The Case

51M African American w/ HTN, ESRD (on HD for 13 years) who underwent a DDRTx in June 2015.

Complications: BK viremia with AKI in Jan 2016---MMF held and tacro dose decreased with improvement in creatinine.

In March 2016, found to have AKI on routine follow up. Also an elevated serum BK virus PCR. Admitted for a renal biopsy.

DDx BKVN v. cellular rejection
More history

Surgical hx: AVF

Social hx: denied

Family hx: noncontributory

Meds:
- Coreg 25mg BID
- Pepcid 20 mg BID
- Prednisone 5 mg daily
- Tacrolimus 2 mg in AM, 1 mg in PM
- Calcitriol 0.5 mcg daily
- Bactrim SS q48hr
Physical Exam

T 97.5 F    BP 136/78    HR 63    Weight 96 kilos

General appearance: alert, appears stated age and cooperative
Head: Normocephalic, without obvious abnormality, atraumatic
Lungs: clear to auscultation bilaterally
Heart: regular rate and rhythm, S1, S2 normal, no murmur, click, rub or gallop
Extremities: extremities normal, atraumatic, no cyanosis or edema
Skin: Skin color, texture, turgor normal. No rashes or lesions
Left forearm AVF-tense, not easily compressible with hypopigmentation on venous and arterial sites
## Labs

### ON ADMISSION:
- **NA**: 139
- **K**: 4.1
- **CL**: 102
- **CO2**: 27
- **BUN**: 38
- **CRE**: 2.4
- **GLU**: 206
- **WBC**: 3.6
- **Hgb**: 11.3
- **Hct**: 33.9
- **Plt**: 94

### Previous labs

<table>
<thead>
<tr>
<th>Date</th>
<th>creat</th>
<th>tacro</th>
<th>BK</th>
</tr>
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<td>12/8/15</td>
<td>2.7</td>
<td>14.9</td>
<td>neg</td>
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<td>2.1</td>
<td>9.9</td>
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<tr>
<td>1/7/16</td>
<td>2.8</td>
<td>7.9</td>
<td>6k</td>
</tr>
<tr>
<td>1/16/16</td>
<td>2.3</td>
<td>7.9</td>
<td>6.6k</td>
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<td>3/28/16</td>
<td>2.8</td>
<td>7.2</td>
<td>10.2k</td>
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<tr>
<td>4/1/16</td>
<td>2.4</td>
<td>6.2</td>
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</table>

UA no protein, no blood, RBC 2, WBC 5, small LE
Biopsy Results

Biopsy 4/4/16 (2 cores, 8 glomeruli)

- DIFFUSE MILD INTERSTITIAL EDEMA, MODERATE TO SEVERE INTERSTITIAL PLEOMORPHIC INFLAMMATORY CELL INFILTRATE ASSOCIATED TUBULITIS

- POSITIVE SV40 STAIN FOR POLYOMA VIRUS

- NEGATIVE C4D STAIN IN PERITUBULAR CAPILLARY

- GLOBAL GLOMERULOSCLEROSIS, 1/8

(g0, cg0, mm0, t2, ct0, i3, ci1, v0, cv1, ah0, ptc0, c4d0).
Management

Re-admitted 4/6/16 for treatment of BKVN with concurrent ACR.

Received IVIG 70g and solumedrol 500 mg the first night.

The next morning he got 70g IVIG and 250 mg of solumedrol.

And was discharged with a prednisone taper.
BK Virus Nephropathy
Introduction

BK Virus (BKV)

- B.K. underwent a renal transplant in ~1971, which was complicated by ureteral obstruction. Electron microscopy revealed viral particles lining the ureter. He also had high antibody titers to the virus. This virus was classified as a member of the polyomavirus family.

BKV

Polyoma virus family, includes JC virus and SV40.
- Double stranded circular DNA
- Codes for 6 proteins (reference 1-3)
  - agnoprotein-->assembly
  - 3 viral capsid proteins (VP1 through 3)
  - 2 enzymatic proteins (large tumor antigen “T” and small tumor antigen “t”)-->gives it immortality

Childhood infection (by age ~20, 80% are seropositive)
Latent until an immunosuppressed state occurs.

BKV renal disease (BKVN or PVAN)

In 1999, it was described as a cause of interstitial nephritis in renal transplant patients. More than half of those affected had significant graft dysfunction, including premature graft loss. Biopsy manifestations included focal areas of

- mononuclear interstitial infiltrates
- Tubulitis
- Tubular atrophy/fibrosis

Ischemic injury to the kidney increases replication of polyoma virus in a mouse model. This occurred in the absence of immunosuppression. (1)

Replication within epithelial cells leads to eventual cell lysis.

The rate of BKVN is believed to be low in the non-renal solid organ transplant (NRSOT) population. (2) There are numerous studies demonstrating BK viruria and BK viremia. Frequently AKI is attributed to calcineurin toxicity (treated with reduction in immunosuppression. Most studies do not have a protocol for follow up. (3)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Decoy cells (%)</th>
<th>BK viruria (%)</th>
<th>BKV (%)</th>
<th>BKNV (%)</th>
<th>Graft loss due to BK (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirsch et al. [8]</td>
<td>29</td>
<td>a</td>
<td>13</td>
<td>6.4</td>
<td>0</td>
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<tr>
<td>Brennan et al. [9]</td>
<td>35</td>
<td>11.5</td>
<td>a</td>
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<tr>
<td>Koukoulaki et al.</td>
<td>25</td>
<td>14</td>
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<td>Almeras et al. [11]</td>
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<td>11</td>
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<td>Thakur et al. [12]</td>
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<td>43</td>
<td>8</td>
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<td>Sood et al. [13]</td>
<td>17</td>
<td>27</td>
<td>2.1</td>
<td>0</td>
<td>a</td>
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<tr>
<td>Hirsch et al. [14]</td>
<td>25.4</td>
<td>13.7</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
</tbody>
</table>

*a* Prevalence of event not reported.
Biopsy

Diagnosis requires
- Findings on kidney biopsy
- Serum BK PCR

What are the possible findings
- Intranuclear viral inclusions-SV40 positive stain (antibody to large T protein)- pathognomonic
- Interstitial WBC infiltration with focal areas of tubular damage
- Tubulitis (also seen in rejection)

Active inflammation and fibrosis are important for determining prognosis of the graft.

A, Transitional epithelium with scattered cells showing PV cytopathic effect (basophilic intranuclear inclusions).

B, SV40 stain highlights scattered intranuclear viral inclusions.

## BK virus infection: an update on diagnosis and treatment

### Table 4.
Summary of BK histology grading systems

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage/Class A</td>
<td>- Any degree of viral infection/cytopathic changes</td>
<td>- Viral infection/cytopathic changes &lt;10%</td>
<td>- Viral infection/cytopathic changes &lt;25%</td>
<td>- Viral Infection detected</td>
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<td>- Any degree of tubular injury</td>
<td>- Interstitial inflammation &lt;10%</td>
<td>- Interstitial inflammation &lt;10%</td>
<td>- Minimal tubular epithelial cell lysis</td>
</tr>
<tr>
<td></td>
<td>- No inflammation</td>
<td>- Tubular atrophy &lt;25%</td>
<td>- Tubular atrophy &lt;10%</td>
<td>- No acute tubular necrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Fibrosis &lt;25%</td>
<td>- Interstitial fibrosis &lt;10%</td>
<td>- Chronicity score &lt; cl3 and &lt;ct3</td>
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<tr>
<td>Stage/Class B</td>
<td>- Any degree of viral infection/cytopathic changes</td>
<td>- Viral infection/cytopathic changes &lt;10-&gt;50%</td>
<td>- Viral infection/cytopathic changes 11-50%</td>
<td>- Viral replication in cortex or medulla</td>
</tr>
<tr>
<td></td>
<td>- Any degree of tubular injury</td>
<td>- Interstitial inflammation 26-&gt;50%</td>
<td>- Interstitial inflammation 11-50% (B1 11-25%, B2 26-50% and B3 &gt;50%)</td>
<td>- Tubular epithelial cell lysis</td>
</tr>
<tr>
<td></td>
<td>- Inflammation &lt;25-&gt;50%</td>
<td>- Tubular atrophy &lt;25%</td>
<td>- Tubular atrophy &lt;50%</td>
<td>- Tubular acute tubular necrosis</td>
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<td>Stage/Class C</td>
<td>- Any degree of viral infection/cytopathic changes</td>
<td>- Viral infection/cytopathic changes &lt;10-&gt;50%</td>
<td>- Variable viral infection/cytopathic changes</td>
<td>- Chronicity score &lt; cl3 and &lt;ct3</td>
</tr>
<tr>
<td></td>
<td>- Any degree of tubular injury</td>
<td>- Interstitial inflammation &lt;10-&gt;50%</td>
<td>- Variable inflammation</td>
<td>- Viral replication in cortex or medulla</td>
</tr>
<tr>
<td></td>
<td>- Tubular atrophy &gt;50%</td>
<td>- Tubular atrophy &gt;50%</td>
<td>- Tubular atrophy &gt;50%</td>
<td>- Chronicity score = cl3 and ct3</td>
</tr>
<tr>
<td></td>
<td>- Interstitial fibrosis &gt;50%</td>
<td>- Interstitial fibrosis &gt;50%</td>
<td>- Interstitial fibrosis &gt;50%</td>
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</tbody>
</table>

Screening

Urine

- BK virus PCR can be used as a tool for screening due to high sensitivity but poor specificity. Up to 30% of transplant patients have BKV shedding with no significance
- Decoy cells (tubular epithelial cells with large, basophilic nuclei with viral inclusions (but poor sensitivity)
- mRNA (BK VP1)...studies are underway

Serum

- BK virus PCR has high sensitivity and specificity

Tissue

- Renal biopsy-gold standard for diagnosis. Not a good screening test, unless there is a system setup for protocol biopsies.

# BK virus infection: an update on diagnosis and treatment

## Table 3.
Summary of BKV screening methods

<table>
<thead>
<tr>
<th>Screening method</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<tbody>
<tr>
<td>Decoy cells</td>
<td>29</td>
<td>100</td>
<td>25</td>
<td>84</td>
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<tr>
<td>Haufen</td>
<td>97</td>
<td>100</td>
<td>100</td>
<td>99</td>
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<tr>
<td>BK urine PCR</td>
<td>40</td>
<td>100</td>
<td>100</td>
<td>78</td>
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<tr>
<td>BK serum PCR</td>
<td>50–60</td>
<td>100</td>
<td>100</td>
<td>88</td>
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</table>
Immune response to BKV

Cellular immunity (CD4 and CD8 T cells) is directed against both nonstructural (“T” and “t” antigens) and capsid proteins (VP1 through 3). The development of anti-BK T cells is related to clearance of BK viremia.

Reduction of total immunosuppression is the first step. This has been demonstrated in numerous observational studies (number of patients ranged from 5 to 38)

- Stopping the anti-metabolite (MMF)
- Reducing the dose of the calcineurin and reducing the target trough level
- Other medical therapy

Cidofovir

Leflunomide
● Malononitrileamide. Approved for RA. Active metabolite inhibits protein kinase activity and pyrimidine synthesis. Immunosuppression was also reduced. Toxicity: liver and bone marrow.

IVIG
● BKV neutralizing antibodies. Infusion reactions can be pre-treated.

Fluoroquinolones
● Have an effect on the helicase (unpack genome) activity of the large T antigen. May be efficacious for prophylaxis.

BKVN and acute rejection can occur simultaneously. But the findings overlap. BKVN effects the tubules and interstitium. If the arteries or glomeruli are involved then rejection is present. It is also possible that a rejection directed against the tubules (Banff type 1A/1B) can be mistaken for BKVN.

NIH clinical trials

- NCT 01789203 is a randomized, placebo controlled trial of ciprofloxacin for the prevention of BKV or BKVN. (currently recruiting)
- NCT 01649609 is a randomized trial comparing the efficacy of reduction of immunosuppression versus substitution of tacrolimus for sirolimus for the treatment of BKV or BKVN. (active)
- NCT 01620268 is an open label trial using a combination of leflunomide and orotic acid in patients with high levels of BK viruria. (recruiting)
- NCT 01624948, patients with BKV will be randomized to either 50% mycophenolate dose reduction or substitution of MMF with everolimus. (completed)
- AND MANY OTHERS...
The End!
