BK Nephropathy

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Case Discussion

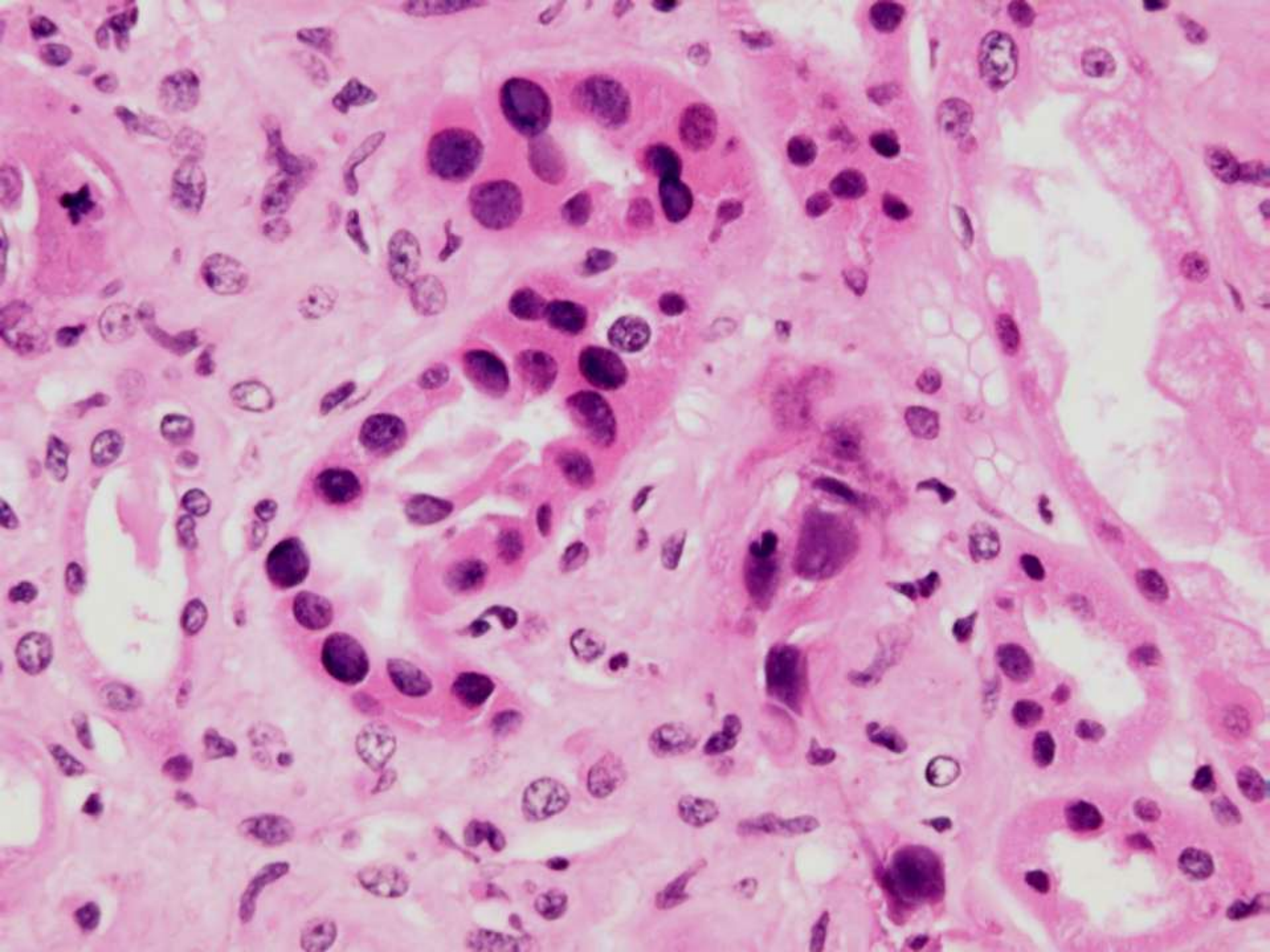
- 62 year old AA male; blood group A: PRA 0%
- ESRD-etiology is not clear (hypertension/chronic GN)-on peritoneal dialysis since June 2007
- History of prostate cancer-diagnosed in 2007
- Listed for a kidney transplant since May 2006

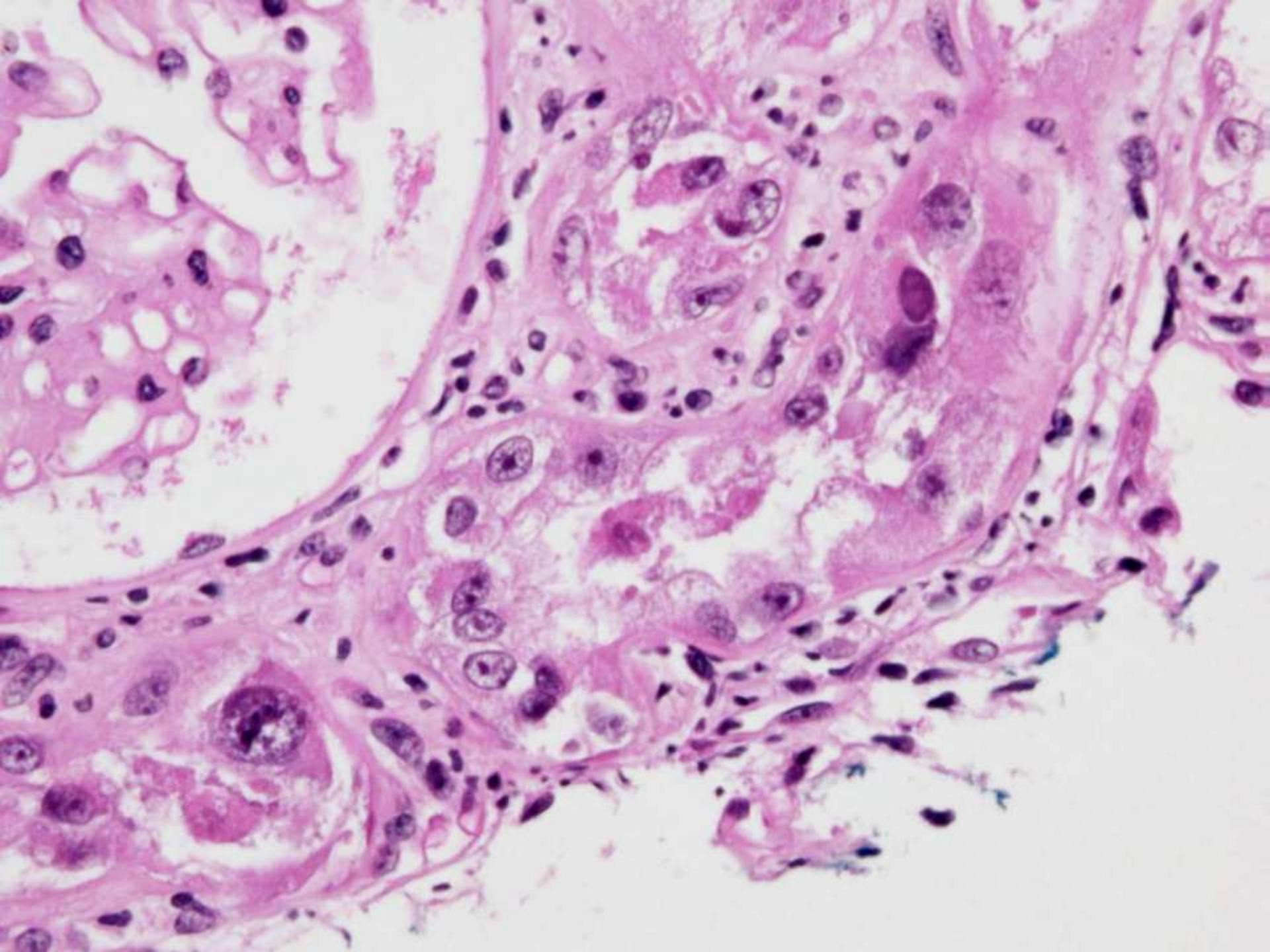
Case Discussion

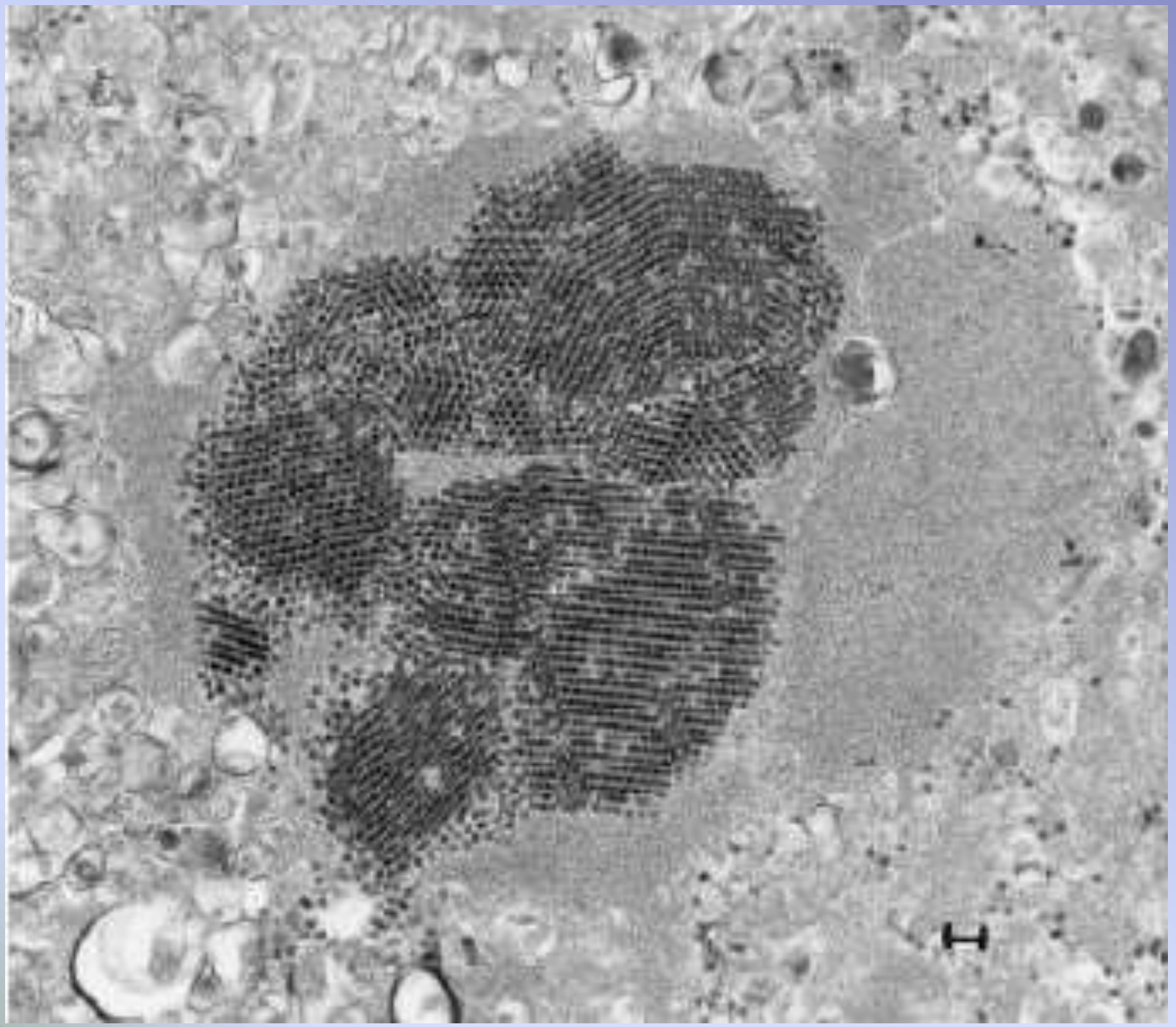
- DD kidney transplant-DCD kidney-on 4/11/2010
- Delayed graft function-continued dialysis until 4/28/2010 (scr is down to 4.8 mg/dl)
- Induction with Thymoglobulin (3 doses)
- Maintenance with tacrolimus + mycophenolic acid + prednisone

Case Discussion

- Scr is down to 1.86 mg/dl on 5/12/2010 (4 weeks posttransplant)
- Scr is up to 2.7 mg/dl on 7/8/2010 (less than 3 months posttransplant): admitted for a kidney biopsy
- Path: consistent with BK nephropathy
- Blood BK viral load 4.3 log on 7/8/2010 -increased to 5.6 log on 8/6/2010



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HISTOPATHOLOGY

- Viral cytopathic effect-**intranuclear inclusion bodies**
  - homogeneous basophilic nuclear change
  - homogeneous inclusion surrounded by halo
  - granular intranuclear inclusion without halo
  - nuclear enlargement with macronucleoli
- Degenerative **tubular epithelial changes** with sloughing and cellular and granular casts
- Variable **interstitial nephritis**
  - mixed inflammatory infiltrate
  - limited tubulitis

Prevalence and Clinical Manifestations

BK Virus

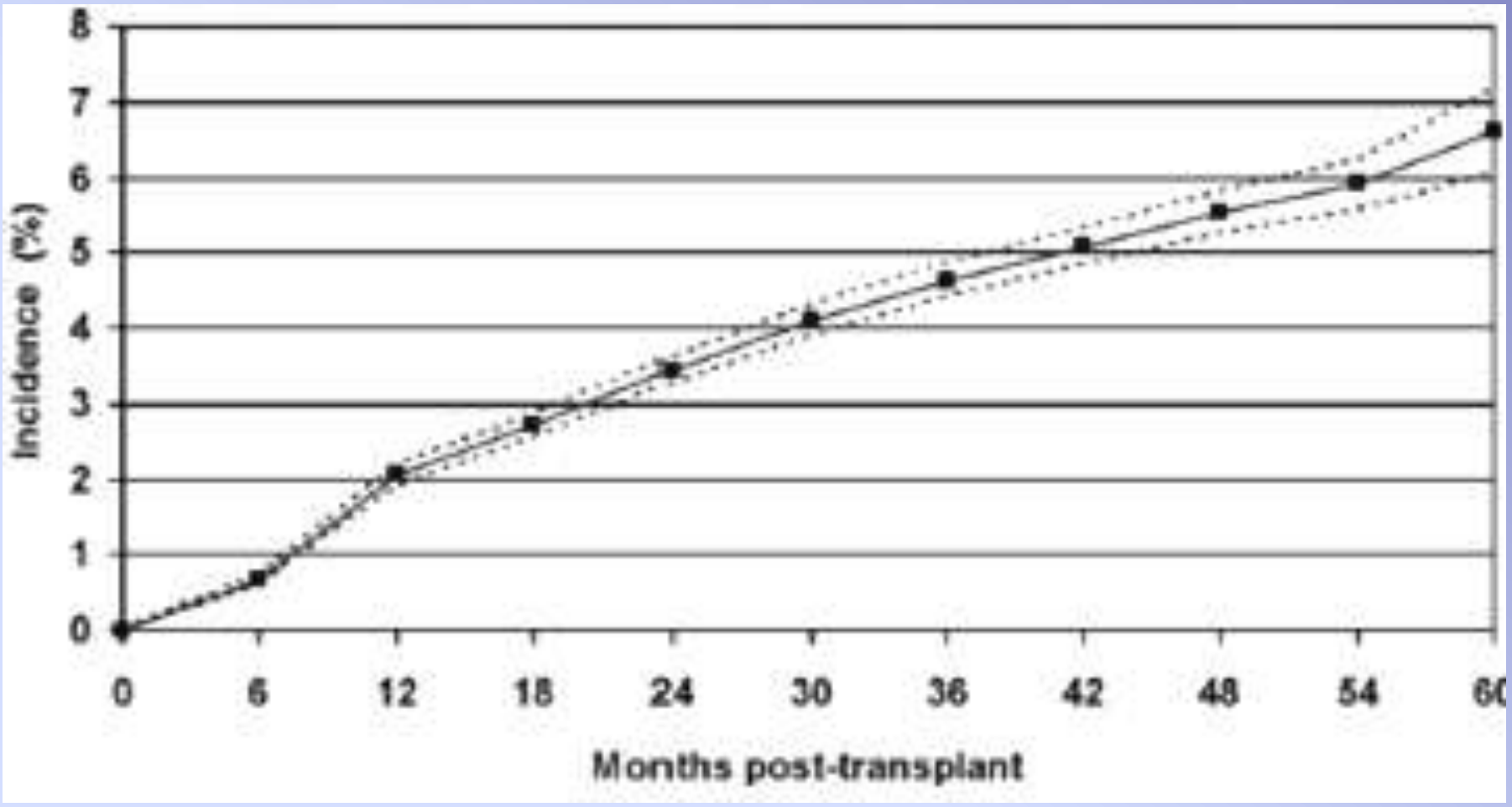
- 1971: described by Gardner SD and colleagues in Lancet: “isolated from urine after renal transplantation”-named BK virus (the initials of the patient who had ***ureteric stenosis***)
- 1983: first report on ***tubulointerstitial nephritis*** (6 year old boy with primary immune deficiency)
- Not truly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

Gardner SD, et al. Lancet 1971

Rosen S, et al. NEJM 1983

UNOS/OPTN

- The term “treatment for BKV”: used since June 2004
- Not specific for BK nephropathy
- Captures the treatment for BK viremia as well
- To capture the other agents used to treat the disease



•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

Linear Progression of Disease

- 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/JC Virus Infection

- 400 **healthy blood donors** aged 20-59 years were tested for BKV- and JCV-specific antibodies against virus-like particles
- IgG seroprevalence:
  - **82% BKV**
  - 58% JCV
- Asymptomatic urinary shedding:
  - 7% BKV
  - 19% JCV
- Neither BKV nor JCV DNA was detected in plasma

Egli A, et al. J Infec Dis 2009

BK Virus-Donors

- 54/67 adult kidney donors (67%): seropositive for BK virus
- Donor seropositivity: associated with a significantly elevated odds ratio of 3.1
- Testing for BK virus serostatus is neither routine, not mandated at this time

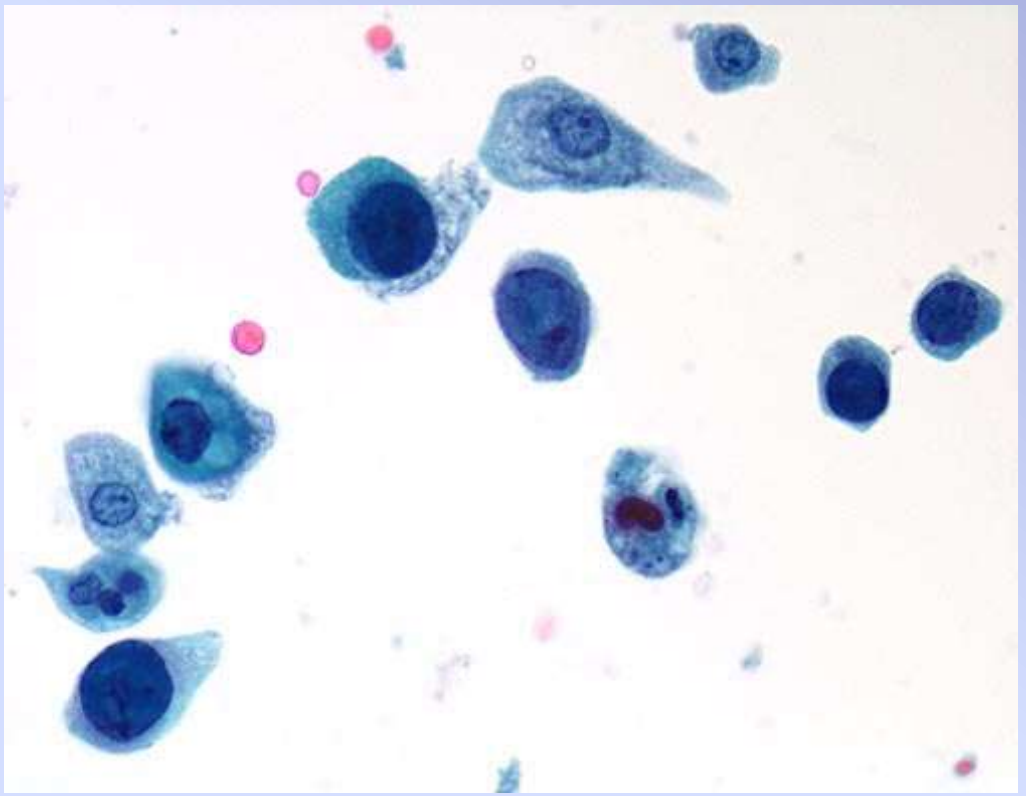
Bohl Dl, et al. AJT 2005

Diagnostic Testing

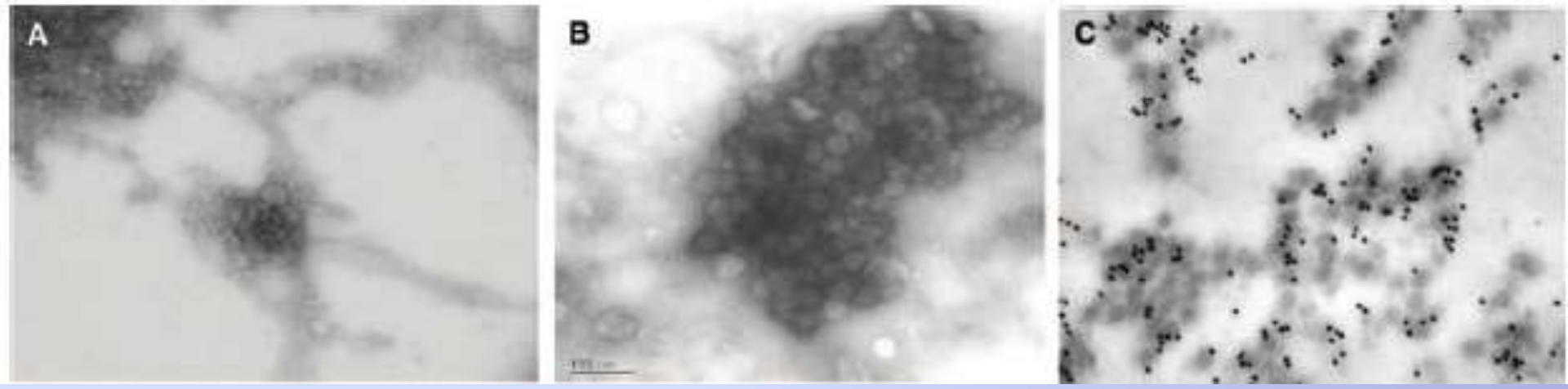
Diagnostic Testing

- **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)



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 HS, 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 HS, 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

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 Transpl. 2003

Matlosz B, et al. Transplant Proc. 2005

Burgos D. Transplant Proc. 2006

BK Nephropathy in Nonrenal Solid Organ Transplants

- Prospective study[1]: 50 Lung Recipients (3.7±2.9yrs)
  - 32% viruria incidence over 17 months
  - No loss of GFR
- Cross-sectional[2]: 34 Nonrenal (23 lung, 8 liver, 2 heart, 1 heart-lung)
  - 15% viruria incidence; no BK viremia; similar GFR
- 9 published[3] cases of BK nephropathy in nonrenal solid organ transplant recipients (2 lung transplants, 6 heart transplants, 1 pancreas transplant)

[1]Thomas LD, et al. J Infect Dis 2007
[2]Barton TD, et al. Transpl Inf Dis 2006
[3]Egli A, et al. AJT 2010

Impact of Preemptive Reduction of Immunosuppression

- 200 adult renal transplant recipients: open-label, prospective, randomized to tacrolimus (n = 134) or cyclosporine (n = 66)
- Urine and blood were collected weekly for 16 weeks and at months 5, 6, 9 and 12 and analyzed for BK viral load
- By 1 year, 70 patients (35%) developed viruria and 23 (11.5%) viremia; neither were affected independently by immunos used
- Viruria was highest with TAC-MMF (46%) and lowest with CsA-MMF (13%), p = 0.005

Brennan DC, et al. Am J Transplant 2005

Impact of Preemptive Reduction of Immunosuppression

- Management of immunosuppression:
  - BK viremia→ discontinuation of AZA or MMF
  - If viremia failed to clear within 4 weeks, the calcineurin inhibitor dose was tapered (CsA levels of 100–200 ng/mL or TAC levels of 3–5 ng/mL)
- After reduction of immunosuppression, viremia resolved in 95%, without increased acute rejection, allograft dysfunction or graft loss
- No BK nephropathy was observed

Brennan DC, et al. Am J Transplant 2005

BK virus and Pre-Emptive Immunosuppression Reduction 5-Year Results

- A retrospective 5-year review
- 5 year follow up in 97% of patients
- Viremia resolved in 95% of patients with reduction of immunosuppression
- 5-year patient survival 91% and graft survival 84%
- Immunosuppression and viremia did not influence graft survival
- Acute rejection: 12% by 5-years after transplant
- No BK nephropathy but no protocol biopsies

Hardinger KL, et al. AJT 2010

Screening and Diagnostic Testing for BK

- Linear progression is an opportunity: from viruria (30-40%) to viremia (10-20%) to nephropathy (1-10%) and graft dysfunction/ loss
- **Blood and/or urine samples every 3 months for first 2 years, then once a year and in the event of allograft dysfunction**
- Careful reduction of immunosuppression and close follow-up for development of acute rejection

HUP DATA

- Since Jan 2008, kidney transplant patients at our institution have been prospectively screened by quantitative BKV blood PCR
- If the result is positive (defined as 10,000 copies/mL or more in the serum or 4.0 log copies/mL or more in the serum); immunosuppression is reduced
- Significant decrease in our incidence of BKVN from 2.2% in the 3 yrs pre-screening to 1.0% in the 3 yrs post-screening period

Treatment

- Patient with ureteric stenosis: “deliberate lowering of his prednisolone dosage following the demonstration of partially obstructed ureter may have led to more rapid resolution of his BK virus infection. We now avoid giving high-dose corticosteroids to a patient excreting polyoma virus”

Harrison P, et al. Lancet 1978

Treatment of Polyomavirus Infection in Kidney Transplant Recipients: A Systematic Review

- A computerized search in MEDLINE, EMBASE,and Cochrane databases (1950–2008); references from review articles and published abstracts from the American Transplant Congress (2005–2008)
- Of 555 identified citations, 40 studies examining the effect of immunosuppression reduction alone or in combination with cidofovir, leflunomide, intravenous immunoglobulin, or ciprofloxacin were included for appraisal
- Three randomized controlled trials and two prospective cohort study

Johnston O, et al. Transplantation 2010

Immunosuppression Reduction Alone

- One randomized controlled trial, seven cohort studies and 13 case series
- Discontinuation of mycophenolate mofetil or azathioprine and reduction of immunosuppression by 25% to 50% were common strategies
- A death-censored graft loss rate of 8/100 patient-years.

Johnston O, et al. Transplantation 2010

A Systematic Review

- **Immunosuppression Reduction With Cidofovir:** one cohort and 11 case series- the death-censored graft loss is 8 patient-years
- **Immunosuppression Reduction With Leflunomide:** Five case series- the death-censored graft loss 13/100 patient-years
- Similar graft loss with the use of cidofovir and leflunomide
- Short follow-up; small number of patients

Johnston O, et al. Transplantation 2010

Studies-Treatment

- A **randomized**, double-blind, placebo-controlled trial in 41 kidney transplant recipients: assigned to human leukocyte **interferon** (total of 15 doses)or placebo
- Immunos: azathioprine and prednisone; in addition, 11 interferon-treated patients and 12 placebo-treated patients received equine antithymocyte globulin
- Failed to demonstrate a clinical effect on BKV infection

Cheeseman SH, et al. J Infect Dis 1980

Studies-Treatment

- Phase 2, proof-of-concept, **randomized**, open-label, parallel-group, 6-month study in renal transplant patients
- **FK778** (n=30) was compared with standard of care (reduction of immunosuppression, n=16) for treatment of newly diagnosed or untreated BKN: confirmed by renal biopsy
- FK778: derived from an active metabolite of leflunomide; suppresses immune reactions by directly binding to dihydro-orotate-dehydrogenase and inhibiting pyrimidine biosynthesis

Guasch A, et al. Transplantation 2010

Studies-Treatment

- FK778 group: greater reduction of urine BK viral load and a statistically significant reduction of viremia (*P*0.049), but renal function was not improved; higher incidence of biopsy-confirmed acute rejection (26.7%) as well as multiple rejection episodes (16.7%)
- Side effects: increased blood creatinine (26.7%), anemia/aggravated anemia (23.3%), aggravated hypertension (20.0%), and hypokalemia (20.0%) in the FK778 group
- **No benefit of FK778 in the treatment of BKN**

Guasch A, et al. Transplantation 2010

Sirolimus and Leflunomide Combination

- BK virus infecting renal tubular cells activates the protein kinase Akt/mTOR pathway
- Sirolimus can reduce BK large T antigen expression-dose-dependent
- Leflunomide can inhibit Akt phosphorylation reducing BK large T antigen expression and BK DNA replication
- Inhibition of intracellular protein kinase pathways activated by BK virus might be an effective therapy

Liacini A, et al. Transplantation 2010

Treatment of BK Nephropathy

- No specific antiviral drug treatment
- **Reduction/adjustment in immunosuppression remains the cornerstone**
- Cidofovir, leflunomide, FK778, quinolones, and intravenous immunoglobulin: no guidelines

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 after BK Nephropathy
An OPTN Database Analysis

- Retrospective review of the OPTN/UNOS database; reported to have a graft loss between June 30, 2004 and December 31, 2008
- 823 graft losses due to BK; of these, 126 have received a re-transplant as of June 5, 2009
- 118/126 grafts still functioning, one graft failure due to BK. Treatment for BK was reported in 17.5% of the re-transplants

Dhamidharka VR, et al. AJT 2010

Re-transplantation after BK Nephropathy
An OPTN Database Analysis

- In the 823 cases, BK was attributed:
  - As the primary cause of graft loss in 407 cases;
  - As a contributory cause of graft loss in 196 cases;
  - In another 220 cases, graft loss occurred after the patient was reported to receive treatment for BK, though the center did not list BKV as a primary or contributory cause of graft loss.
- Re-transplant occurred at a median of 314 days (10th–90th percentiles: 0–1550 days) after graft failure

Dhamidharka VR, et al. AJT 2010

Table 2: Graft and patient survival in 68 retransplants performed through December 31, 2007

Survival type	No. of transplants	Year post transplant	No. of recipients with follow-up	No. of recipients with functioning graft or no. of recipients alive	Survival rate
Graft	68	1	59	56	95.5
		2	33	29	93.6
		3	14	10	93.6
Patient	68	1	58	57	98.5
		2	32	31	98.5
		3	11	10	98.5

- Similar to prior reports, the short-term graft and patient survival with re-transplantation after BK appears to be excellent
- Longer-term outcomes remain unknown at this time

Dhamidharka VR, et al. AJT 2010

Re-transplantation

- Possible despite persistent/increased risks
- 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

Guidelines

- **2009 American Society of Transplantation Infectious Diseases Group**
- Urine screening every 3 months in first 2 years, then annually until the 5th year; if plasma screening is performed, then at monthly intervals
- Reduce immunosuppression for presumptive BKVN (plasma BK viral load >1x10^4 for >3 weeks)

- **2009 KDIGO Transplant Work Group**
- Plasma BK nucleic acid testing monthly for first 3-6 months, then every 3 months till month 12, or if elevated serum creatinine or after treatment of acute rejection
- Reduce immunosuppression if plasma nucleic acid load persistently >1×10^4

Studies

- CMX001 (**Chimerix, a lipid conjugated formulation of cidofovir**) in Post-transplant Patients With BK Virus Viruria-terminated
- BK treatment study: use of **Levaquin** for 30 days vs placebo in patients with BK viremia (from Brigham and Women's Hospital)-active
- A Randomized, Placebo-Controlled, Dose-Escalation Study to Assess the Safety and Effect of **Cidofovir** in Renal Transplant Recipients With BK Virus Nephropathy (NIAID)-active
- Polyomavirus BK Nephropathy After Renal Transplantation: Randomized Clinical Trial to Demonstrate That Switching to **mTOR Inhibitor** is More Effective Than a Reduction of Immunosuppressive Therapy (Hannover Medical School)-not started yet

Studies

- A randomized, controlled, multicenter clinical trial-use of **sirolimus and leflunomide**: Kinase Inhibition to decrease Nephropathy Intervention Trial (Canada)
- Haufen Diagnostic Biomarkers of BK Renal Disease (UNC, Chapel Hill and Astellas): To prospectively test whether the detection of three-dimensional, cast-like polyomavirus aggregates, termed **Haufen**, in voided urine samples can serve as an accurate biomarker of intra-renal disease, i.e. polyoma-BK-virus nephropathy

Case Discussion

- Reduction of immunosuppression: MMF was stopped; then tacrolimus dose was reduced to a target level 3-5
- BK viral load continued to be high: switched to cyclosporine-currently on CsA (last level 63) and prednisone
- Last BK viral load in July 2011: 3.5 log copies/ml (3250 copies/ml) and scr 1.85 mg/dl-stable; 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
- Studies needed