Drug-induced Kidney Disease

Background

• Acute & chronic kidney disease commonly complicate drug therapy
• Potentially nephrotoxic medications are constantly being released for use in clinical practice
• These drugs are often not tested in the patient populations who subsequently receive them
Drug-induced Kidney Disease
Background

• Culprit Drugs & Nephrotoxins
  – Therapeutic Medications
    • Prescribed
    • Over-the-counter
  – Diagnostic Agents
    • Contrast material
  – Alternative Medications
    • Herbal Remedies/Supplements
    • Contaminants
  – Environmental Pollutants
    • Heavy Metals
    • Organic Solvents
Drug-induced Kidney Disease

Background

Potential Compartments of Drug-induced Renal Injury

- **Prerenal**
  - Hemodynamic

- **Intrinsic Renal**
  - Vasculature
  - Glomerulus
  - Interstitium
  - Tubules

- **Postrenal**
  - Collecting system
Drug-induced Kidney Disease

Background

• Categories of Drug-induced Kidney Disease
  – Acute Kidney Injury (AKI)
  – Proteinuria/Nephrotic Syndrome
  – Tubulopathies
  – Chronic Kidney Disease
Drug-induced Kidney Disease

Risk Factors

• Patient Specific Factors
  – Kidney disease
  – Volume status

• Kidney Specific Factors
  – Drug handling
  – High metabolic rates

• Drug Specific Factors
  – Immune effects (haptens)
  – Insolubility
  – Pharmacogenetics
  – Immune response genes
  – ↑ local concentration
  – Biotransformation → ROS
  – Innate nephrotoxicity
  – Drug combinations
Drug injury can occur at multiple sites along the Nephron

Clinical Examples

Proximal convoluted tubule

Distal convoluted tubule

Glomerulus

Interstitium

Renal (arcuate & interlobular) Arteries

Loop of Henle

Thick ascending limb

Collecting duct
Case 1

- 70 yo male with h/o metastatic thyroid cancer seen in nephrology consultation for **new onset proteinuria**
- Thyroid malignancy was treated with total thyroidectomy in 2001
- Recurrent tumor encasing his trachea was resected and he was treated with radioactive iodine (2004)
- In 2005, rapidly progressive thyroid cancer with multiple pulmonary metastases prompted entry into **VEGF-Trap protocol (9/05)**-weekly SQ injection of drug
- Tumor regressed & metastatic disease stabilized
- Medications: levothyroxine, lisinopril 30 mg/d, calcium, vitamins B complex, C & E, no herbal remedies or over the counter meds
- Exam unremarkable with BP=145/80 mmHg, P=75/min; no edema, rash or petechiae
Time

Urine Pro (g/day)

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<th>Value</th>
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<tr>
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<td>9/06</td>
</tr>
<tr>
<td>7/06</td>
<td>10/06</td>
</tr>
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</table>

**Hypertension**

- Doxazosin 8 mg/day started: 5/06
- VEGF-Trap started: 5/06
- VEGF-Trap stopped: 7/21
- Lisinopril 30 mg/day started: 6/06
- D/C Doxazosin: 6/5
- Lisinopril 10 mg/day started: 5/7

**Renal Consult**

- Spironolactone 50 mg/day started: 7/27
Case 1

Laboratory Data

• **Electrolytes:**
  Na+, 138 mEq/l; K+, 4.1 mEq/l; Cl, 102 mEq/l; HCO3, 25 mEq/l; BUN, 18 mg/dl; sCr, 1.1 mg/dl (baseline 0.8 mg/dl)

• **Serologies:** negative Hepatitis B & C; negative Cryoglobulins; C3-82; C4-20; RH factor < 20

• **Serum immunofixation:** faint monoclonal component (IgG lambda); SPEP, no discrete abnormal bands; Serum free light chains, negative

• **Urinalysis:** SG, 1.012; 3+ protein; otherwise neg

• **Urine sed:** bland without cells or casts

• **24 urine protein:** 4.6 grams; UPEP-no abnormal bands

• **Urine immunofixation:** no monoclonal components

**Renal Biopsy**
• Mild mesangial hypercellularity and matrix widening
• Endothelial cell swelling
• Closed capillary loops
Endothelial cell swelling

Loss of fenestrations

Endothelial cell swelling

Closed capillary loops

Electron Microscopy

Courtesy of Mike Kashgarian
Final Diagnosis

• “Glomerular Endotheliosis” secondary to Anti-VEGF therapy (VEGF-Trap)
  – Capillary loop occlusion
  – Severe endothelial cell swelling
  – Loss of endothelial cell fenestrations
  – Fibrin deposition (not shown)
  – Focal effacement foot processes
Time

Urine Pro (g/day)

1.0

2.0

3.0

4.0

5.0

BP increased

Doxazosin 8 mg/day

VEGF-Trap

started

5/06

Lisinopril

10 mg/day

6/06

7/06

8/06

9/06

10/06

11/06

Renal Consult

Spironolactone 50 mg/day

(7/27)

VEGF-Trap

Stopped

(7/21)

Lisinopril

30 mg/day

D/C Doxazosin

Kidney

Biopsy

(8/8)

VEGF-Trap

Stopped

(10/19)

6.2 g/24 hr

Kidney

Biopsy

(8/8)

VEGF-Trap

Restarted

(8/15)

12/05

Renal Consult

Spironolactone 50 mg/day

(7/27)

VEGF-Trap

Stopped

(7/21)

Lisinopril

10 mg/day

1/06

3/06

4/06

VEGF-Trap

Restarted

(8/15)
**VEGF Ligands and Receptors**

**VEGF (A)**
- Promotes angiogenesis
- Maintains fenestrated endothelium
- Modifies vascular tone

**HIF**
- Hypoxia stimulates HIF
- HIF binds hypoxia response element in VEGF promoter

**VEGF (B)**
- **VEGFR-2** (Flk-1/KDR)
  - 7 Ig-like domains
  - Single transmembrane spanning region
  - Split tyrosine-kinase domain

**VEGF (C)**
- **VEGFR-3** (Flt-4)
  - Lymphangiogenesis

**VEGF (D)**
- **PlaGF**
  - VEGFR-1 (Flt-1)
  - Angiogenesis

Agents targeting the VEGF Pathway

**Anti-VEGF antibodies**
- Bevacizumab

**Soluble VEGF receptors**
- VEGF-Trap

**Anti-angiogenesis therapy**
- Malignancies
- Age-related MD
- Diabetic retinopathy

**VEGF receptor inhibitors**
- Sorafenib
- Sunitinib

Lessons from Pre-eclampsia

Effect of sFLT-1

- Abnormal and early release of high circulating levels of sFlt1 occurs
- High levels of circulating sFlt1 scavenge unbound plasma VEGF and PIGF
Kidney Disease associated with anti-VEGF therapy

Predictions from Pre-eclampsia

• Insufficient VEGF will permit the following:
  1. Increased vascular tone ⇒ **Hypertension**
  2. Dysfunction of glomerular endothelium and podocytes ⇒ **Proteinuria**
VEGF in the Kidney

- VEGF is produced by visceral epithelial cells (podocytes)
- VEGF receptors are present on glomerular endothelium
- VEGF maintains normal functioning of glomerular endothelial cells and podocytes
Inhibition of VEGF

- Healthy, wild type CD1 mice
- Single injection of anti-VEGF Ab (2 doses) +/- recombinant VEGF
- Measured urine Pro/Cr ratios
- Kidney tissue examined for immunohistochemistry & EM

Anti-VEGF antibody induces:

- Dose-dependent Proteinuria
- Swelling and detachment of glomerular endothelial cells
- Some disruption of slit diaphragms
- Downregulation of nephrin (restored with VEGF)

Sugimoto H et al JBC, 2003
• Disruption of glomerular endothelial cells and loss of glycocalyx
• Disruption of slit diaphragms (↓Nephrin)
• Mesangiolysis with fibrin deposition
<table>
<thead>
<tr>
<th>Bevacizumab Trials</th>
<th>Bevacizumab (mg/kg/dose)</th>
<th>Concurrent chemotherapy</th>
<th>Proteinuria</th>
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<tbody>
<tr>
<td></td>
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<td>Control</td>
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<tr>
<td>Kabbinavar et al., 2003 J Clin Onc (Colorectal cancer) N=99</td>
<td>5 10</td>
<td>FU/LV</td>
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<tr>
<td>Yang et al., 2003 NEJM (Renal cancer) N=116</td>
<td>5 10</td>
<td>none</td>
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<tr>
<td>(Renal cancer)</td>
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<tr>
<td>Johnson et al., 2004 J Clin Onc (CLL) N=98</td>
<td>7.5 15</td>
<td>carboplatin paclitxel</td>
<td>2%</td>
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<tr>
<td>(Breast cancer)</td>
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<tr>
<td>Miller et al., 2005 J Clin Onc (NSCLC) N=444</td>
<td>15/3wk</td>
<td>capecitabine</td>
<td>7.4</td>
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<tr>
<td>Hurwitz et al., 2004 NEJM (Colorectal cancer) N=790</td>
<td>5</td>
<td>irinotecan FU/LV</td>
<td>21.7%</td>
</tr>
<tr>
<td>Zhu X. et al AJKD 2007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kabbinavar et al., 2005 J Clin Onc (Colon cancer) N=204</td>
<td>5</td>
<td>FU/LV</td>
<td>23%</td>
</tr>
</tbody>
</table>
# Systematic Review/Metaanalysis of Oncology Trials utilizing Anti-VEGF Ab

## Relative Risk of Proteinuria

### Low Dose Bevacizumab

<table>
<thead>
<tr>
<th>Citation</th>
<th>Effect Name</th>
<th>Year</th>
<th>Treated</th>
<th>Control</th>
<th>Effect</th>
<th>Lower</th>
<th>Upper</th>
<th>NTotal</th>
<th>PValue</th>
<th>RR</th>
<th>95% CI</th>
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<tr>
<td>Hurwitz 2004</td>
<td>low dose proteinuria</td>
<td>2004</td>
<td>104 / 333</td>
<td>86 / 337</td>
<td>1.222</td>
<td>0.952</td>
<td>1.567</td>
<td>790</td>
<td>0.114</td>
<td>1.4</td>
<td>1.1-1.7</td>
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<td>low dose proteinuria</td>
<td>2003</td>
<td>7 / 32</td>
<td>2 / 32</td>
<td>3.500</td>
<td>0.786</td>
<td>15.578</td>
<td>64</td>
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<td>low dose proteinuria</td>
<td>2003</td>
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<td>6.038</td>
<td>70</td>
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<td>20 / 104</td>
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<td>1.239</td>
<td>3.151</td>
<td>204</td>
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<tr>
<td>Yang 2003</td>
<td>low dose proteinuria</td>
<td>2003</td>
<td>15 / 37</td>
<td>15 / 40</td>
<td>1.091</td>
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<td>172 / 597</td>
<td>127 / 608</td>
<td>1.360</td>
<td>1.114</td>
<td>1.660</td>
<td>1205</td>
<td>0.003</td>
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</table>

**RR: 1.4 (95% CI, 1.1-1.7)**

### High Dose Bevacizumab

<table>
<thead>
<tr>
<th>Citation</th>
<th>Effect Name</th>
<th>Year</th>
<th>Treated</th>
<th>Control</th>
<th>Effect</th>
<th>Lower</th>
<th>Upper</th>
<th>NTotal</th>
<th>PValue</th>
<th>RR</th>
<th>95% CI</th>
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<tr>
<td>Johnson 2003</td>
<td>high dose proteinuria</td>
<td>2003</td>
<td>14 / 34</td>
<td>2 / 32</td>
<td>6.588</td>
<td>1.623</td>
<td>26.737</td>
<td>66</td>
<td>0.001</td>
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<tr>
<td>Kabbinavar 2003</td>
<td>high dose proteinuria</td>
<td>2003</td>
<td>8 / 32</td>
<td>4 / 35</td>
<td>2.461</td>
<td>0.839</td>
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<tr>
<td>Miller 2005</td>
<td>high dose proteinuria</td>
<td>2005</td>
<td>51 / 229</td>
<td>16 / 215</td>
<td>2.993</td>
<td>1.762</td>
<td>5.084</td>
<td>444</td>
<td>0.000</td>
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<tr>
<td>Yang 2003</td>
<td>high dose proteinuria</td>
<td>2003</td>
<td>25 / 39</td>
<td>15 / 40</td>
<td>1.708</td>
<td>1.075</td>
<td>2.718</td>
<td>79</td>
<td>0.018</td>
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<tr>
<td>Fixed Combined (4)</td>
<td></td>
<td></td>
<td>99 / 334</td>
<td>37 / 322</td>
<td>2.337</td>
<td>1.692</td>
<td>3.228</td>
<td>656</td>
<td>0.000</td>
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</tbody>
</table>

**RR: 2.3 (95% CI, 1.7-3.2)**

Zhu X. et al AJKD, 2007
Anti-VEGF Nephropathy

• Published cases
  – Thrombotic microangiopathy (n=4)
  – FSGS* (n=2)
  – MPGN (n=)
  – Cryoglobulinemic GN (n=1)
  – Immune complex GN (n=1)
  – Glomerular endotheliosis (n=1)

• Unpublished cases observed at Yale
  – Minimal Change disease (n=1)
  – MPGN (n=1)
  – Glomerular endotheliosis (n=1)

Case 2

- 69 year old male develops AKI in the hospital
- PMH: HTN, hyperlipidemia, CKD (baseline serum Cr=1.6 mg/dl), CVD, PVD, anemia
- Medications: statin, amlodipine, losartan, FeSO4, furosemide, calcitriol,
- Underwent revascularization of right leg (fem-pop bypass), given 1 u pRBCs, 1 L of NS & 1.5 L of Hextend for BP support (OR SBP: mid-90s-120s)
- Examination: BP-122/68  P-105
  - H&N- increased JVP
  - Lungs- basilar crackles
  - Heart- S1S2, + S4, 1/6 SM, no S3 or rub
  - Extremities- trace edema, mild erythema over bypass site
- Oliguria developed over the next 24-48 hrs (resistant to high dose IV furosemide 200 mg)
• **Laboratory Results: (3 days post-op)**
  
  – **Electrolytes:** $\text{Na}^+ = 129 \text{ mEq/L}$, $\text{K}^+ = 5.1 \text{ mEq/L}$, $\text{HCO}_3^- = 18 \text{ mEq/L}$, $\text{Cl}^- = 96 \text{ mEq/L}$
  
  – **BUN** = 69 mg/dl  \hspace{1cm} **Cr** = 4.2 mg/dl
  
  – **Hb** = 9.8 mg/dl \hspace{1cm} **Plt** = 285 x1000/uL
  
  – **Urinalysis:** SG = 1.012, pH = 5.5, Protein-1+, Glucose-negative, Blood-negative, Leukocyte esterase-negative
  
  – **Urine Na**$^+$ = 98 mEq/L, FENa$^+$ = 2.2%

**Urine Sediment**

![Image of Urine Sediment]
Osmotic Nephropathy

Hydroxyethyl starch

IVIG (sucrose)

Courtesy of Mike Kashgarian

Courtesy of Glen Markowitz
Osmotic Nephropathy
Hydroxyethyl Starch

• Hydroxyethyl Starch (HES)
  - Colloid volume expander used in OR & ICU
  - Amylopectin + hydroxyethyl groups in 0.9% saline or LR
  - Characterized by MW & molar substitution
    - MW: on average- 130 to 670 kDa; range 10 to 1,250 kDa
    - Molar substitution: 0.4 to 0.75 (40-75/100 glucose molecules)
    - Hextend (6% HES 670/0.75 in LR), others (6% HES 130/0.4 in NS)

• Pharmacology
  - Administered intravenously
  - Distributed in intravascular space
  - Excreted by the kidneys (40-64% in 24 hours), <1% biliary

• Pathogenesis
  - Reabsorption via pinocytosis, no enzymes to metabolize intracellular substances
  - Accumulation of cellular H₂O due oncotic gradient

Jungheinrich C. Clin Pharmacokin, 2005
Markowitz GS, Perazella MA. Clin Chim Acta, 2006
Osmotic Nephropathy
Hydroxyethyl Starch

• Animal Studies
  – IV sucrose and dextran induce renal injury & histopathologic lesions in a
time course similar to humans with osmotic nephropathy

• Humans
  – First described in renal transplant recipients & brain-dead donors (DGF)
  – HES (vs gelatin, etc) caused ↑ AKI in sepsis & CABG (+/- studies)
  – Demonstrated in many case reports/series
    • Medical, surgical and gynecologic patients in ICUs
  – Yale Nephrology fellows collected 7 patients with AKI from HES (kidney
    biopsy proven, n=3) over 12 month period (7/05-7/06)
    • Risk factors: kidney disease, DM, old age, large HES volumes > 1 liter

• Risk Factors
  - Underlying kidney disease (CKD or AKI)
  - Volume of HES (> 1.0 to 1.5 L)

• Prevention/Treatment
  - Avoid or use low volume in at risk patient, otherwise supportive care,
sometimes dialysis is required

Ebcioğlu Z et al. KI, 2006;
Markowitz GS, Perazella MA. Clin Chim Acta, 2006
Osmotic Nephropathy

Drugs

- Sucrose (IVIG)
- Hydroxyethyl starch
- Dextran
- Mannitol
- High or low osmolar radiocontrast
- Gadolinium contrast?
Case 3

• 57 year old obese female presents with malaise, weakness, frequent “oily” stools for several weeks and AKI (increased serum Cr from baseline)

• PMH: HTN, T2-DM, arthritis, CKD (baseline serum Cr=2.1 mg/dl), GERD, asthma, hypothyroid

• Medications: diltiazem 240 mg qd, singular 10 mg qd, furosemide 40 mg qd, pantoprazole 20 mg qd, colchicine 0.6 mg prn, orlistat 120 mg tid (up from bid), no herbal products, NSAIDs or ascorbic acid

• Examination: BP-130/80 P-86 Afebrile
  – H&N- mild conjunctival pallor, normal JVP
  – Lungs-clear
  – Abdomen- obese
  – Extremities- Trace ankle edema, no rash
• **Laboratory Results:**
  - **Electrolytes:** Na\(^+\)=136 mEq/L, K\(^+\)=4.8 mEq/L, HCO\(_3^-\)=26 mEq/L, Cl\(^-\)=99 mEq/L
  - **BUN=22 mg/dl** Cr=3.8 mg/dl -> 5.8
  - **Hb=10.2 mg/dl** Plt=286 x1000/uL
  - **Urinalysis:** SG=1.016, pH=6.5, Protein-trace, Blood-negative, Glucose-negative, Leukocyte esterase-negative
  - **Urine Na\(^+\)= 65 mEq/L, FENa\(^+\)=2.4%, Pro/Cr ratio=0.45

**Renal Ultrasound**
- 10.4 cm kidneys
- Slight increased echogenicity

**24 hour urine Oxalate**
- 1.64 mmol → 0.12 mmol
- Normal < 0.58 mmol/24 hours)
Crystal Nephropathy
Orlistat- Calcium Oxalate

Courtney et al. NDT, 2007
Singh et al. AJKD, 2006
Orlistat
– Xenical™ 120 mg bid-tid; Alli™ 60 mg bid
– Intestinal lipase inhibitor approved for weight loss
– Induces fat malabsorption

Pathogenesis
– Lessons from Enteric Hyperoxaluria

– Increased urinary oxalate & calcium-oxalate activity (marker for stone formation) in animals

Singh et al. AJKD, 2006; Courtney et al. NDT, 2007
Crystal Nephropathy
Orlistat- Calcium Oxalate

• Humans
  – 2 biopsy-proven cases reported in the literature
  – CKD 2/3, DM, HTN, diuretics, orlistat (120 mg tid)
  – 1 recovered, 1 dialysis dependent

• 3 cases of orlistat-induced kidney disease
  – Observed recently at Yale (10/06-9/07)
  – Crystal nephropathy (n=2) & crystalluria (n=1)
  – CKD stages 3/4, met syndrome, diuretics, orlistat- 120 mg tid
  – AKI reversible in the 2 cases, but CKD slightly worse

• Risk Factors
  – CKD, diuretics, ↑dose of drug (↑fat malabsorption),
  – High oxalate/low calcium diet?

• Prevention/Treatment
  – ↓drug dose, Ca++ supplement?, volume expand, stop drug

Singh et al. AJKD, 2006; Courtney et al. NDT, 2007
CaPhos deposits within cytoplasm & tubular lumina (H & E stain)

CRystal NEPHropathy

Oral sodium phosphate solution

CRYSTAL NEPHROPATHY

- AKI & CKD

RISK FACTORS

- Reduced GFR
- Old Age
- Volume depletion
- ACE I/ARB
- Diuretics
- Slow bowel transit
- Colitis

Markowitz GS et al. JASN, 2005;
Khurana A et al. ASN poster, 2006
Crystal Nephropathy
Ciprofloxacin

CRYSTAL NEPHROPATHY
- AKI
  - 5 cases published
- Crystalluria

RISK FACTORS
- Reduced GFR
- ACE I
- Old Age
- High Dose
- Alkaline Urine (pH > 6.0)

Crystal Nephropathy, Crystalluria and Nephrolithiasis

Drugs

- Acyclovir
- Indinavir
- Triamterene
- Sulfadiazine
- Methotrexate
- IV Vitamin C
- Methoxyflurane
- Ampicillin
- Orlistat
- Ciprofloxacin
- OSPS
Case 4

- 69 year old female presents with fatigue and renal failure
- PMH: HTN, T2 DM, GERD, osteoarthritis, osteoporosis, COPD. Developed severe GERD 6 months prior-initially took tums & OTC cimetidine X 2 months without relief
- Medications: enalapril, amlodipine, glyburide, combivent inhaler, lansoprazole (3 months), calcium tablets, no OTC or herbal products at this time
- No allergies
- Examination: BP-135/82  P-89  T-98.7
  - H&N- pink conjunctiva, normal JVP
  - Lungs- clear
  - Heart- S1S2, no S3, rub or 1/6 systolic ejection murmur
  - Abdomen- benign with normal BS, no flank tenderness
  - Extremities- no edema or rash
• **Laboratory Results:**
  - **Electrolytes:** Na+=132, K+=5.1, HCO₃⁻=18, Cl⁻=104
  - BUN=49 mg/dl  \hspace{1cm} Cr=2.9 mg/dl
  - Hb=11.2 mg/dl  \hspace{1cm} Plt=335 x1000/μL
  - WBCs=12 per mm³  \hspace{1cm} Eosinophils=2%
  - **Urinalysis:** SG-1.015, pH-5.5, Protein-1+, Blood-trace positive, Leukocyte esterase-positive
  - Urine Na⁺=55 mEq/L, FENa⁺=3.2%

**Urine Sediment**
Acute Interstitial Nephritis
lymphocytes, plasma cells, eosinophils
Interstitial edema ± fibrosis, tubulitis

Courtesy of Glen Markowitz
Drug-induced Acute Interstitial Nephritis
Proton Pump Inhibitors (PPIs)

• AIN associated with omeprazole
  – First case of biopsy-proven AIN (confirmed with drug rechallenge) was described with omeprazole in 1992\textsuperscript{1}
  – Subsequent reports of AIN associated with omeprazole (n=29) appeared in the literature over the next 12 years
  – Of these 29 cases, 23 were biopsy-proven AIN

• AIN associated with other PPIs
  – In 2004, first case reports of AIN from other PPIs
  – Lansoprazole (n=2), pantoprazole (n=2), rabeprazole (n=1), esomeprazole (n=1)
  – All biopsy-proven cases
Drug-induced Acute Interstitial Nephritis
Proton Pump Inhibitors (PPIs)

- Retrospective case review (1993-2003) in Australia
  - 18/28 (64%) cases of biopsy proven AIN were associated with PPI use
  - Median age
    • 74 years (65-79)
  - Mean duration of PPI exposure prior to diagnosis:
    • 11 weeks (3-24)
  - Common presenting symptoms:
    • Nonspecific in most, fatigue and nausea (39%), weight loss (22%)
  - Biopsy findings:
    • Classic findings with interstitial eosinophils (83%)

Drug-induced Acute Interstitial Nephritis
Proton Pump Inhibitors (PPIs)

- Retrospective case review (2002-2005) in Auckland, New Zealand
  - 15/87 (7.7%) cases of AIN were associated with PPIs
  - Median age
    - 78 years (55-86)
  - Duration of PPI exposure prior to diagnosis:
    - 10 days - 18 months
  - Common presenting symptoms:
    - Nonspecific in 11, insidious onset of AKI, 4 with “fever/chills”
    - Urine sediment with pyuria (sterile), some hematuria
  - Renal biopsy proven in 12/15

Simpson et al. Nephrology, 2006
Drug-induced Acute Interstitial Nephritis
Proton Pump Inhibitors (PPIs)

• TGA data registry review (1991-2004)
  – 34 cases of “biopsy-proven AIN” associated with PPIs
    • Omeprazole (n=27), pantoprazole (n=2), esomeprazole (n=2), rabeprazole (n=3)
  – 10 cases of “suspected interstitial nephritis”
    • Omeprazole (n=1), pantoprazole (n=3), esomeprazole (n=2), rabeprazole (n=4)
  – 20 cases of “unexplained acute renal failure” associated with PPIs
  – 26 cases of “renal impairment” associated with PPIs

Drug-induced Acute Interstitial Nephritis
Proton Pump Inhibitors (PPIs)

• Centre for Adverse Reactions Monitoring (CARM) data registry review (New Zealand)\(^1\)
  – 110 cases of “drug-induced AIN” noted
    • 35 (32%) due to PPIs, 24 (22%) due to NSAIDs, 25 (23%) due to antibiotics, 6 (5%) due to diuretics

• WHO Collaborating Centre on International Drug Monitoring (Uppsala, Sweden)\(^2\)
  – Databank contains more than 3.7 million spontaneous reports of adverse drug reactions from > 80 countries
  – 150 reports of PPI-associated AIN
    • Omeprazole (n=109), Lansoprazole (n=18), Pantoprazole (n=15), Rabeprazole (n=10), Esomeprazole n=(7)

1. Simpson et al. Nephrology, 2006;
Drug-induced Acute Interstitial Nephritis
Proton Pump Inhibitors (PPIs)

Methicillin*
Other drugs*
PPIs#§

- Hem
- Pyu
- RF
- Pro
- Eos

*Rossert. Kidney Int, 2001; #Geevasinga et al. Clin Gastro Hep, 2006; §Data from other cases
Drug-induced Acute Interstitial Nephritis
Proton Pump Inhibitors (PPIs)

CKD results in many with PPI-induced AIN

Simpson et al. Nephrology, 2006
Drug-induced Acute Interstitial Nephritis

Drugs

- B-Lactams
- Sulfa drugs
- Quinolones
- Anticonvulsants
- H₂ Blockers
- NSAIDs
- Allopurinol
- Rifampin
- Diuretics
- Indinavir
- Atazanavir
- PPIs
Drug-induced Kidney Disease:
Multiple sites along the Nephron

- Glomerulus
- Afferent Arteriole
- Efferent Arteriole
- Loop of Henle
- Thick ascending limb
- Distal convoluted tubule
- Collecting duct
- Collecting System
- Proximal convoluted tubule
- Renal (arcuate & interlobular) Arteries
- Interstitium
Thank You
Drug-induced Glomerular Injury

FSGS
- Pamidronate
- Lithium
- Interferon
- Heroin

Membranous GN
- Gold
- PCN, BCN
- Captopril
- NSAIDs
- COXIBs

Minimal Change
- NSAIDs
- COXIBs
- Lithium
- IFN-α

Thrombotic MA
- Gemcitabine
- Mitomycin C
- CSA, Tacrolimus
- Contraceptives
- Quinine
- IFN-α

Anti-VEGF Rx
- TMA (n=2)
- FSGS* (n=2)
- IC GN (n=1)
- Cryo GN (n=1)
- MCD (n=2)
- GlomEndo (n=2)
- MPGN (n=1)

Izzedine H. et al, AJKD 2007
Why is the Kidney Vulnerable to Nephrotoxins (Drugs)?

• Patient Specific Factors
• Kidney Specific Factors
• Drug Specific Factors
Patient Specific Factors

- True or effective intravascular volume depletion
  - Prerenal azotemia
  - Sluggish urine flow

- Allergic response to certain medications
  - Immune response genes

- Altered pharmacogenetics
  - Renal transporters
    - loss or gain of function mutations
    - altered regulation of the carrier (transport regulating kinases)
  - Cytochrome P450 enzyme gene polymorphisms
    - alter metabolism of drugs

- Age (elderly)
- Sex (female)
- Race

- AKI or CKD
- Nephrotic syndrome
- Cirrhosis
- Obstructive jaundice

- Metabolic perturbations
  - Electrolyte and acid-base disturbances
    - urine pH
    - urine crystal inhibitors
Kidney Specific Factors

High drug delivery:
(RBF = 25% of cardiac output)

High metabolic rates & workload of cells

Cellular uptake of toxin

↑ Local drug concentration in medullary cells/interstitium

2O₂ → H₂O₂ + O₂ → OH•

Renal biotransformation of drugs: ↑ toxic metabolites & reactive intermediates
Insoluble in urine (crystal formation)

↑ Concentration of toxin within cells (transporter competition)

Combination of nephrotoxins

• NSAIDs
• Contrast
• ACE/ARB
• Cisplatin
• Aminoglycosides

Immune effects

• Haptens
• Molecular mimicry
• Ab formation

↑ Renal exposure to drug

• Duration of Rx
• Route of administration

Direct nephrotoxicity

Drug Specific Factors