Cases: CMV, HCV, BKV and Kidney Transplantation

Simin Goral, MD

University of Pennsylvania
Medical Center

Disclosures

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Case-CMV

- 39 yo female with end stage renal disease (on PD since 12/2011); seen for transplant evaluation in 1/2012
- PMH: type 1 diabetes since age 9, hypertension, hyperlipidemia, diabetic retinopathy, umbilical hernia repair and lysis of adhesions, and two pregnancies
- Listed for simultaneous pancreas and kidney (SPK) transplantation in 3/2012

Case-CMV

- Received SPK on 7/3/2013: CDC high-risk donor (history of drug use)
- **CMV status: Donor positive; recipient negative (D+, R-)-high-risk for CMV**
- Induction: Solumedrol 500 mg during surgery and Thymoglobulinx5 doses
- Maintenance immunosuppression: tacrolimus (target 8-10), MMF (500 mg twice daily), and prednisone 5 mg daily

CMV-Transplantation

- **CMV infection:** evidence of CMV replication regardless of symptoms; “defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen”
- **CMV disease:** evidence of CMV infection with attributable symptoms-can be further categorized as a viral syndrome (ie, fever, malaise, leukopenia, and/or thrombocytopenia), or as tissue invasive (“end organ”) disease

CMV and Solid Organ Transplant Recipients

-What is the incidence of CMV infection in high-risk (D+, R-) solid organ recipients?

- A- Less than 10%
- B- 11-29%
- C- 30-50%
- D- 51-66%
- E- 67-90%

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Risk Factors for CMV Disease

- CMV serostatus (D+R- the highest risk)
- Type of transplanted organ (lung>kidney)
- Demographic factors (such as age)
- Genetic factors (such as natural killer cell receptor repertoire)
- Intensity of immunosuppression (use of MMF vs AZA, and induction therapy)

CMV and Prophylaxis

-Does she need CMV prophylaxis?

- A-Yes
- B-No
- C-Maybe
- D-Not sure

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Case-CMV Prophylaxis

-Which strategy would be the most effective and safe in this particular patient?

- A-Acyclovir 400 mg po qid x 3 months
- B-Valacyclovir 1000 mg po tid x 6 months
- C-Ganciclovir 1000 mg po bid x 3 months
- D-Valganciclovir 900 mg po qd x 6 months
- E-Maribavir 400 mg po bid x 3 months

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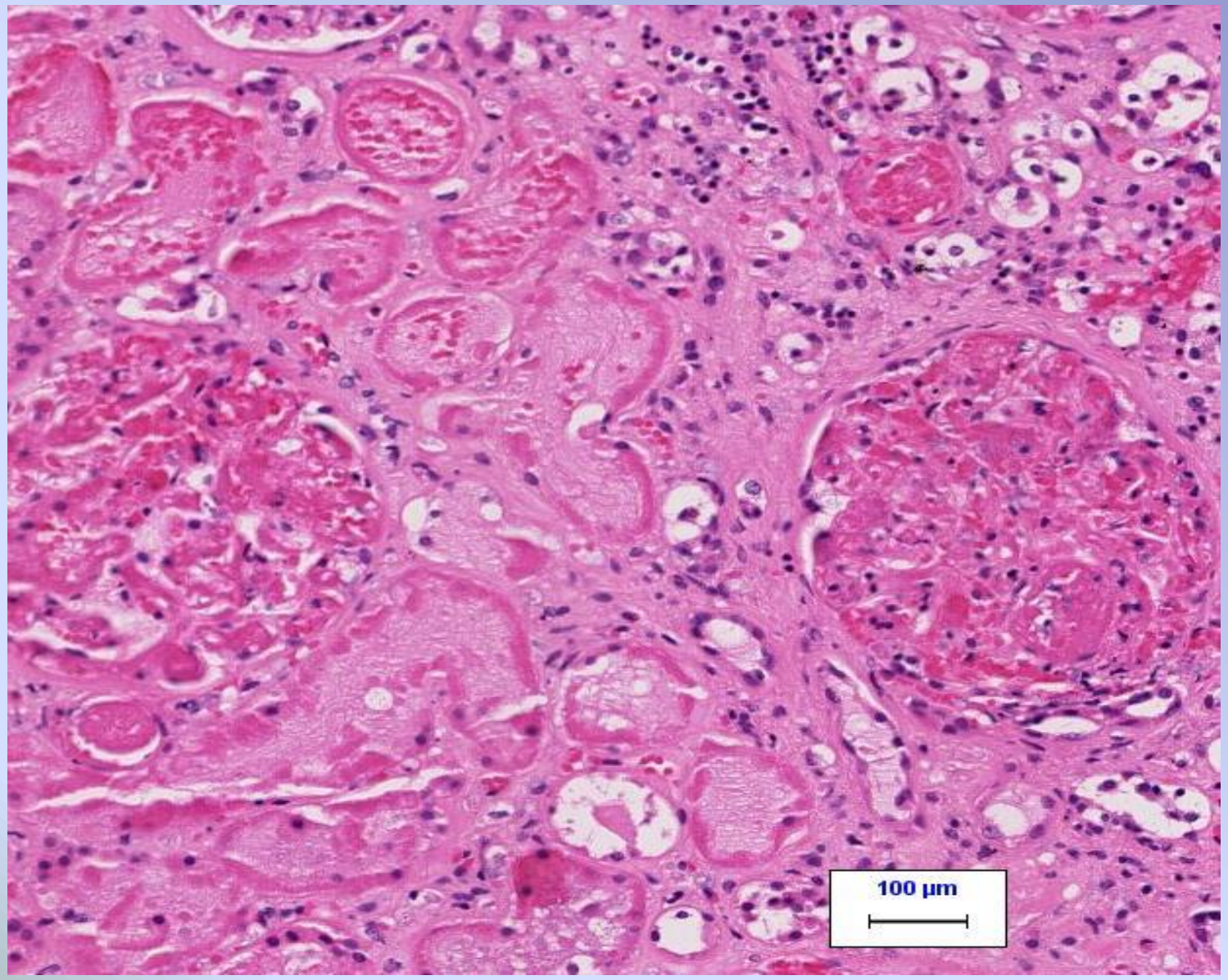
- E-Maribavir 400 mg po bid x 3 months

Case-CMV

- **Started on valganciclovir 900 mg daily**-planned for 6 months
- **5 weeks posttransplant**: admitted with fever, cough and elevated creatinine
- Renal ultrasound with doppler studies: normal
- DSA (donor-specific antibody): negative at 4 weeks posttransplant
- Serum creatinine (scr) better with IV fluids

Case-CMV

- **6 weeks posttransplant**: scr 1.2 mg/dl, TAC level 11, normal pancreas enzymes; CMV blood PCR: negative
- **8 weeks posttransplant**; admitted with low grade fever, abdominal pain and anuria x 6 hours
- Serum creatinine: up to 4 mg/dl


100 µm

Case-CMV

-What is your diagnosis?

- A-Steroid resistant cellular rejection
- B-Transplant pyelonephritis
- C-CMV glomerulopathy/thrombotic microangiopathy
- D-Antibody-mediated rejection
- E-Infarction with coagulative necrosis

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Case-CMV

- No flow to the kidney on ultrasound
- Transplant nephrectomy: twisted 360 degrees around its vascular pedicle
- Path: renal vein thrombosis, severe congestion and hemorrhage, and infarction with coagulative necrosis; **no CMV**

Case-CMV

- Back on dialysis; still on immunosuppression due to functioning pancreas; work-up started to relist her for a second kidney transplant
- **Valganciclovir dose changed to 450 mg every other day-renal dosing**
- CMV blood PCR checked due to low WBC: **low positive 4 months** posttransplant; then **positive 7 days later at 953 copies/mL** (3.0 log); no symptoms; WBC 3.6, liver enzymes are normal

Case-CMV Disease

-What would you like to do next?

- A-Increase the valganciclovir dose
- B-Switch to acyclovir
- C-Switch to cidofovir
- D-Switch to IV ganciclovir
- E-Add CMV immunoglobulin

Case-CMV Disease

What would you like to do next?

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- B-Switch to acyclovir
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- **D-Switch to IV ganciclovir**
- E-Add CMV immunoglobulin

Case-CMV

- Started on IV ganciclovir after each dialysis session**-continued for 4 months**
- Persistently low level CMV positive
- **CMV increased to 3.8 log 6 months posttransplant on IV ganciclovir**
- WBC 2.8, ALT and AST (liver enzymes) are slightly elevated

Case-Persistent CMV

-What would you like to do now?

- A-Increase the IV ganciclovir dose
- B-Switch to IV Cidofovir
- C-Add CMV vaccine
- D-Test for antiviral drug resistance
- E-Stop the therapy and monitor

Case-Persistent CMV

-What would you like to do now?

- A-Increase the IV ganciclovir dose
- B-Switch of IV acyclovir
- C-Add CMV vaccine
- **D-Test for antiviral drug resistance**
- E-Stop the therapy and monitor

Case-CMV

- Was found to have **ganciclovir resistance- genotype with UL97 mutation**
- Treated with **Maribavir** as part of a research protocol-**CMV negative now**
- Had positive stress test-had cardiac cath-severe coronary artery disease: s/p CABG-5 vessel; still waiting for a second kidney transplant

Antiviral Drug Resistance

- Risk factors: prolonged antiviral drug exposure (median, 5 months),ongoing active replication due to lack of CMV immunity (D+/R-), intense immunosuppression, or inadequate antiviral drug delivery
- Mainly in the D+/R- group: usual incidence of resistance after viremia 5-12%
- During prophylaxis: incidence 0-3%

Antiviral Drug Resistance

- Genotypic testing includes the UL97 kinase and the UL54 DNA polymerase genes that contain known resistance mutations for current antivirals
- Commercially available
- Turnaround time less than 1 week
- Most common, in patients previously treated with ganciclovir, is **UL97 mutation**

Alternate Therapy for Drug-Resistant CMV

- No controlled trial data
- Minimization of immunosuppression
- IV ganciclovir dose escalation (up to 10 mg/kg every 12 hours)-beware of bone marrow suppression and needs renal dosing
- Others: foscarnet, cidofovir, maribavir (oral benzimidazole L-riboside inhibitor of the CMV UL97 kinase) and letermovir (inhibits the viral terminase complex-studies are ongoing)

CMV-Consensus Guidelines

- Perform donor and recipient **CMV IgG serology** pretransplantation for risk stratification-do not recommend IgM testing
- Repeat serologic testing at the time of transplant if pretransplant serology is negative
- In adults, an equivocal result in the donor be assumed to be positive, whereas in the recipient this result be assigned to the highest appropriate CMV risk group

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CMV-Consensus Guidelines

- For D+/R− kidney recipients, prophylaxis for 6 months is preferable
- To avoid transfusion-transmitted CMV, use of leukoreduced or CMV-seronegative blood products (strong, moderate) especially in the highest risk group, D−/R−-recommended
- Treatment of rejection with antilymphocyte antibodies in at-risk recipients should result in re-initiation of prophylaxis or preemptive therapy for 1 to 3 months

Cotton CN, et al. Transplantation 2018

CMV-Consensus Guidelines

- Valganciclovir-recommended in patients with mild to moderate CMV disease who can tolerate and adhere to oral medication
- IV ganciclovir is preferred as initial treatment of life-threatening CMV disease when optimal drug exposure is essential
- Suboptimal dosing may increase the risk for clinical treatment failure and the development of resistance
- MDRD or CKD-Epi formulas are better to use for drug dosing

Cotton CN, et al. Transplantation 2018

CMV-Consensus Guidelines

- CMV viral load should be monitored at weekly intervals while on therapy
- If there is leukopenia, changing (val)ganciclovir to another agent is not recommended before the addition of GCSF and/or stopping other myelosuppressive drugs
- Drug resistance: suspected in patients with a prior (val)ganciclovir exposure >6 weeks and clinical treatment failure despite at least 2 weeks of treatment or development of CMV viremia during prophylaxis

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Case-Hepatitis C

- 56 yo AA male; on dialysis since 1/2015; blood group B
- Has history of diabetes, hypertension, history of **hepatitis c**
- Came in for kidney transplant evaluation
- **No potential living donors**

Case-Hepatitis C

- HCV viral load 6.3 log-never been treated
- s/p liver biopsy: stage 2 fibrosis, no evidence of cirrhosis; no varices
- Liver enzymes, serum albumin and platelets are normal
- Waiting time for a DD kidney in the region: **average 5-6 years**

Pro-Treat HCV Pretransplant

- Can remain active on the waitlist during therapy
- Cure of HCV is likely
- Prevent disease transmission
- Avoid drug-drug interactions with immunos
- Possible decreased risk of:
  - Progressive liver disease
  - Posttransplant GN
  - New onset diabetes posttransplant

Con-Do Not Treat HCV Pretransplant

- New DAAs are more efficacious and safe posttransplant; interferon can not be used posttransplant
- Potential drug-drug interactions
- Pretransplant cure eliminates HCV+ organ
  - Longer waiting time
  - Increased kidney discard rate

Case-Hepatitis C

What would you recommend for this patient to do?

- A-List for DD kidney transplant and start treatment with interferon and ribavirin
- B-List for DD kidney transplant and start treatment with DAAs
- C-List for DD kidney transplant; no HCV treatment now; advise to accept HCV positive kidneys and offer HCV treatment with DAAs posttransplant
- D-Kidney transplant is contraindicated in this setting; no listing

Hepatitis C

What would you recommend for this patient to do?

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Case-BKV

- 41 yo AA male; ESRD due to hypertension
- DD kidney transplant in 12/2010
- ATG inductionx3 doses; on tacrolimus, MMF and prednisone
- Serum creatinine stable 1.9-2.1 mg/dl
- No history of acute rejection

Case-BKV

Posttransplant BK monitoring should include:

- A-BK blood PCR monthly for 6 months then at 9 and 12 months
- B-BK blood PCR every 3 months during the first 2 years, then annually up to 5 years
- C-BK urine PCR monthly for 6 months then at 9 and 12 months
- D- BK urine PCR at 3 mo, 6 mo, and 12 mo, then at 24 months
- E-No viral monitoring necessary

Case-BKV

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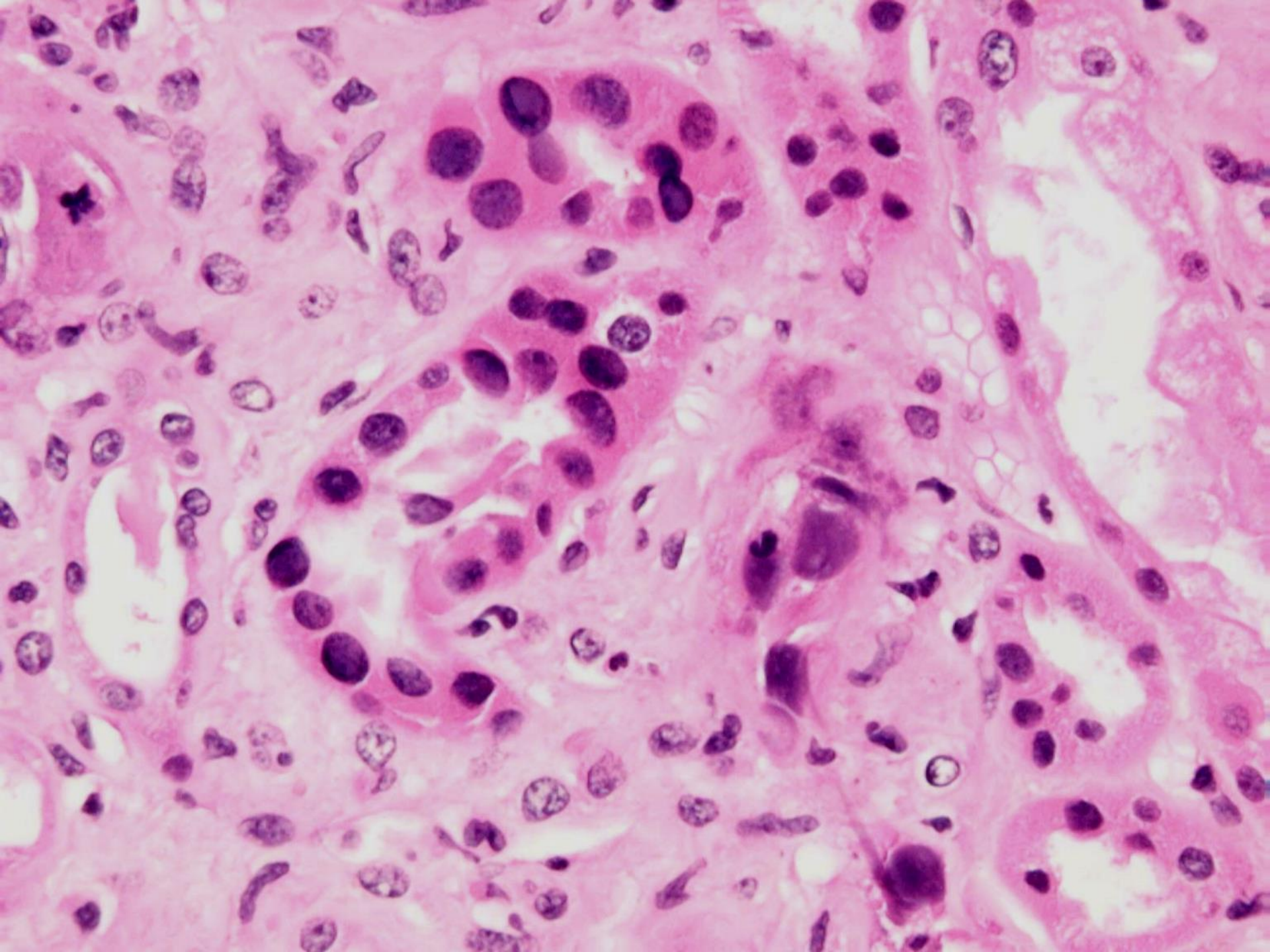
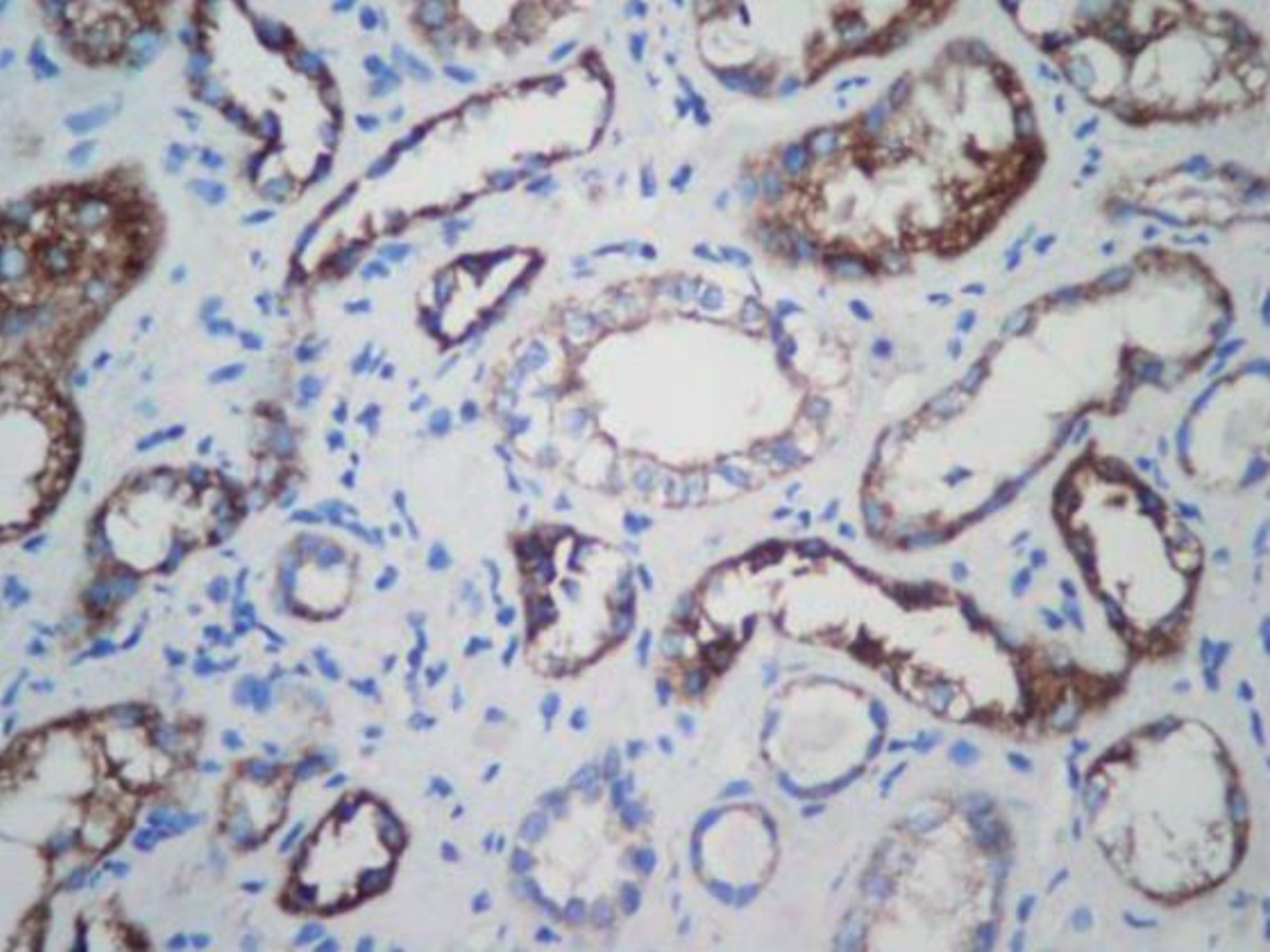
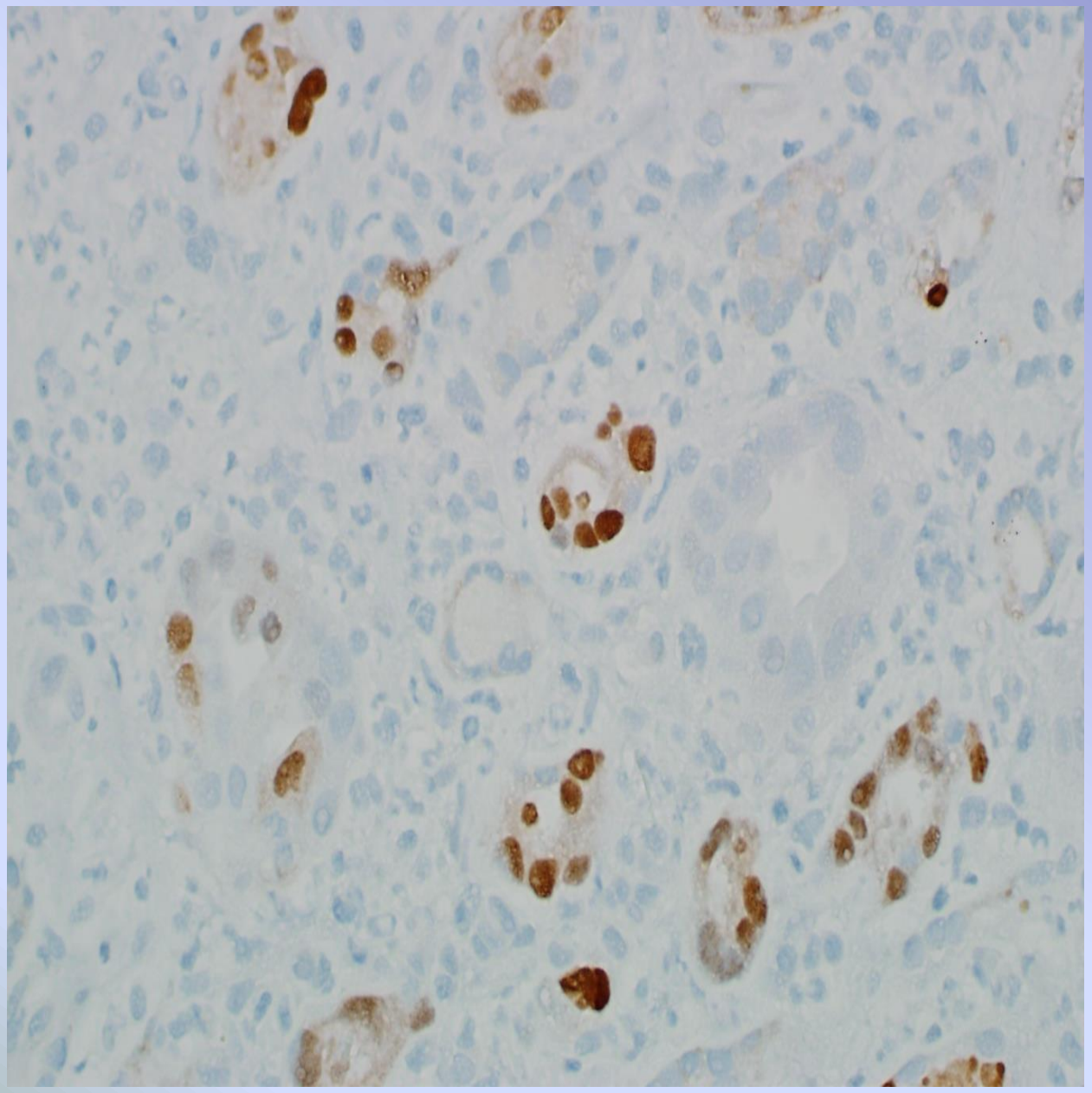
Case-BKV

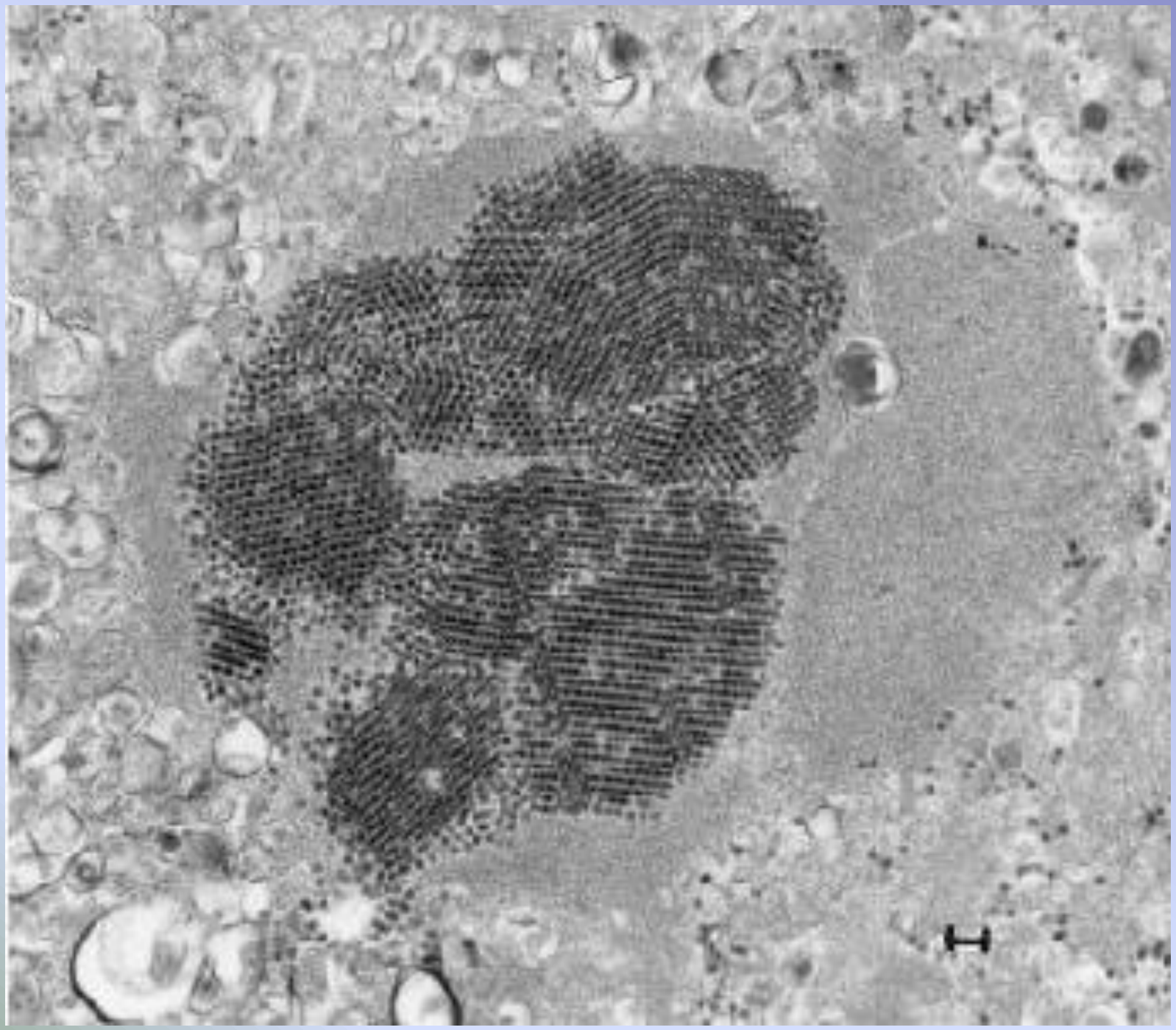
- BK viral load: never positive; negative in 12/2014 (4 years posttransplant)
- BK is checked due to slightly elevated serum creatinine
- BK viral load (blood) 5.1 log in May 2015
- Kidney biopsy is done





Immunostain for SV40 large T antigen-positive in the tubular nuclei of several tubules





Case-BKV

Which one of the following would you recommend?

- A-Switch tacrolimus to rapamycin
- B-Stop the mycophenolate mofetil
- C-Start leflunomide
- 4-Start cidofovir
- 5-Stop the tacrolimus

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- E-Stop the tacrolimus

Case-BKV

- Persistent BK viremia despite stopping MMF (5.8 log)
- Switched from tacrolimus to cyclosporine with 12-hour trough cyclo levels between 50-80
- Now has new DSA-class II
- Creatinine remains stable at 1.9-2.2 mg/dl

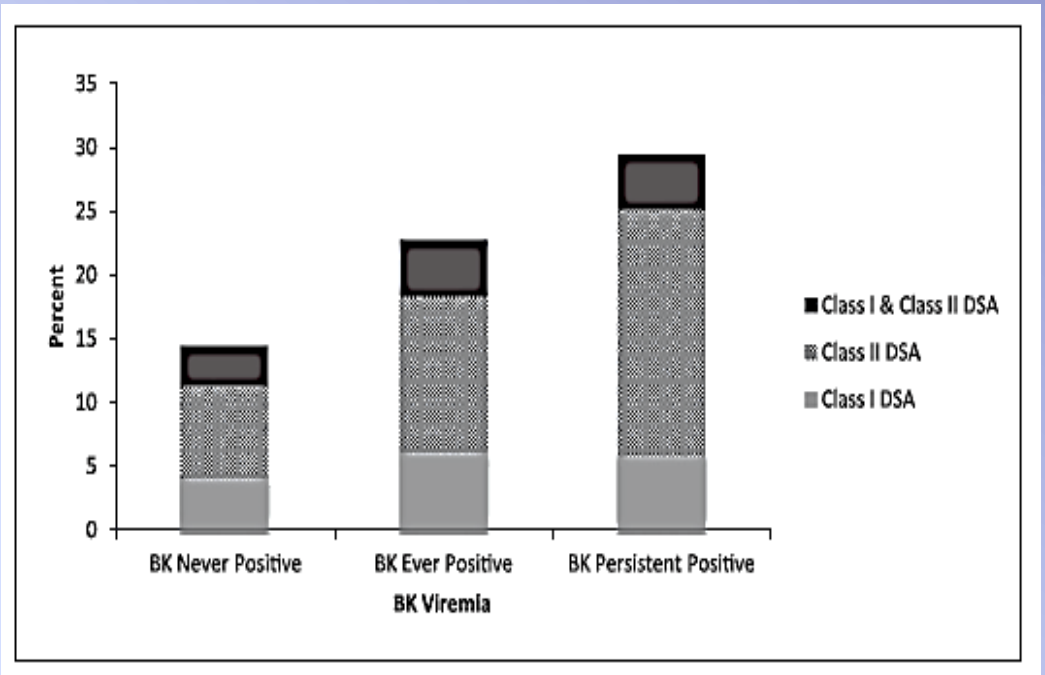
Persistent BK Viremia-*De Novo* Donor Specific Antibodies (DSA)

- BK and DSA screening at 1, 3, 6 and 12 months; then at 24 months at Penn
- 785 patients; data collected 1/2008-12/2012
- 132 (17%) had detectable BKV during the study period
- The median time to BKV detection: 138 days (IQR 94-216); 48% of patients were diagnosed at 3-month routine screening time point
- Persistent BKV defined as lasting ≥ 140 days; 52% of the infected patients had persistent BKV

Sawinski D, et al. JASN 2015

Persistent BK Viremia-DSA

- After a median follow-up of 3 years, no significant difference in terms of patient or allograft survival between patients with and without BK viremia



- *Persistent BK viremia was strongly associated with the development of class II DSA but not class I DSA*

Sawinski D, et al. JASN 2015

Case-BKV

What would you do next?

- A-Switch to rapamycin
- B-Switch back to tacrolimus
- C-Start leflunomide
- D-Start levofloxacin
- E-Start IVIG

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Case-BKV

- Started on IVIG-tolerated it well
- Creatinine remained stable
- BK viral load is down to 2.6 log
- Class II DSA still there but MFI levels are decreasing
- Currently on cyclosporine (higher target levels around 120-140) and prednisone
- Work-up is planned for persistent microscopic hematuria