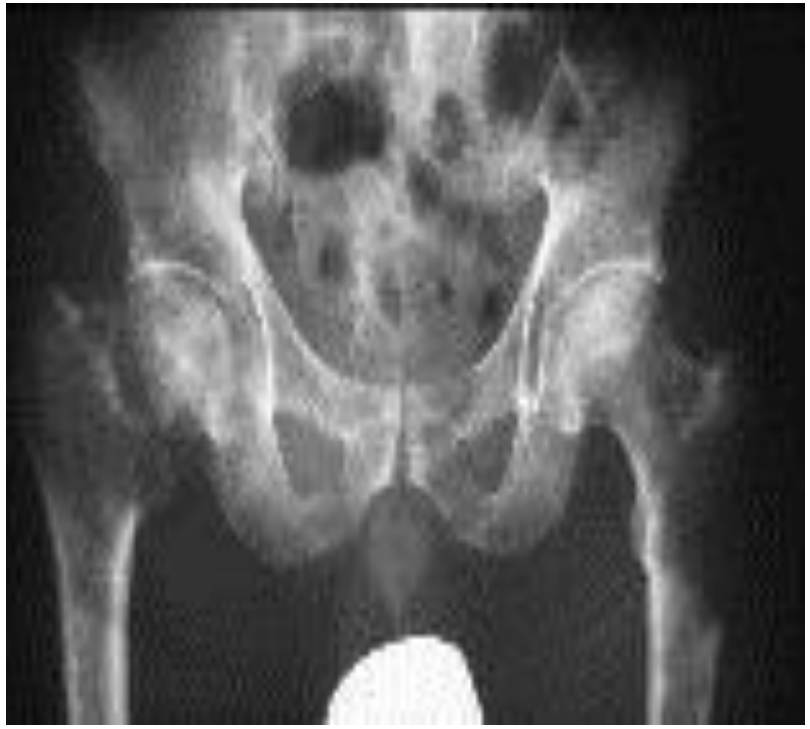
Amyloid Fibrils EM





Radiographs





Treatment of Myeloma Renal Disease

- Assure hydration status with alkalization of the urine but avoid fluid overload
- Allopurinol
- Bortezomib-dexamethasone-cyclophosphamide or
- Bortezomib-thalidomide-dexamethasone can decrease light chain production and may improve cast nephropathy
- Dialysis if needed (poor outcomes)
- ?role of plasmapheresis

Hypercalcemia of Malignancy

- Malignancy: Thyroid, lung, breast, renal cell, prostate, myeloma, leukemias/lymphomas, Tumor lysis syndrome
- *Very* poor prognostic sign
- Always (or almost always) presents with *dehydration*

Mechanisms:

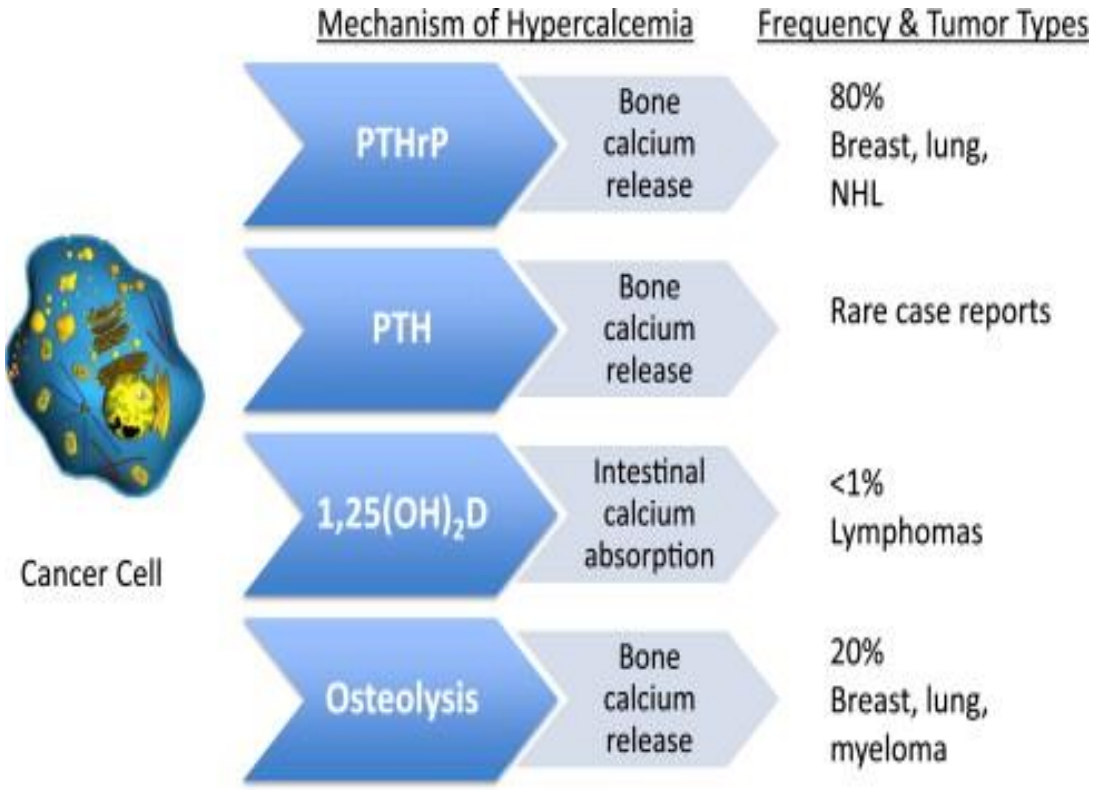
1. Direct bone invasion/osteolysis
2. Elevated PTHrP
3. Humoral hypercalcemia of malignancy: production of cytokines/osteoclast activating factors-releasing Ca^{++} from bone
4. Excess Calcitriol-like factors (increased GI absorption) granulomatous diseases (Sarcoid, TB)

Presentation

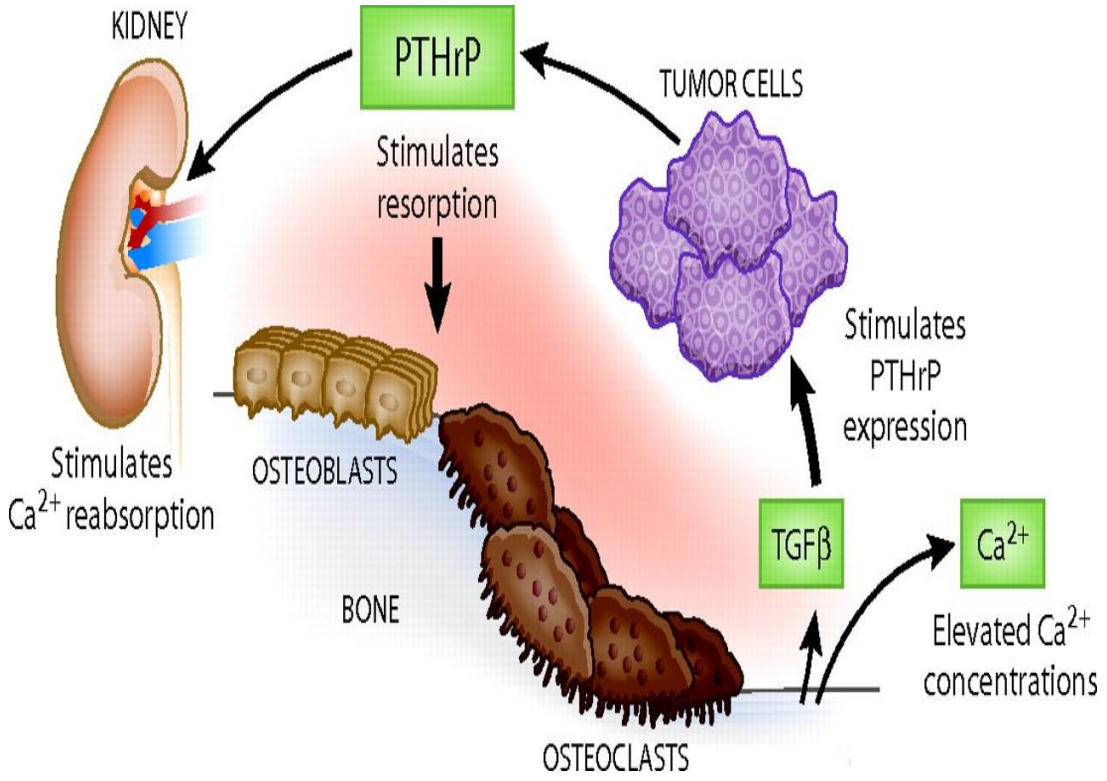
- Decreased cognition, fatigue
- Anorexia, N,V, constipation
- Abdominal and bone pain
- Pancreatitis
- Short QT, ST changes pseudo MI pattern
- HTN
- AKI, Nephrogenic DI

N AM J Med Sci 2011;7(11): 483-493.

Hypercalcemia of Malignancy



Reagan P, *AJKD* 2014;63:141-147



Mundy G *JASN* 2008;19:672-675

Treatment of Hypercalcemia of Malignancy

1. Aggressive IV Normal saline:
   a. Restores BP, perfusion
   b. Increased Na/water delivery to the kidney decreases reabsorption of Na and Ca^{++}
2. Once hydrated: Loop diuretic (reduces Ca uptake in the TAL) do NOT use Thiazides!!!!! WHY?
3. Calcitonin
4. Bisphosphonates (if renal function is normal and phosphorus is not elevated)
5. Steroids
6. Denosumab

Treatment of Hypercalcemia of Malignancy

Intervention	Onset	Duration
Normal saline 2-4l/da	Immediate	2-3 days
Calcitonin 4-8 U/kg SQ 6-12 hours	4-6 hours	2-3 days
Loop diuretic (once hydrated!)	~5-10 minutes	1-4 hours
Bisphosphonates	48 hours	~3 weeks
Corticosteroids	7 days	~7days
Denosumab	7-10 day	3 months

Sternlicht *Ther Clin Risk Manag* 2015; 11: 1779-1788

Tubulointerstitial Diseases-Conclusions

- Often overlooked as a cause of Chronic Renal Disease
- Look for Drug causes or Sepsis as a cause of Acute Renal Failure (i.e. AIN or ATN)
- Tubulointerstitial Diseases frequently have electrolyte abnormalities, acid-base disorders, and anemia as a common feature.