# BK Nephropathy

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# Case Discussion

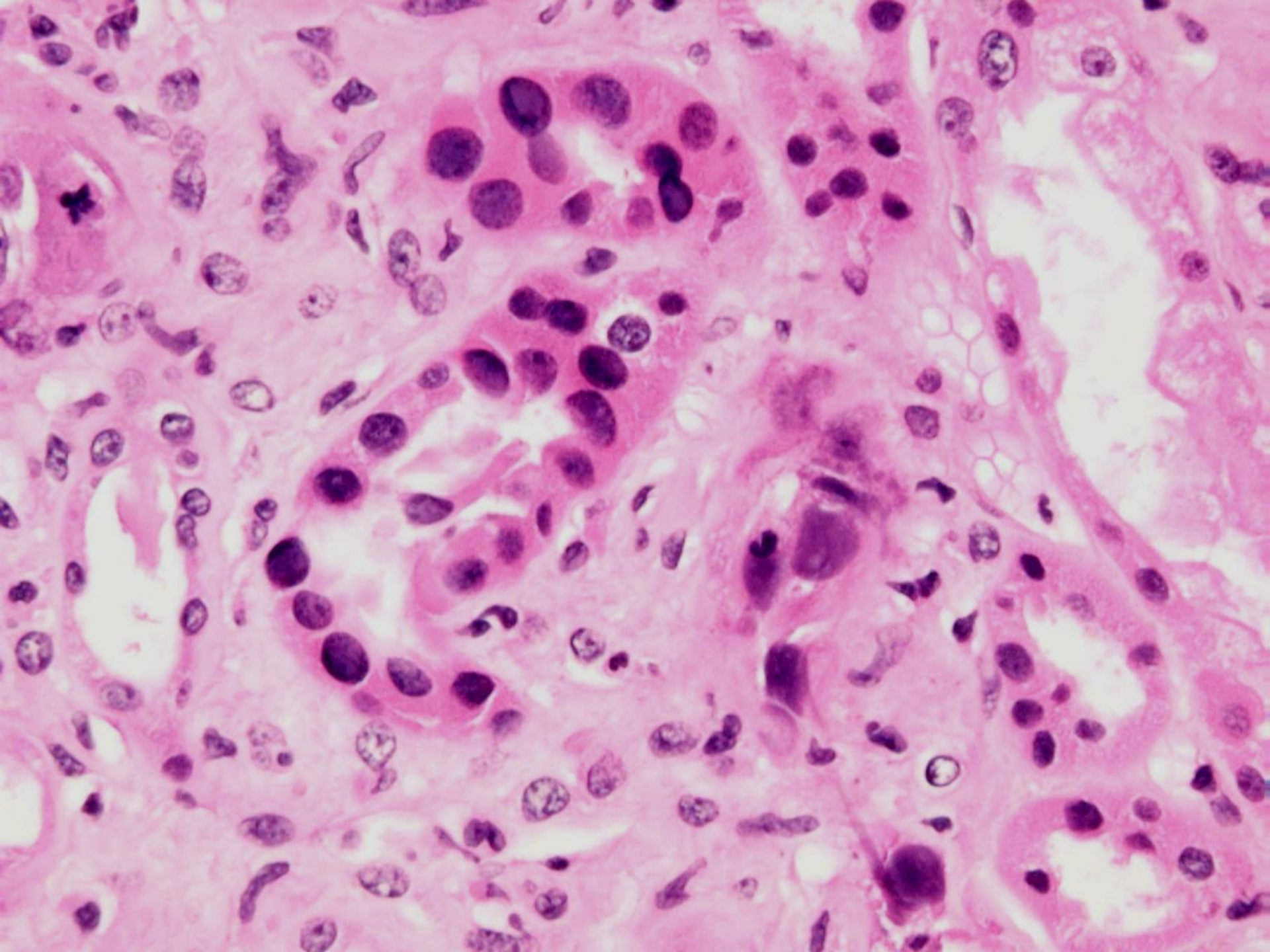
- 62 year old African American male; blood group A and PRA 0%
- ESRD-etiology is not clear-was on peritoneal dialysis since June 2007
- History of prostate cancer-diagnosed in 2007
- Listed for a kidney transplant since May 2006

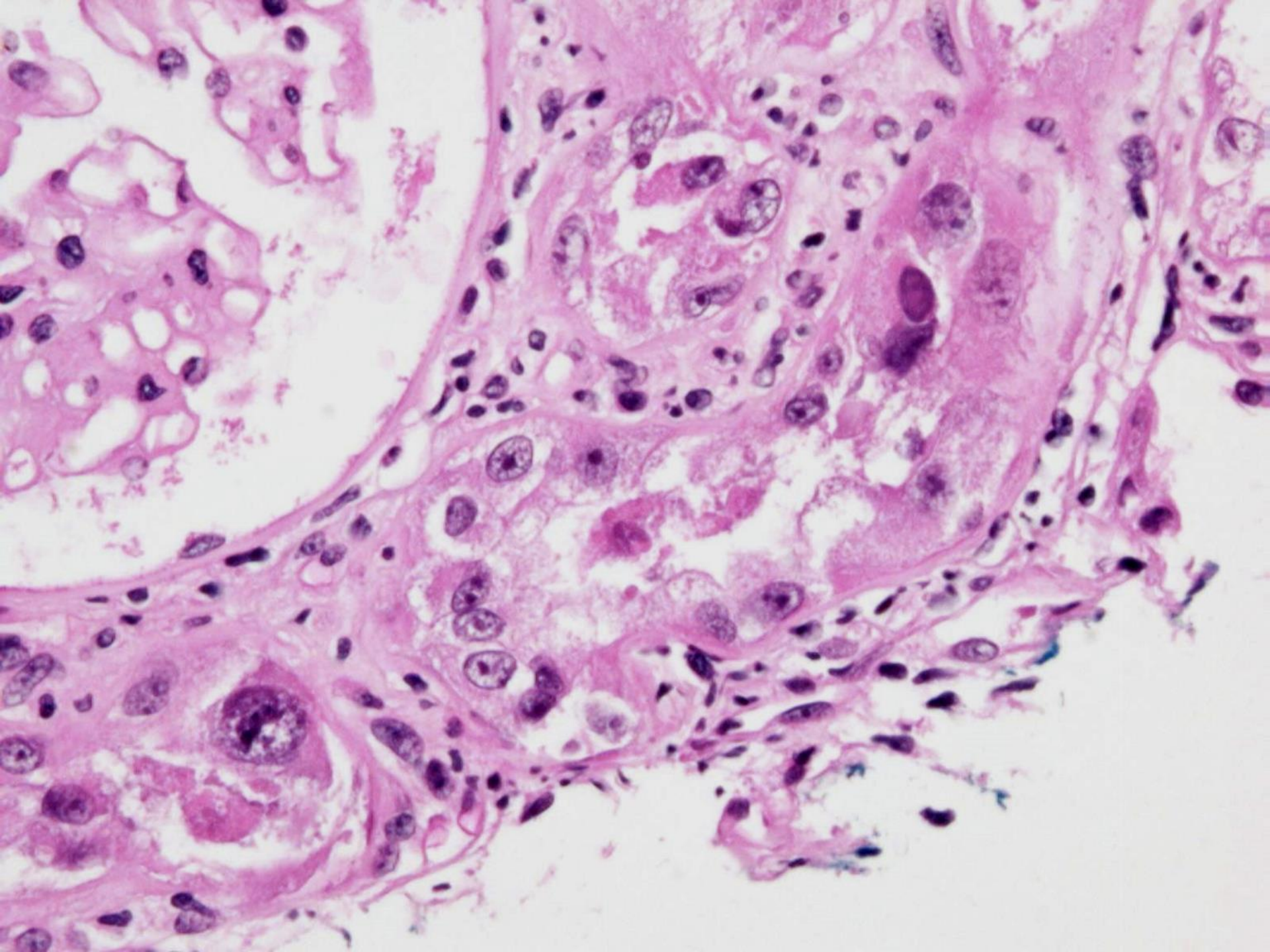
# Case Discussion

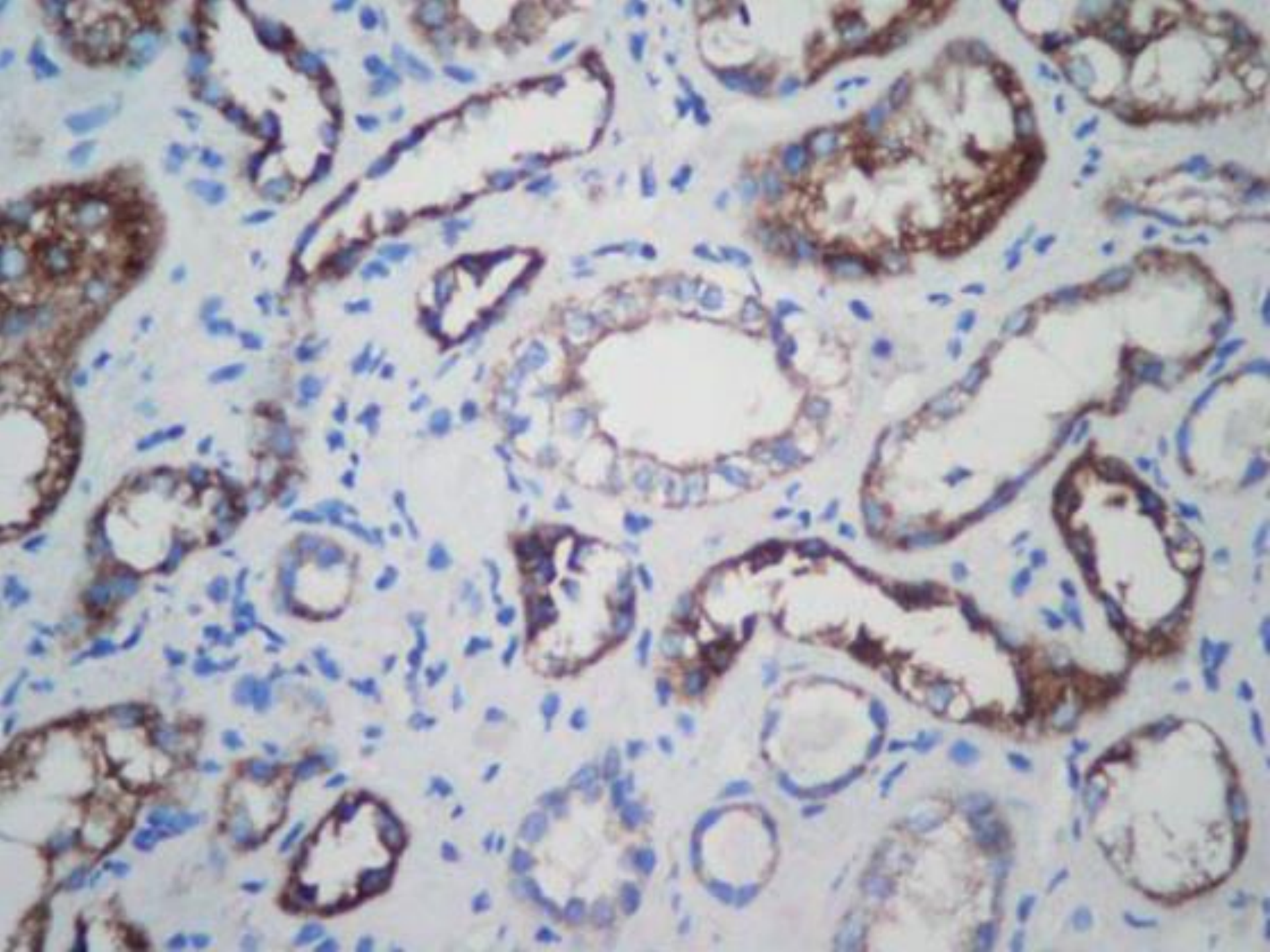
- DD kidney transplant-DCD kidney-on 4/11/2010
- Delayed graft function-continued dialysis for 2 weeks
- Induction with rATG (3 doses)
- Maintenance with tacrolimus + mycophenolic acid + prednisone

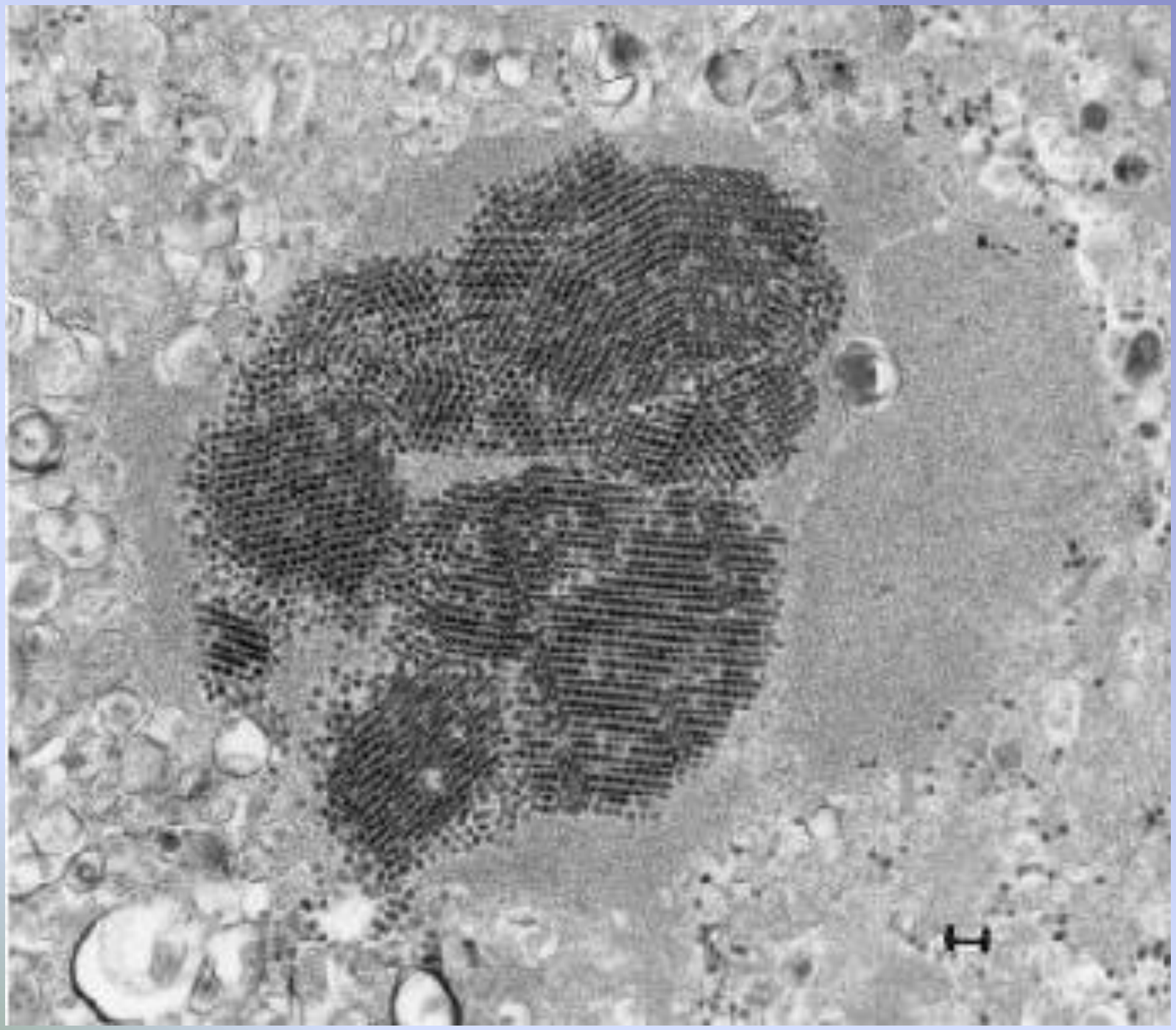
# Case Discussion

- Scr is down to 1.86 mg/dl at 4 weeks posttransplant
- Scr is up to 2.7 mg/dl 11 weeks posttransplant
- Blood BK viral load 4.3 log at the time of the biopsy-increased to 5.6 log 4 weeks later









# Case Discussion

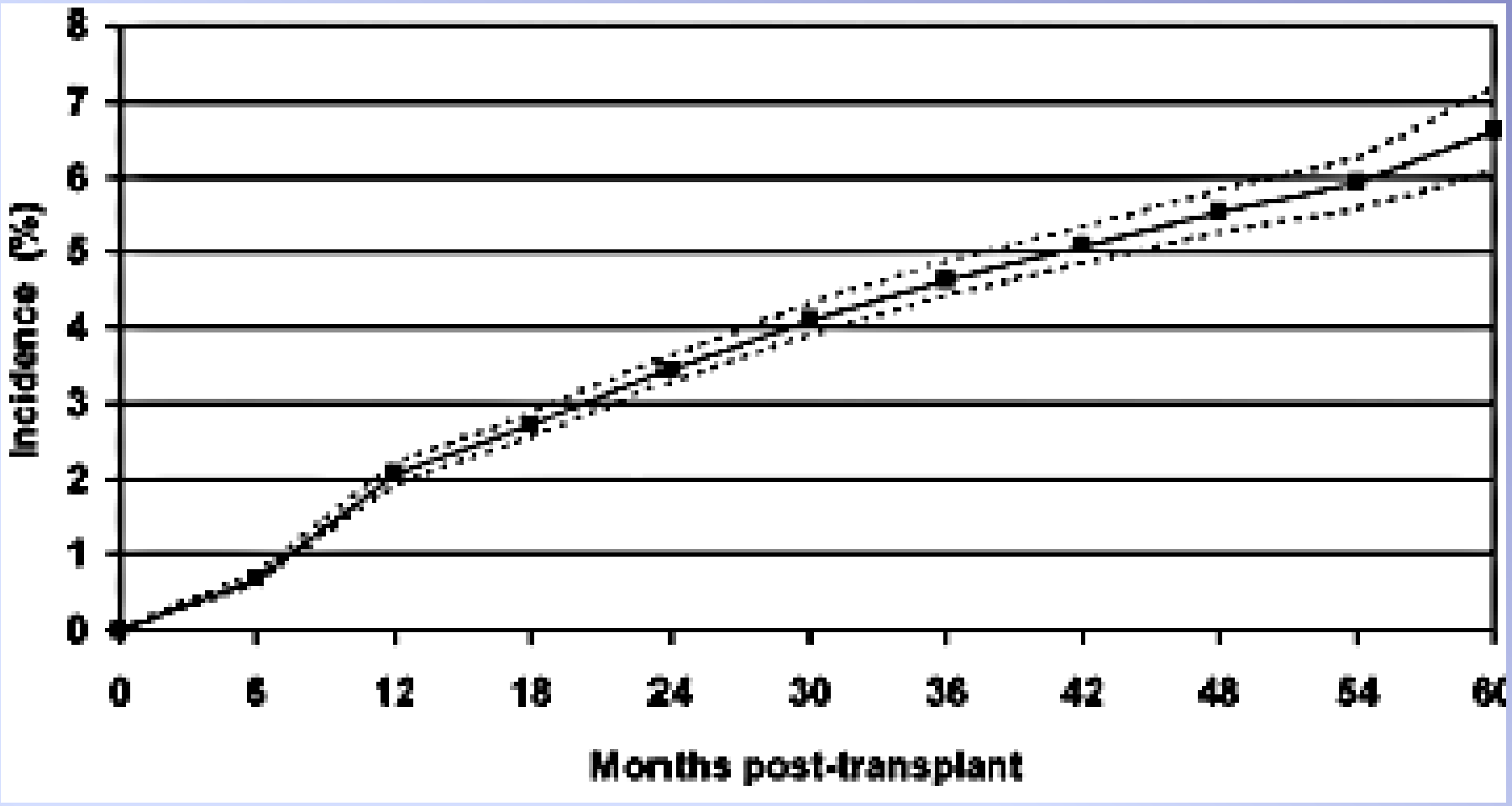
- Path: consistent with BK nephropathy
  - Viral cytopathic effect-**intranuclear inclusion bodies**
  - Degenerative **tubular epithelial changes** with sloughing and cellular and granular casts
  - Variable **interstitial nephritis**

# BK Virus

- 1971: described by Gardner SD and colleagues in Lancet: “isolated from urine after renal transplantation”-named BK virus (the initials of the patient who had ***ureteric stenosis***)
- 1983: first report on ***tubulointerstitial nephritis*** (6 year old boy with primary immune deficiency)
- Not truly appreciated until mid 1990’s

*Gardner SD, et al. Lancet 1971*

*Rosen S, et al. NEJM 1983*




Kaplan-Meier estimated incidence of treatment of BK virus , 2003 to 2006 OPTN database (n=48,292): 0.7% at 6 months posttransplant; 2.18% at 1 year, 3.45% at 2 years, and 6.6% at 5 years

Higher center volume and living kidney donation: protective; more BK in more recent transplant years

*Dharnidharka VR, et al. Transplantation 2009*

# BK Virus

- Belongs to a family of DNA viruses called polyomaviruses-originally Papovavirus-(includes JC virus, KI, WU and MC viruses)
- Reported in 10-60% of kidney transplant recipients→BK nephropathy in 1-5% of patients→ graft loss in up to 60% of patients

# BK Virus

- Primary Infection:
  - Childhood nonspecific viral illness-respiratory
- Long-lived latency in uroepithelium and renal tubular cells (not in reticuloendothelial cells-like herpes viruses)
- Antibodies against BKV: 50% of children by age 3, 60-90% by age 10, and 80-90% by age 20
- Reactivation in immunocompromised individuals

# Linear Progression of Disease

- Asymptomatic **viruria**→ **viremia**→ parenchymal damage → progressive deterioration of graft function (**BK nephropathy**), hemorrhagic cystitis, ureteral ulceration/stenosis, and progressive multifocal leukoencephalopathy (PML)

# BK Virus-Donors

- Pretransplant samples from donor and recipients
- 54/81 adult kidney donors (67%): seropositive for BK virus
- BKV infection developed in 25 (46%) of 54 recipients who received kidneys from seropositive donors compared to 4 (15%) of 27 recipients who received kidneys from seronegative donors

*Bohl Dl, et al. Am J Transplant 2005*

# BK Virus-Donors

- BK viruria in recipients from seropositive donors occurred earlier (median onset: 45 days vs. 370 days, $p < 0.001$) with longer durations (median duration: 157 vs. 7 days, $p = 0.009$) and higher peak urine titers
- Donor seropositivity: associated with a significantly elevated odds ratio of 3.1
- Early BKV infection in kidney transplant recipients is usually of donor origin
- Testing for BK virus serostatus is neither routine, not mandated at this time

*Bohl Dl, et al. Am J Transplant 2005*

# Risks for BK Nephropathy

- Degree of overall immunosuppression
- Prior treatment for acute rejection, especially treatment with pulse steroids or lymphocyte-depleting agents
- Donor seropositivity; seronegative recipients
- Male Sex; older age; deceased donor
- Degree of HLA mismatch and prolonged cold ischemia time
- Ureteral stent placement (four-fold increase)
- Renal injury (I.e. immune injury-rejection, proinflammatory cytokines, ischemia-reperfusion injury)

*Fishman JA. Am J Transplant 2003*

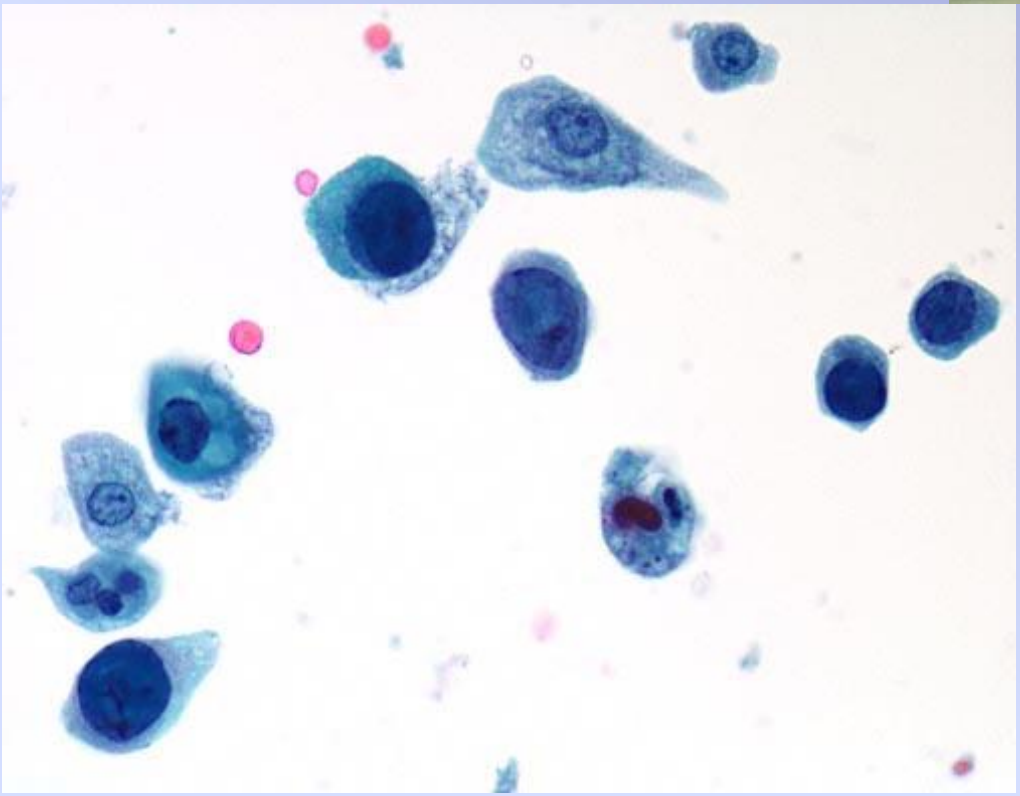
*Matlosz B, et al. Transplant Proc 2005*

*Burgos D. Transplant Proc 2006*

# Diagnostic Testing

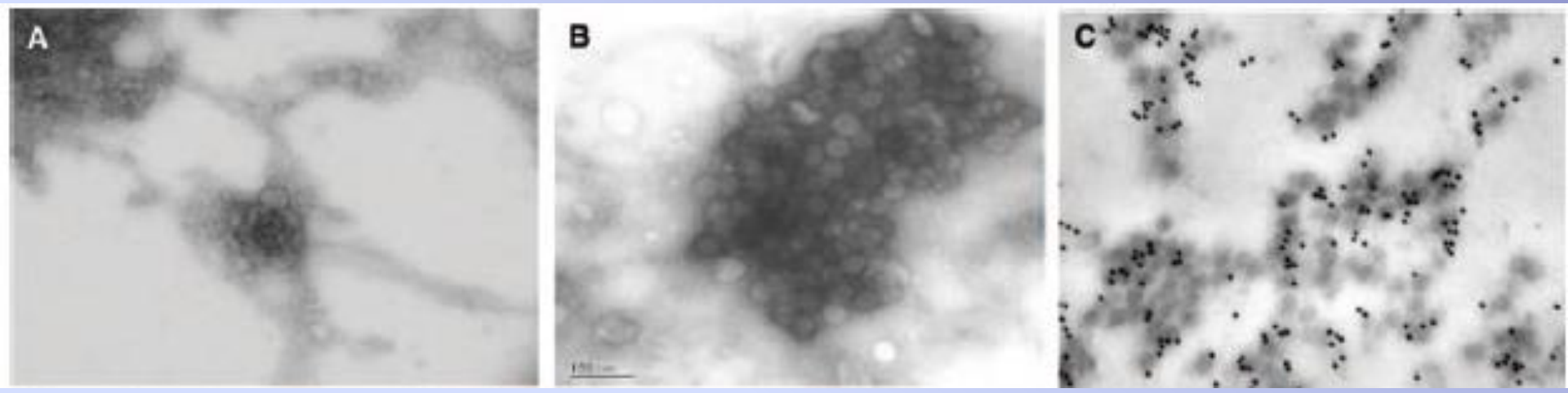
- **Urine:**
  - Decoy Cells
  - DNA PCR
  - EM-Haufen
  - Urinary cytokines: IL-3 and IL-6 (Opelz et al)
  - Urinary cell mRNA profiles (Suthanthiran et al)
- **Blood**
  - DNA PCR (Quant); PPV ~60% (plasma BK level >10,000 copies/ml-associated with 93% specificity for presence of BK nephropathy- *Hirsch HH, et al. 2006*)
- **Renal biopsy:** gold standard

# Urine “Decoy cells” (intranuclear viral inclusions in tubular epithelial cells)



•May be mistaken for degenerative or tumor cells

# Haufen: Cast-like, Three-dimensional Polyomavirus Aggregates in the Urine




- Negative-staining electron microscopy: 194 urine samples from 139 controls (negative) and 143 samples from 21 patients (all positive) with BK nephropathy
- Detection of Haufen (cluster or stack in German) in the urine correlated tightly with biopsy confirmed BK (concordance rate 99%)

*Singh HK, et al. JASN 2009*

# Haufen: Cast-like, Three-dimensional Polyomavirus Aggregates in the Urine

- Densely arranged viral aggregates
- Haufen-positive urine sample: multiple small and large polyoma virus aggregates with significant Tamm-Horsfall protein content
- Comes from the injured renal tubular segments/out of the affected nephrons
- 100% sensitive and 99% specific for identifying biopsy-proven BK nephropathy
- Biomarker for intrarenal BK virus infection-noninvasive; not recommended as a mass screening tool at this time

*Singh HK, et al. JASN 2009*

**Table 1. Diagnostic Testing for BK Virus Nephropathy**

| Test | Threshold Value | Correlation With PVAN on Biopsy |
|---|---|---|
| Decoy cells | >10 cells/cytospin | + |
| Urine BK virus DNA quantitative PCR | $>1 \times 10^7$ copies/mL | ++ |
| Blood/plasma BK virus DNA quantitative PCR | $>1 \times 10^4$ copies/mL | +++ |

Abbreviations: PCR, polymerase chain reaction; PVAN, polyomavirus-associated nephropathy.

| | **Sensitivity** | **Specificity** | **PPV** |
|---|---|---|---|
| **Decoy Cells (>10/cytospin)** | 25% | 84% | 5-20% |
| **Viruria (>$10^7$ copies/ml)** | 100% | 92% | 31% |
| **Viremia (>$10^4$ copies/ml)** | 100% | 96% | 50-60% |

*Wiseman AC. Am J Kid Dis 2009*
*Viscount HB, et al. Transplantation 2007*

# BK Virus Testing

- Viremia detection by molecular PCR amplification is associated with higher PPV and NPV for BK nephropathy than viruria by decoy cells or PCR
- **Same laboratory and same assay-different primers and assay techniques**
- A negative biopsy does NOT rule out BK nephropathy due to the possibility of sampling error and the focal nature of the infection (sensitivity is not 100%)
- Biopsy: viremia is accompanied by elevation in serum creatinine or high-level viremia despite reduction of immunosuppression

# HUP DATA

- Since January 2008, kidney transplant patients at our institution have been prospectively screened by quantitative BK blood PCR (at 3, 6, and 12 months then yearly)
- Detectable BK viremia was defined as ≥2.6 log copies/mL
- Retrospective analysis was performed for any patient transplanted between January 2008-December 2011 who had ≥1 BK viral load drawn until June 2012 at a protocol time-point

*Trofe J et al, Abstract (Poster) ATC 2013*

# HUP DATA

- **Results:** 622/691 (90%) patients had BK screening with ≥ 1 value by protocol; at least 1 BK viral load ≥ 2.6 log copies/mL occurred in 106 (17%) patients
- BK viral load ≥ 2.6 log copies/mL were most often detected at the 3 months screen

*Trofe J et al, Abstract (Poster) ATC 2013*

# Time of First BKV Detection ≥ 2.6 log copies/mL at Protocol Time-Point

| | |
|---|---|
| **3 months** | 51 (48%) |
| **6 months** | 34 (32%) |
| **12 months** | 18 (17%) |
| **24 months** | 1 (0.9%) |
| **36 months** | 2 (2%) |
| **48 months** | None |

- New onset BK viremia at ≥ 24 months was rare, questioning the utility of protocol screening beyond 12-24 months unless renal dysfunction is present

*Trofe J et al, Abstract (Poster) ATC 2013*

# Screening and Diagnostic Testing for BK

- Blood and/or urine samples **every 3 months for the first 12 months**, then **once a year** and in the event of **allograft dysfunction**
- New onset BK viremia after 24 months posttransplant is rare

# Screening and Diagnostic Testing for BK

- AST Infectious Disease Community of Practice guidelines and KDIGO guidelines: earlier (**starting at 1 month posttransplant**) and more frequent screening (**monthly** plasma screening for the **first 6 months**, then **every 3 months** until **2 years** posttransplant)-may be more appropriate in high incidence transplant centers

*Hirsch HH, et al. Am J Transplant 2013*
*Kasiske BL, et al. Kidney Int 2010*

# Treatment of BK Nephropathy

- Cidofovir, leflunomide, quinolones, and intravenous immunoglobulin: no randomized prospective clinical trial
- Careful reduction of immunosuppression and close follow-up for development of acute rejection- remains the cornerstone
- **No specific antiviral drug treatment**

# Treatment of BK Nephropathy

- Multicenter prospective studies are needed:
  - Stratifying histologic grading and renal function
  - Use of viral load or other techniques for diagnosis
  - Evaluation of different treatment strategies: assessing the possibility of chronic allograft dysfunction due to systematic reduction of immunosuppression
  - Longer follow-up

# Re-transplantation

- Possible despite persistent/increased risks
  - The short-term graft and patient survival with re-transplantation after BK appears to be excellent
  - Longer-term outcomes remain unknown

*Dhamidharka VR, et al. Am J Transplant 2010*

- Not enough data to recommend nephrectomy of failed allograft prior to re-transplantation
  - **Nephrectomy is not necessarily protective**
- Pre-transplant clearance of viremia is necessary

# Recent Articles

## Polyomavirus BK Replication in *De Novo* Kidney Transplant Patients Receiving Tacrolimus or Cyclosporine: A Prospective, Randomized, Multicenter Study

- DIRECT study: a prospective 6-month, open-label multicenter study; with a follow-up visit at month 12; randomizing *de novo* KT patients to CsA or Tac between 2003-2005
- Tac dosing was based on C0 targets: 10–15 ng/mL during months 1–3 and 5–10 ng/mL during months 4–6

*Hirsch HH, et al. Am J Transplant 2013*

# Polyomavirus BK Replication in *De Novo* Kidney Transplant Patients Receiving Tacrolimus or Cyclosporine: A Prospective, Randomized, Multicenter Study

- Univariate analysis: CsA-MPA with lower rates of viremia than Tac-MPA at month 6 (10.6% vs. 16.3%, p = 0.048) and 12 (4.8% vs. 12.1%, p = 0.004) and lower plasma BKV loads at month 12 (3.9 vs. 5.1 $\log_{10}$ copies/mL; p = 0.028)
- Multivariate models: CsA-MPA with less viremia than Tac-MPA at month 6 and month 12
- Viremia at month 6 was also independently associated with higher steroid exposure until month 3 (OR 1.19 per 1 g), and with male gender (OR 2.49) and recipient age (OR 1.14 per 10 years) at month 12

*Hirsch HH, et al. Am J Transplant 2013*

# Polyomavirus BK Replication in *De Novo* Kidney Transplant Patients Receiving Tacrolimus or Cyclosporine: A Prospective, Randomized, Multicenter Study

- At baseline, BK viruria was detected in 19 (5.0%) of 378 patients with residual urine production: none of these developed viremia, and only 8 remained viruric posttransplant : less than 5 $\log_{10}$ copies/mL
- Baseline BK viremia was found in 3 (0.5%) of 609 patients, but none had detectable viruria or viremia posttransplant
- The highest rates of viruria and **viremia** were observed at month 6 (25.4% and **13.7%**, respectively) which then decreased at month 12 (20.3% and **8.6%**, respectively)

*Hirsch HH, et al. Am J Transplant 2013*

# Recent Articles

- Lower prevalence of BK virus infection in African American renal transplant recipients: a prospective study (23% vs 47%) *Sood P, et al. Transplantation 2012*
- Ciprofloxacin Prophylaxis (250 mg twice daily for 30 days) in Kidney Transplant Recipients Reduces BK Virus Infection at 3 Months But Not at 1 Year

  *Wojciechowski D, et al. Transplantation 2012*
- Factors influencing viral clearing and renal function during polyomavirus BK-associated nephropathy after renal transplantation: peak viral load, tacrolimus treatment, delayed diagnosis, and viral reduction time influence outcomes in patients with BKVN

  *Schwarz A, et al. Transplantation 2012*

# The Banff 2009 Working Proposal for Polyomavirus Nephropathy: A Critical Evaluation of Its Utility as a Determinant of Clinical Outcome

**Table 1:** Salient features of histologic grading systems applied to study patients

| | Banff working proposal[1] | University of Maryland[3] | American Society of Transplantation[3] |
|---|---|---|---|
| Class A | Variable number of virus infected cells with no or minimal injury to tubular epithelial cells. | Variable number of virus infected cells with any degree of tubular injury but no or negligible inflammation | Virus infection and cytopathic effect in <25% of biopsy, with no/negligible inflammation specified to be <10% of tissue |
| Class B | Tubular epithelial cell necrosis or lysis with denudation of basement membrane across a length of more than 2 cells[2] | Variable number of virus infected cells with any degree of tubular injury and significant inflammation affecting less than 25% (pattern B1), 25–50% (pattern B2) or >50% (pattern B3) of the core biopsy | Essentially similar to University of Maryland, except that B1, B2 B3 are assigned progressively increasing degrees of cytopathic effect, atrophy and fibrosis |
| Class C | Any degree of tubular injury with interstitial fibrosis affecting >50% of cortex | Variable number of infected cells with any degree of tubular injury and tubular atrophy/fibrosis affecting >50% of core biopsy | Same as University of Maryland System |

*Masutani K, et al. Am J Transplant 2012*

# The Banff 2009 Working Proposal for Polyomavirus Nephropathy: A Critical Evaluation of Its Utility as a Determinant of Clinical Outcome

- Data suggesting that inflammation and fibrosis are important prognostic parameters in determining the outcome of BKVN, whereas BKV induced tubular injury and histologic viral load are not informative.
- The Banff Working Proposal 2009 needs to be modified to incorporate the degree of inflammation into the morphologic criteria used for staging this disease.

*Masutani K, et al. Am J Transplant 2012*

# Ongoing Studies

- Quinolone Prophylaxis for the Prevention of BK Virus Infection in Kidney Transplantation: A Pilot Study: randomized, placebo-controlled: levofloxacin use for 3 months-500 mg daily: BK viruria-Canada
- Safety and Efficacy of Mycophenolic Acid Withdrawal With Conversion to Zortress (Everolimus) in Renal Transplant Recipients With BK Virus Infection: randomized, open-label-UCSF
- Using mTOR Inhibitors in the Prevention of BK Nephropathy: randomized, open-label, low dose TAC and MPA vs rapamycin and MPA: Columbia University

# Follow-up

- Reduction of immunosuppression: mycophenolic acid was stopped; tacrolimus dose was reduced to a target level of 3-4
- BK viral load continued to be high: switched to cyclosporine-currently on cyclosporine (last level 56) and prednisone (5 mg daily)
- Last BK viral load in July 2013 (over 3 years posttransplant): 2.6 log copies/ml and scr 1.8 mg/dl; HLA antibodies are negative

# Summary

- Outcome of established BK Nephropathy = NOT GOOD
- No direct immunoprophylactic strategy/drug
- No vaccine against BK virus
- Screening is very important
  - Blood BK viral load
- Immunosuppression reduction: patients should be monitored with a serum creatinine checked every 1-2 weeks and BK viral load repeated at 2-4 week intervals
- Studies needed