Transplant Board Review

Anil Chandraker MD FRCP FASN FAST

Chief, Renal Medicine

UMass Chan School of Medicine/UMass Memorial Health Care

BRIGHAM HEALTH

BWH BRIGHAM AND WOMEN'S Department of Medicine

HARVARD MEDICAL SCHOOL

TEACHING AFFILIATE

Anil Chandraker MD

- Glasgow University Medical School
- Medicine Residency, Manchester Royal Infirmary
- Nephrology Fellowship@West Midlands
- Nephrology Fellowship@BWH/MGH
- Professor of Medicine@Umass Chan
- Lecturer in Medicine (Part Time)@BWH/HMS
  - Clinical focus: Kidney Transplantation
  - Research focus: Regulatory T cells, BK Nephropathy, Tx Genetics

Disclosures

- Vertex: Chair, Drug Monitoring Committee, VX20-880-101 study
- Allovir: Lead PI, Viralym-M treatment for BK viremia
- Amgen: Investigator Initiated Rapatha Rx in Transplant patients
- eGenesis: Clinical Scientific Advisory Board
- Natera: Renasight Scientific Advisory Board

Objectives

- Case vignettes to:

  Highlight common kidney transplant questions and issues including crossmatching, DGF, rejection, donor and recipient evaluation

Gout after kidney transplant; which one of the following is true?

A. Is commonly associated with the use of Tacrolimus

B. Is usually treated with NSAIDs

C. If allopurinol is prescribed to a patient on MMF, the dose of allopurinol should be reduced

D. Use of allopurinol with azathioprine needs careful monitoring

E. Colchicine is contraindicated in transplant patients

Gout after kidney transplant. Which one of the following is true?

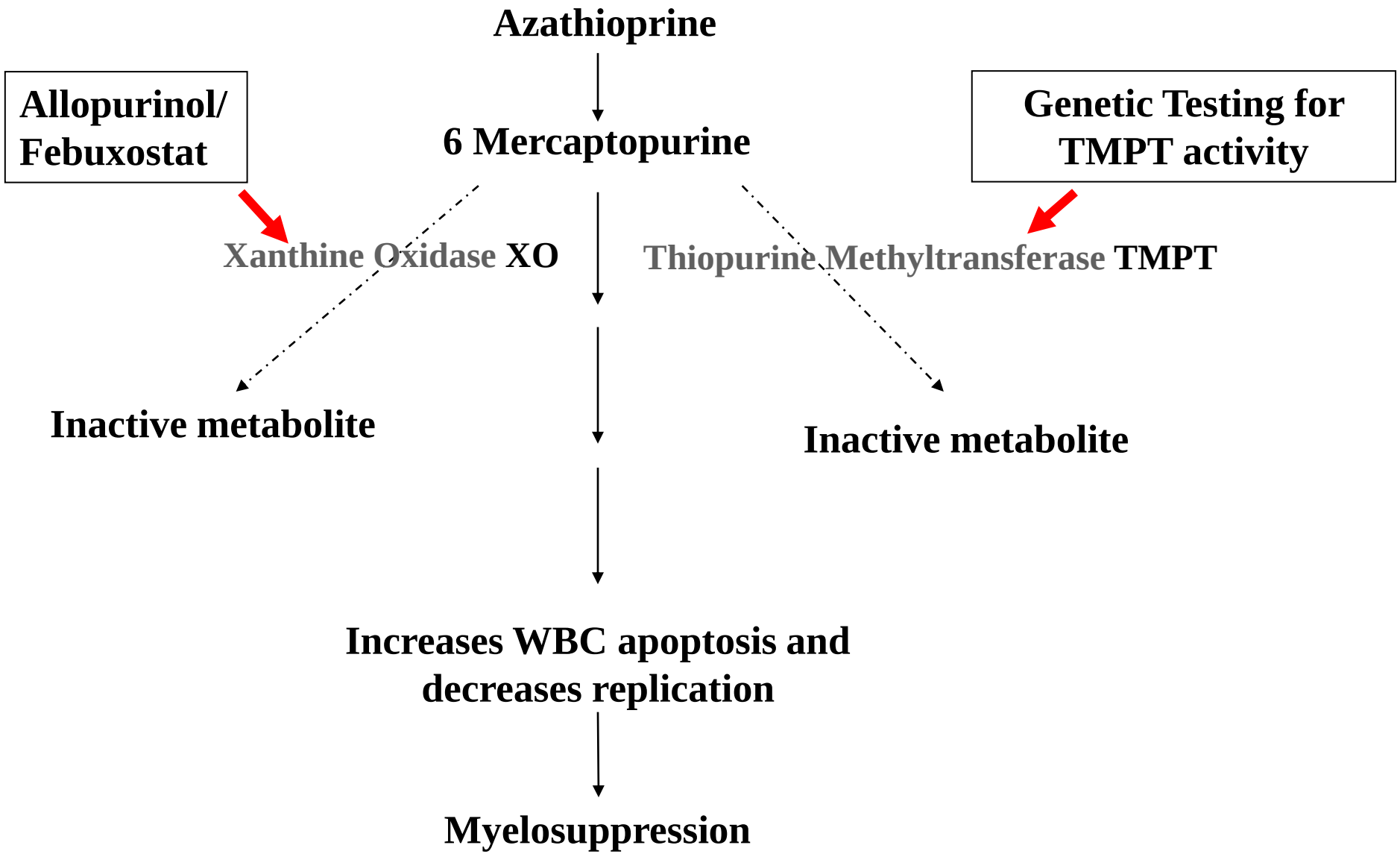
A. Is commonly associated with the use of Tacrolimus

B. Is usually treated with NSAIDs

C. If allopurinol is prescribed to a patient on MMF, the dose of allopurinol should be reduced

D. Use of allopurinol with azathioprine needs careful monitoring

E. Colchicine is contraindicated in transplant patients


Azathioprine
Allopurinol/ Febuxostat
6 Mercaptopurine
Genetic Testing for TMPT activity
Xanthine Oxidase XO
Thiopurine Methyltransferase TMPT
Inactive metabolite
Inactive metabolite
Increases WBC apoptosis and decreases replication
Myelosuppression

Case 1

A 66 year old male is admitted 3 wks after uncomplicated deceased donor kidney transplantation with increased serum creatinine. He feels quite well but notices some reduction in urine output and mild pain over the allograft.

Meds are MMF 1g bid, prednisone 15mg qd, tacrolimus 3mg bid, valgancyclovir 450mg qd, SMX-TMP 400mg qd.

Two days prior to admission, Cr was 1.5 and tacrolimus trough was 9.4; today's Cr is 2.3.

Case 1 cont’d

The pre-transplant T-cell crossmatch was negative and the allograft functioned immediately. He received thymoglobulin induction.

Medical hx includes ESRD secondary to IgA nephritis, 1 previous transplant lost after 6 months from severe rejection, BPH, HTN.

Exam: P 80, BP 150/90, mild tenderness over the allograft site; otherwise unremarkable.

Initial management of should include all of the following except:

A. Tacrolimus trough concentration

B. Check for single antigen anti HLA antibodies

C. Ultrasound to r/o allograft hydronephrosis

D. Empiric IL2 receptor blocker eg basiliximab

E. Ultrasound to exclude urine leak

Initial management of should include all of the following except:

A. Tacrolimus trough concentration

B. Check for single antigen anti HLA antibodies

C. Ultrasound to r/o allograft hydronephrosis

D. Empiric IL2 receptor blocker eg basiliximab

E. Ultrasound to exclude urine leak

Case 1 cont’d

Initials tests show tacrolimus trough = 6.5, WBC 4.5, Hct 30, platelets 160,000

Urgent ultrasound shows no hydronephrosis and no perinephric collection

Anti HLA antibody testing is pending

Which of the following is the next most appropriate step in management ?

A. CMV viral load

B. Increase tacrolimus dose

C. Reduce tacrolimus dose

D. Empiric Steroid Pulse

E. Allograft biopsy

Which of the following is the next most appropriate step in management ?

A. CMV viral load

B. Increase tacrolimus dose

C. Reduce tacrolimus dose

D. Empiric Steroid Pulse

E. Allograft biopsy

Case 1 cont’d

An uncomplicated biopsy is performed. Light microscopy shows no tubulitis but does show neutrophil capillaritis. Staining for C4d is positive in the perititubular capillaries.

Single anti HLA antibody testing shows previously detected anti HLA antibodies but no donor specific antibodies (DSA)

Which one of the following is true ?

A. The diagnosis is recurrent IgA nephropathy
B. The most likely diagnosis is acute polyoma virus infection
C. Even though there is no DSA plasmapheresis is the treatment of choice
D. Allograft nephrectomy is indicated
E. The diagnosis in cellular mediated rejection

Which one of the following is true ?

A. The diagnosis is recurrent IgA nephropathy
B. The most likely diagnosis is acute polyoma virus infection
C. Even though there is no DSA plasmapheresis is the treatment of choice
D. Allograft nephrectomy is indicated
E. The diagnosis in cellular mediated rejection

Incidence and Prognosis of AMR

- Antibody mediated rejection resulting in graft dysfunction is estimated to occur in **3 to 10 % of all renal transplants**
- It is estimated that as much as **30 % of acute rejection** episodes noted today have an antibody component
- In general: antibody-mediated immunologic processes portend **a worse prognosis**
  - Lederer et al reported a 4 year 50% graft survival for C4d+ patients compared with an 8 year 50% graft survival for C4d negative patients
  - Poduval et al reported a one year graft loss of 65% for grafts with diffuse C4d + diagnosis compared with 33% for focal and negative C4d grafts

Which one of the following is NOT included in the diagnostic criteria for acute antibody mediated rejection?

A. Capillaritis

B. Fibrinoid necrosis

C. Diffuse positivity of C4d staining in the glomeruli

D. Donor specific antibodies in recipient serum

E. Histologic findings of ATN

Which one of the following is NOT included in the diagnostic criteria for acute antibody mediated rejection?

A. Capillaritis

B. Fibrinoid necrosis

C. Diffuse positivity of C4d staining in the glomeruli

D. Donor specific antibodies in recipient serum

E. Histologic findings of ATN

Diagnostic Criteria for Acute AMR in Kidney Transplant recipients

Characteristic histologic features including:

Grade 1

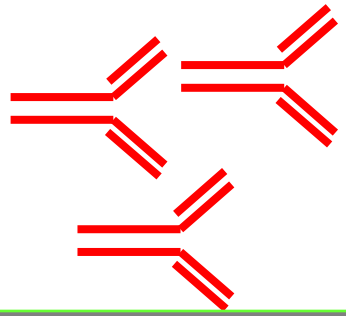
Grade 3

1) ATN
2) glomerulitis/capillaritis
3) margination of neutrophils/monocytes in the PTC
4) fibrin thrombi
5) interstitial hemorrhage
6) severe or necrotizing vasculitis

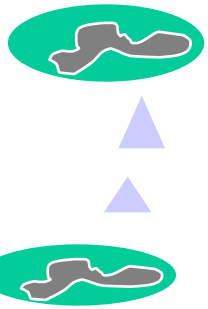
Diffuse, linear C4d staining in the Peri-Tubular Capillaries

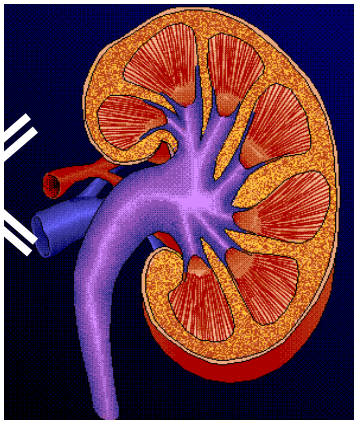
Identification of DSA

Severe antibody-mediated rejection (AMR): hyperacute or acute



Preformed or rapidly formed anti-donor antibody*



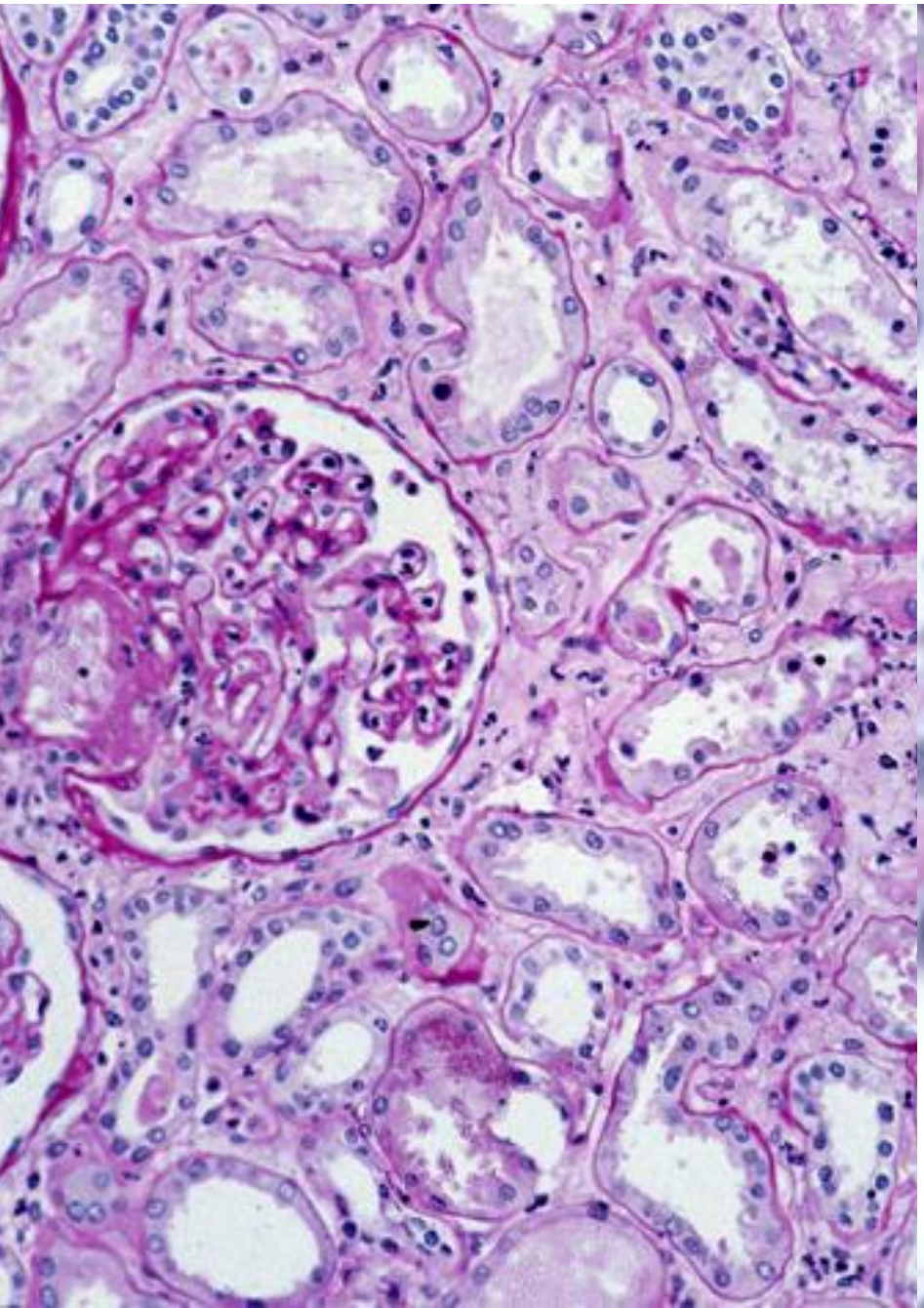


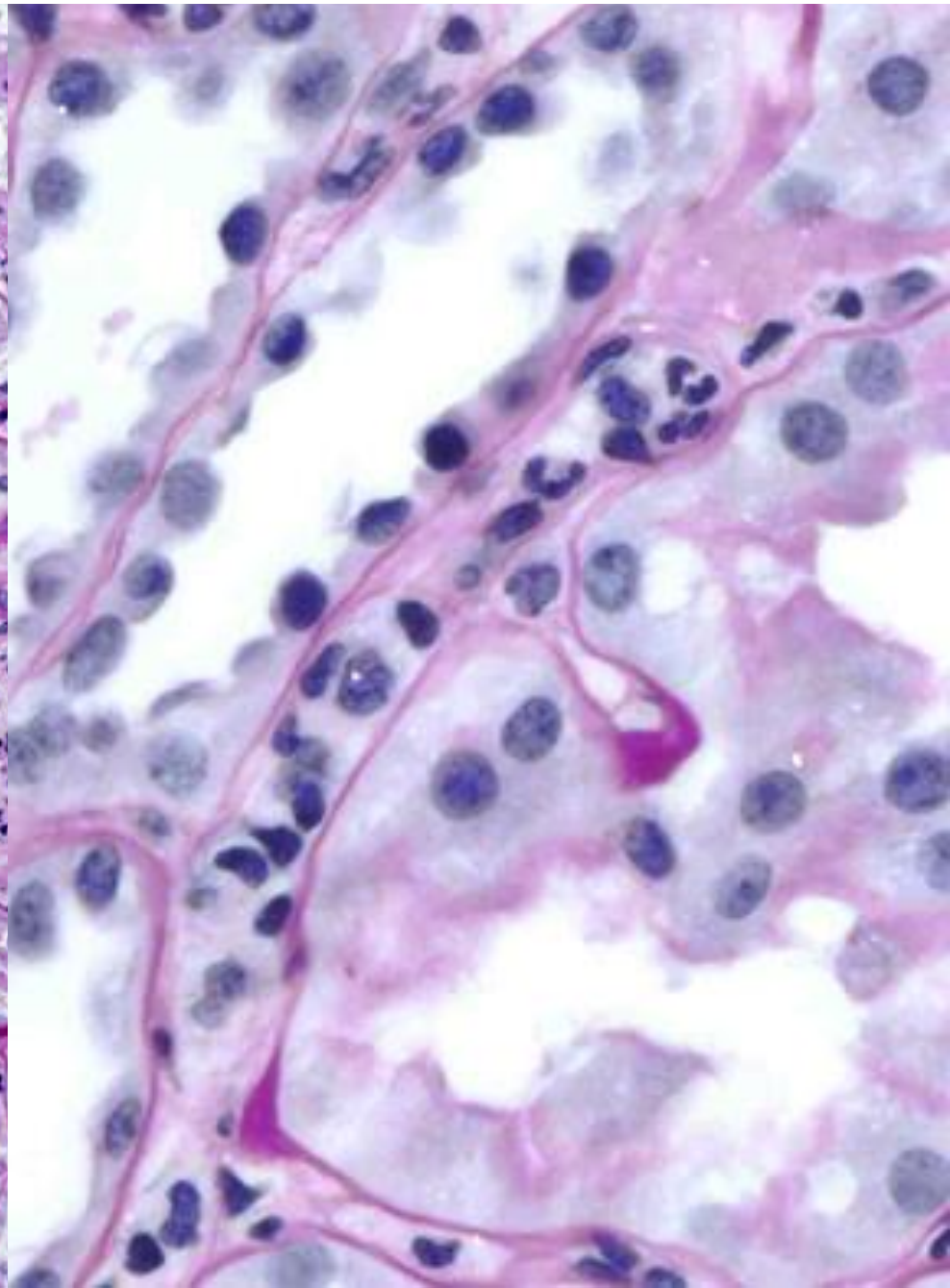
Binding of Ab to endothelium, recruitment of complement and neutrophil polymorphs

*Directed against HLA or ABO or other antigens

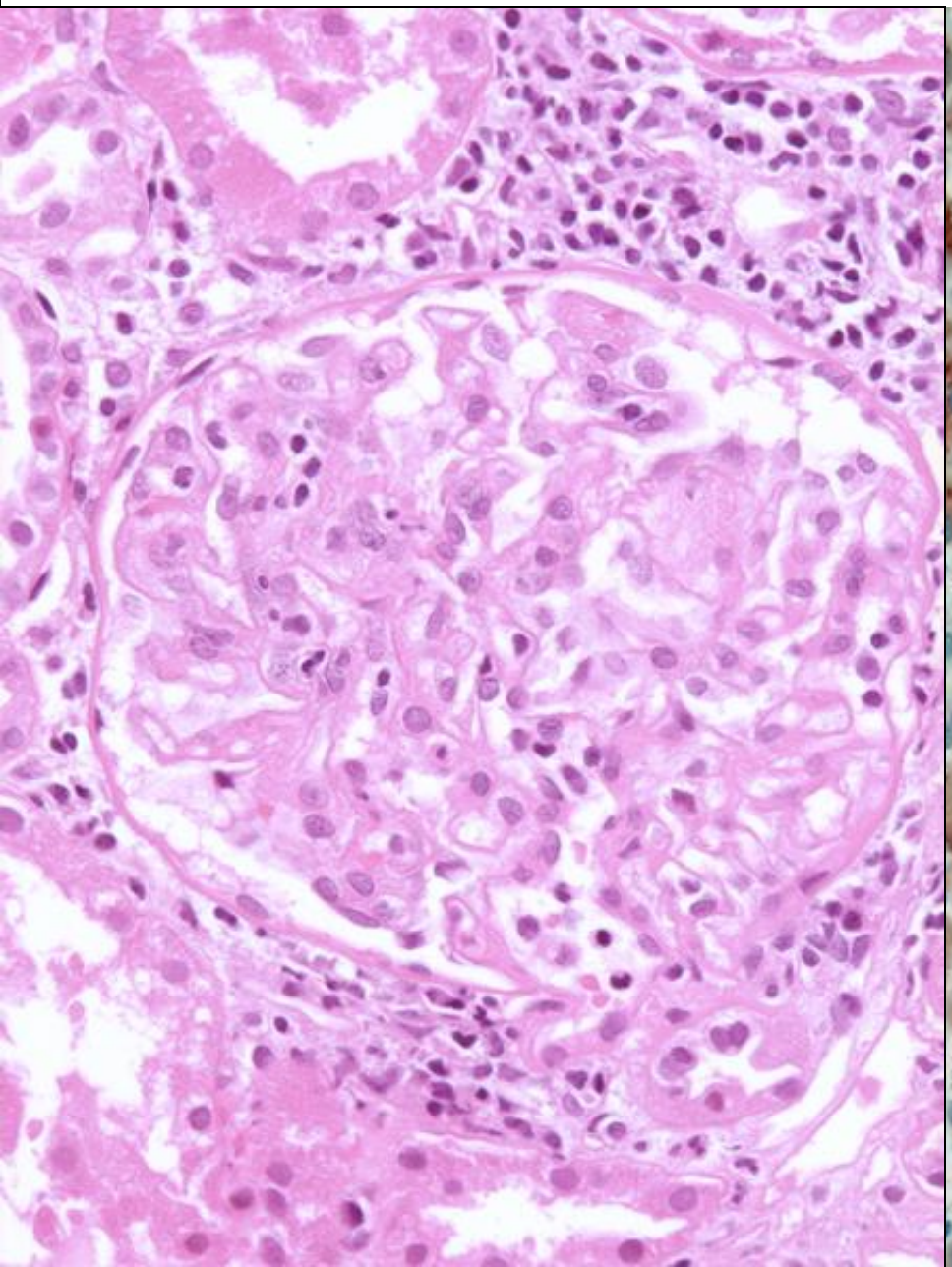
Massive inflammation, thrombosis and graft loss

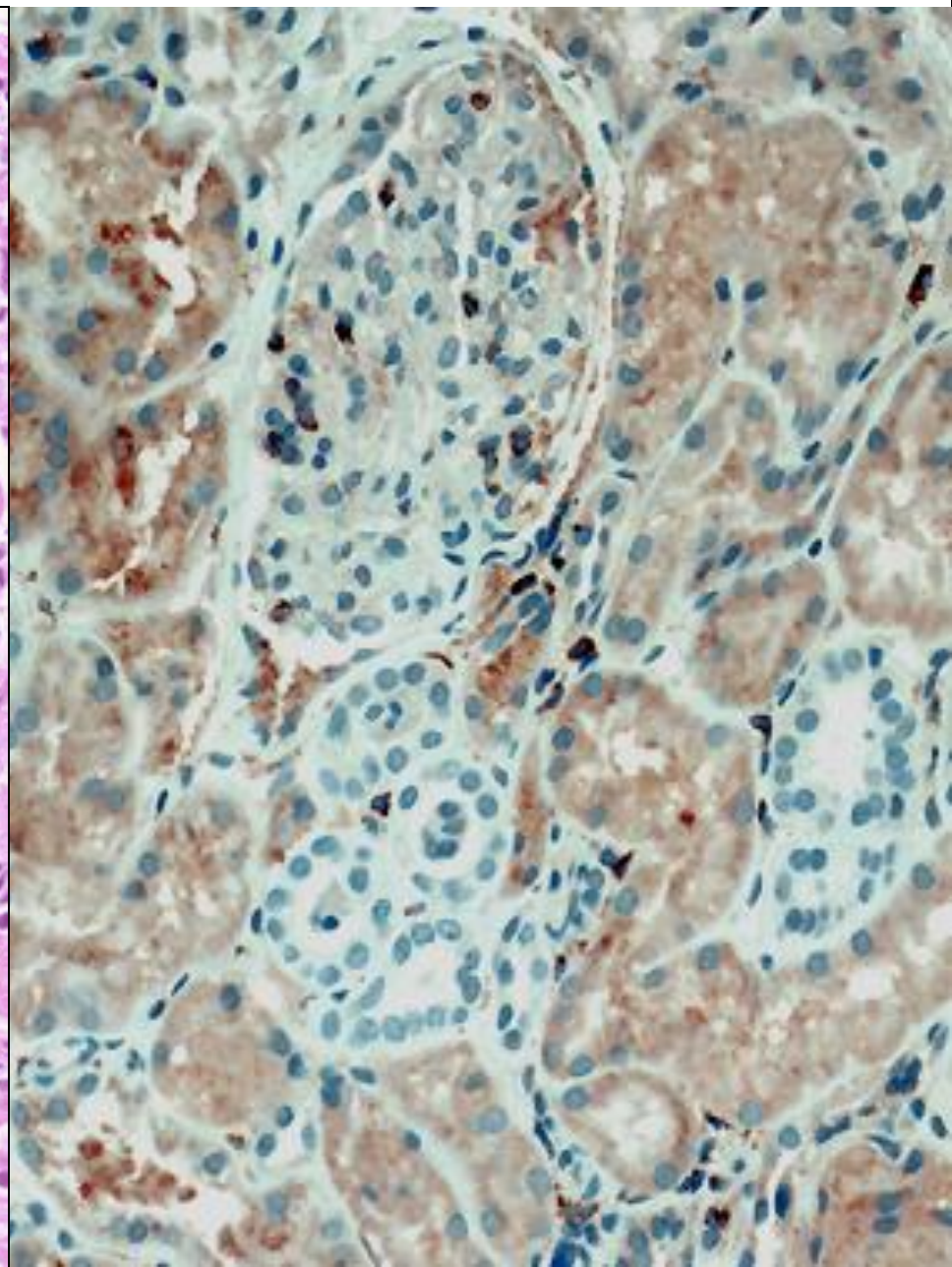
Polys in peritubular capillaries



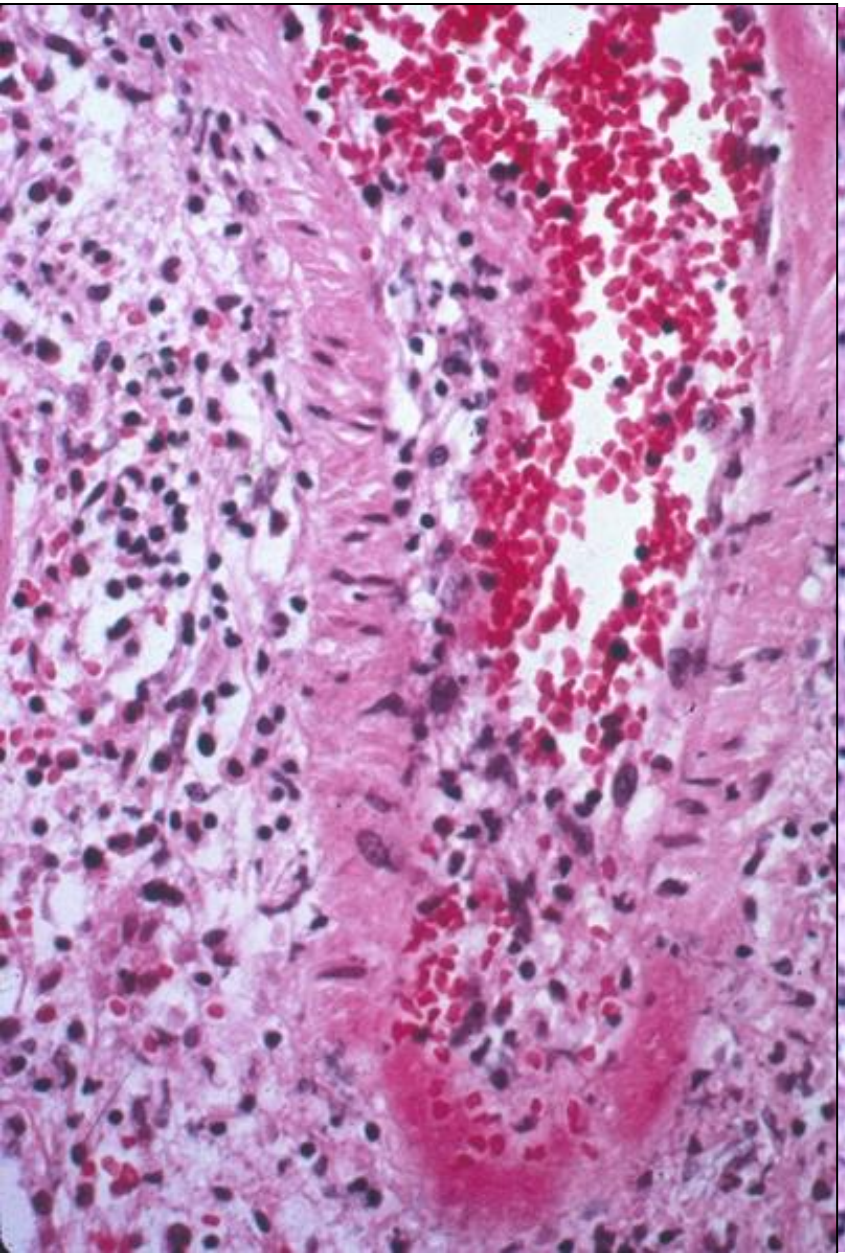


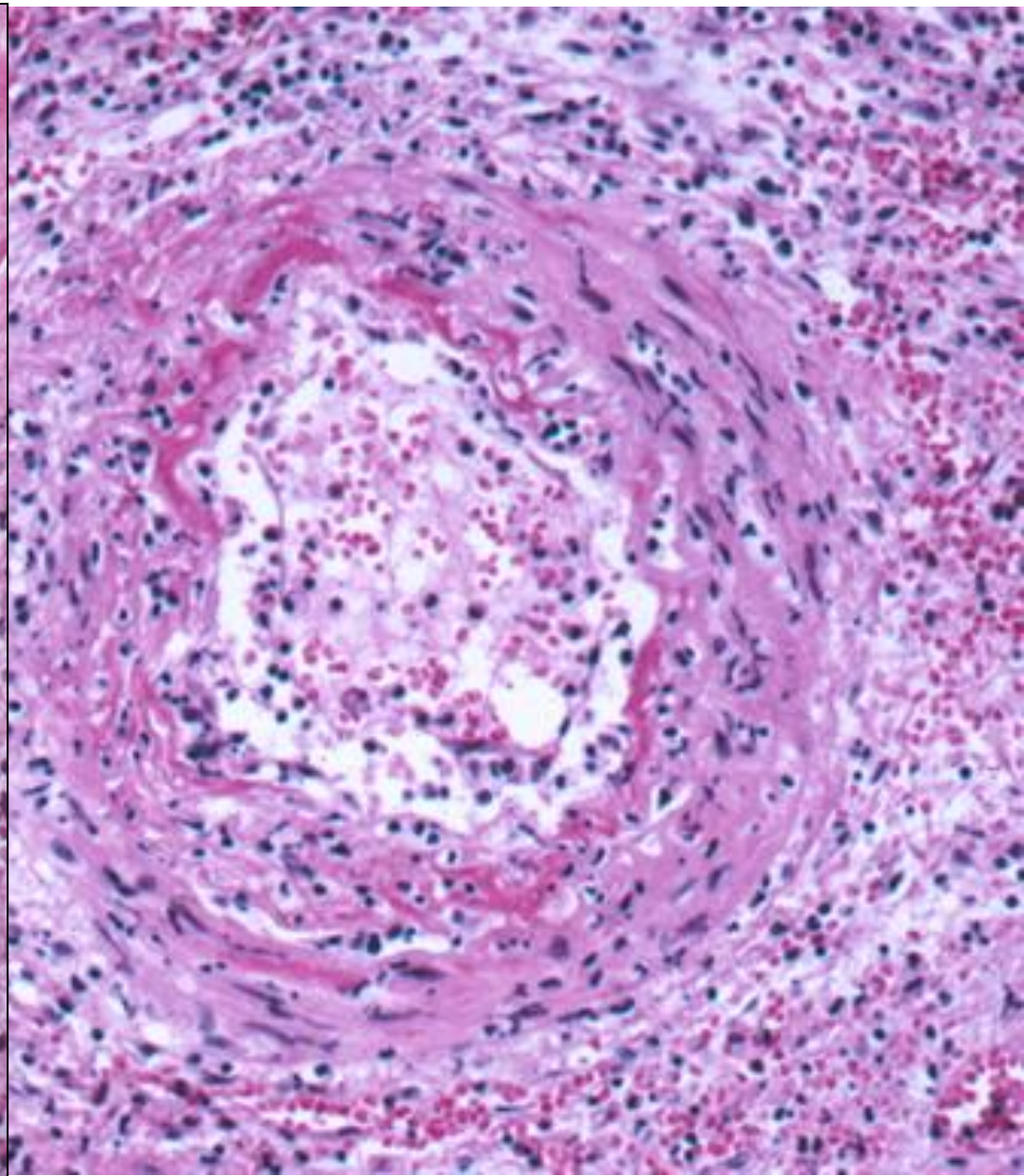
Glomerular Neutrophils and Macrophages



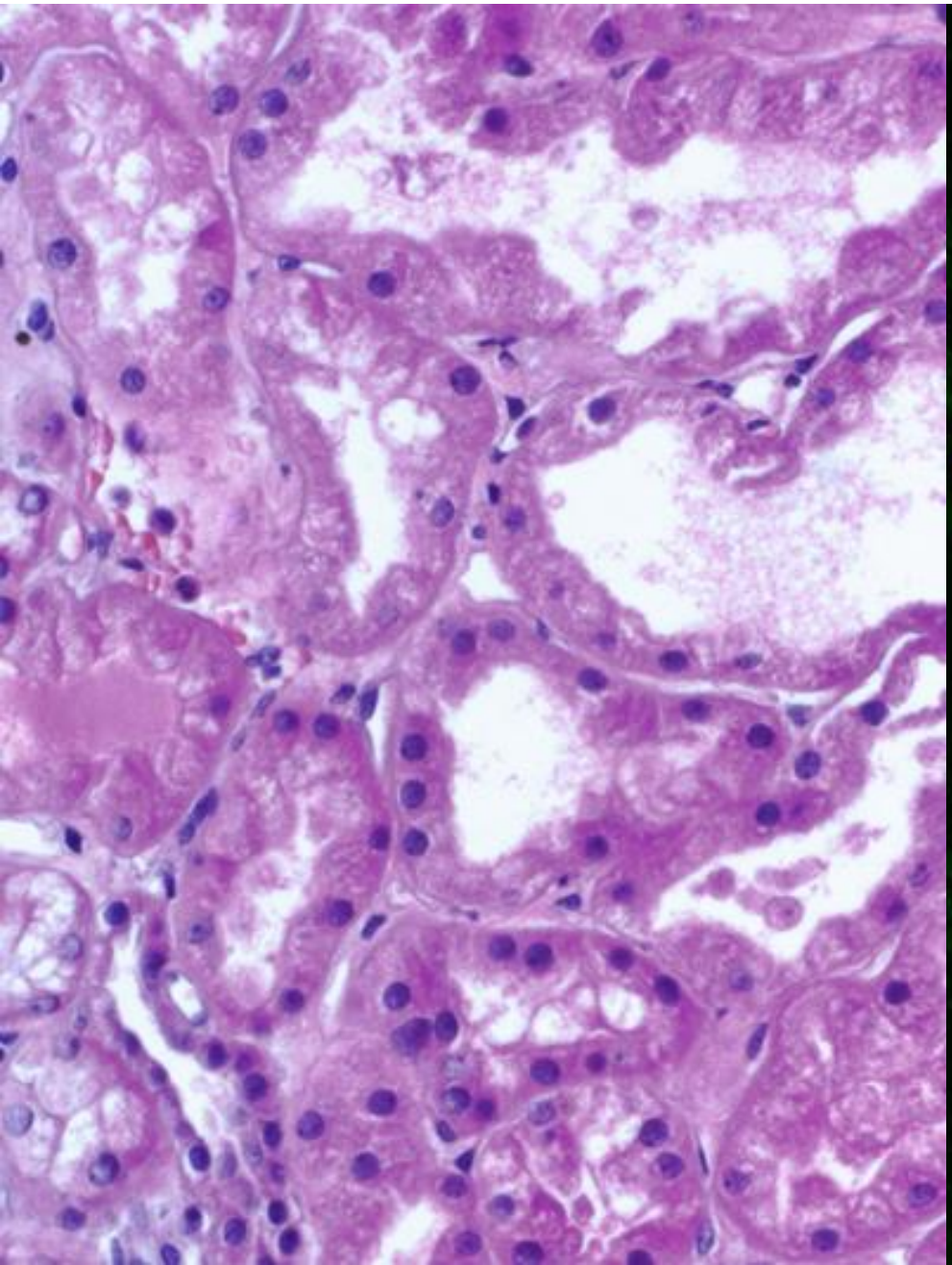


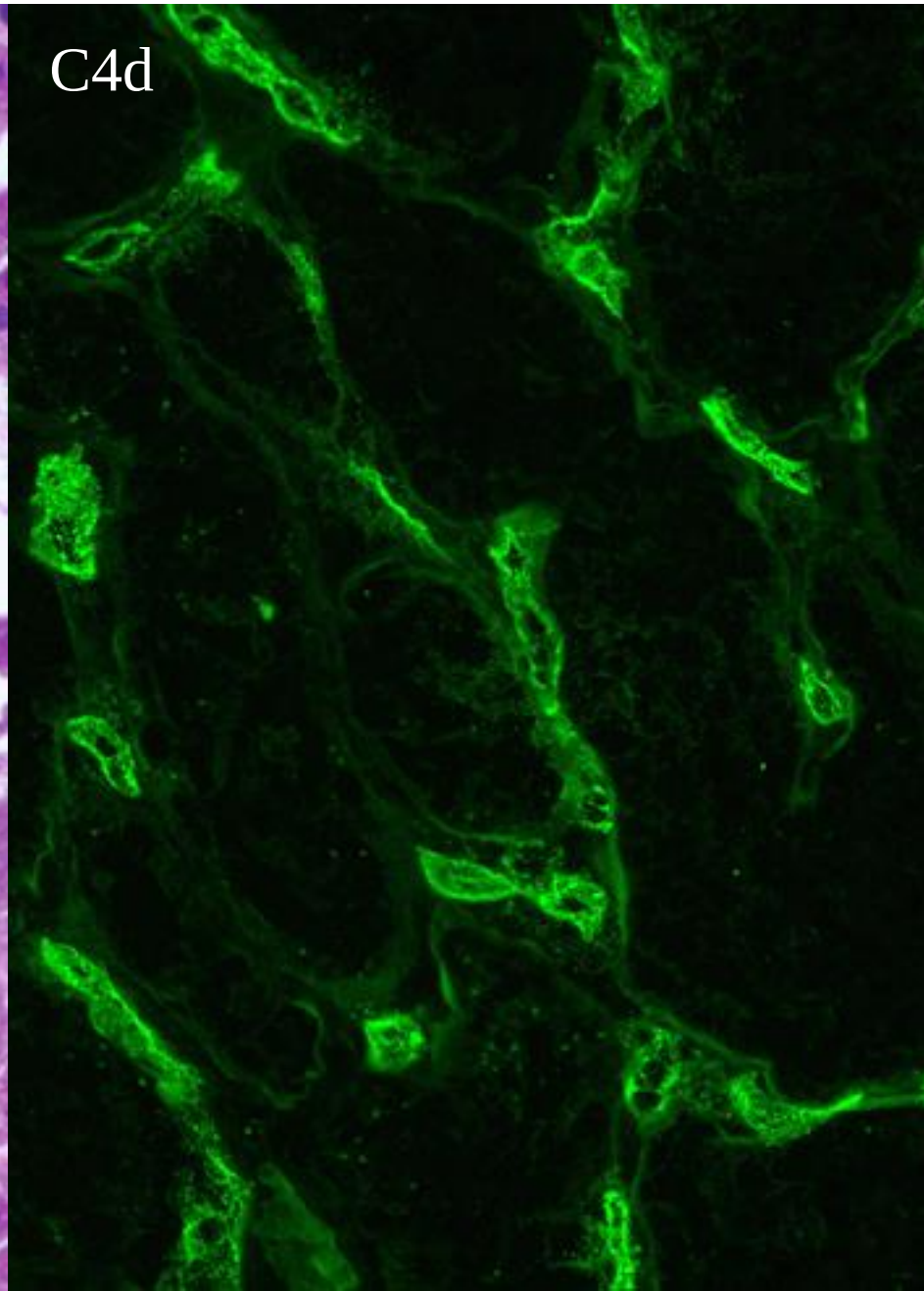
Fibrinoid Necrosis of Arteries



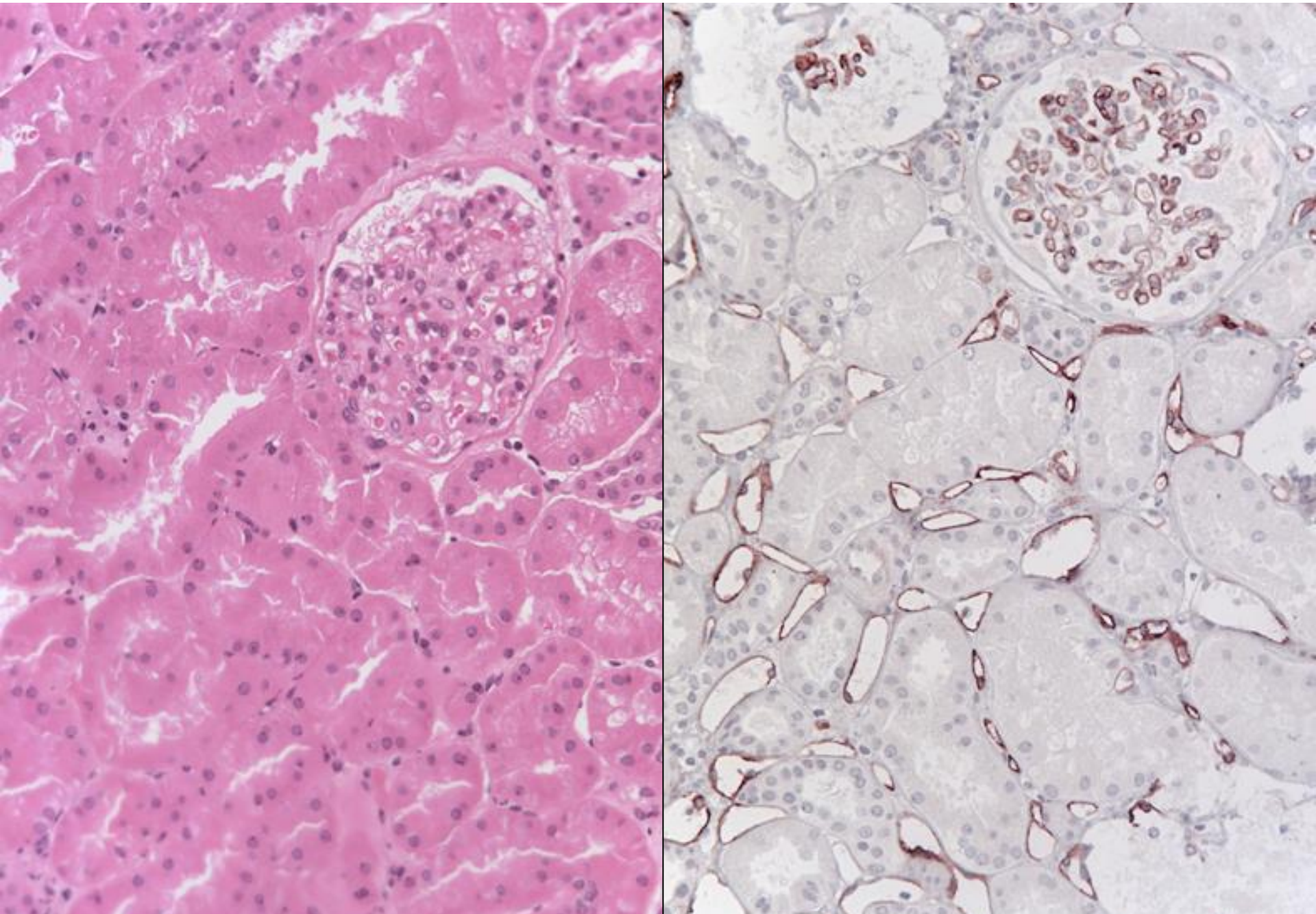


“ATN” Day 9 Oliguria





“Normal” Protocol Biopsy with C4d+



Mycophenolate mofetil: Which one is correct?

A. Inhibits lymphocyte IMPDH thereby reducing lymphocyte synthesis of RNA and DNA

B. Is associated with fewer GI adverse effects than azathioprine

C. Trough blood concentrations are routinely used to guide dosing

D. Is nephrotoxic at standard doses

E. Rarely affects proliferation of non-lymphocyte cells at standard doses

Mycophenolate: Which one is correct?

A. Inhibits lymphocyte IMPDH thereby reducing lymphocyte synthesis of RNA and DNA

B. Is associated with fewer GI adverse effects than azathioprine

C. Trough blood concentrations are routinely used to guide dosing

D. Is nephrotoxic at standard doses

E. Rarely affects proliferation of non-lymphocyte cells at standard doses

Mycophenolate inhibits IMPDH the rate-limiting enzyme in *de novo* guanine nucleotide biosynthesis needed for both DNA and RNA. Lympocytes are more dependent on this enzyme for polynucleotide synthesis. Azathioprine inhibits purine synthesis.

In theory, MMF would be very ‘lymphocyte selective’ but at standard doses, however it does cause marrow suppression, anemia etc.

Most trials show that MMF is more effective than azathioprine in preventing acute rejection but that it is also associated with more GI adverse effects. Neither drug is nephrotoxic.

Monitoring of blood concentrations of MMF or azathioprine is not routine. Azathioprine should be used with great caution – and at low dose - with allopurinol as allopurinol inhibits its metabolism; this can lead to pancytopenia.

For living donation, in which of the following conditions would donation be considered to be okay.

A. ‘Donor’ history of gestational diabetes mellitus
B. ‘Donor’ history of kidney stones in preceding 2 years
C. ‘Donor’ age <18 years
D. CT - angiographic evidence in donor of bilateral fibromuscular dysplasia
E. Heterozygous for APOL1 high risk genotype

For living donation, in which of the following conditions would donation be considered to be okay.

A. ‘Donor’ history of gestational diabetes mellitus
B. ‘Donor’ history of kidney stones in preceding 2 years
C. ‘Donor’ age <18 years
D. CT - angiographic evidence in donor of bilateral fibromuscular dysplasia
E. Heterozygous for APOL1 high risk genotype

APOL1

- Two common coding sequence variants in APOL1—G1 and G2—strongly predispose to kidney disease confer disease risk in an autosomal recessive manner so that persons with the 0 or 1 variant do not have increased risk, whereas those with 2 variants (G1/G1, G1/G2, or G2/G2 genotype) are at markedly higher risk for kidney disease, including
- FSGS (odds ratio, 17 [95% CI, 11 to 26]),
- HIV- associated nephropathy (odds ratio, 29 [CI, 13 to 68])
- “hypertension-associated ESRD’ (odds ratio, 7.3 [CI, 5.6 to 9.5])

Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. 2010;329:841–5.

Which of the following conditions can recur early after transplant and frequently (>40%) causes loss of the allograft?

A. IgA nephropathy

B. Membranous GN

C. MPGN

D. FSGS

E. SLE nephritis

Which of the following conditions can recur early after transplant and frequently (>40%) causes loss of the allograft?

A. IgA nephropathy

B. Membranous GN

C. MPGN

D. FSGS

E. SLE nephritis

Estimated rates of recurrence of renal disease and consequent graft loss

Disorder	Recurrence Rate (%)	Graft loss in those with recurrence
FSGS	30	50
Membranous	3-10	30
IgA	30-60	10-30
MPGN type I	15-30	30
MPGN type II	80	10-20
SLE	<3	<5
Anti GBM	10	<5

Which patient needs to wait longest disease free before getting their transplant?

A. 64 yr old male with Basal Cell Carcinoma 1 year ago
B. 34 yr old female with cervical CIS 2 years ago
C. 55 yr old male with Duke C Colon CA 4 years ago
D. 67 yr old ex-smoker with lung CA (resected) 3 years ago
E. 58 yr old female with DCIS 3 years ago

Which patient needs to wait longest disease free before getting their transplant?

A. 64 yr old male with Basal Cell Carcinoma 1 year ago
B. 34 yr old female with cervical CIS 2 years ago
C. 55 yr old male with Duke C Colon CA 4 years ago
D. 67 yr old ex-smoker with lung CA (resected) 3 years ago
E. 58 yr old female with DCIS 3 years ago

Guidelines for CA Waiting Periods

No wait

- Bladder CA (superficial, low-grade)
- Non-melanoma Skin

1 year

- Cervical (in situ)
- Wilm's

2 years

- Bladder CA (most)
- Breast (in situ)
- Cervical (local invasive)
- Colorectal (Duke A)
- HD, NHL, PTLD, Leukemia
- Lung
- Melanoma (in situ)
- Prostate (most)
- Renal Cell (most)
- Testicular
- Thyroid

5 years

- Breast (most)
- Colorectal (most)
- Melanoma (most)
- Renal Cell (advanced)

Never

- Breast (Grade III or IV)
- Multiple Myeloma
- Prostate (advanced)

Canadian Society of Transplantation consensus guidelines on eligibility for kidney transplantation. CMAJ 2005 Nov 8;173(10):1181-4.

Which one of the following donor characteristics is generally not considered a contra-indication to living kidney donation?

A. BP >140/90 with mild hypertensive retinopathy

B. Age <18 years

C. BMI >40 kg/m2

D. Horseshoe kidney

E. Six HLA Ag mismatches with the potential recipient

Which one of the following donor characteristics is generally not considered a contra-indication to living kidney donation?

A. BP >140/90 with mild hypertensive retinopathy

B. Age <18 years

C. BMI >40 kg/m2

D. Horseshoe kidney

E. Six HLA Ag mismatches with the potential recipient

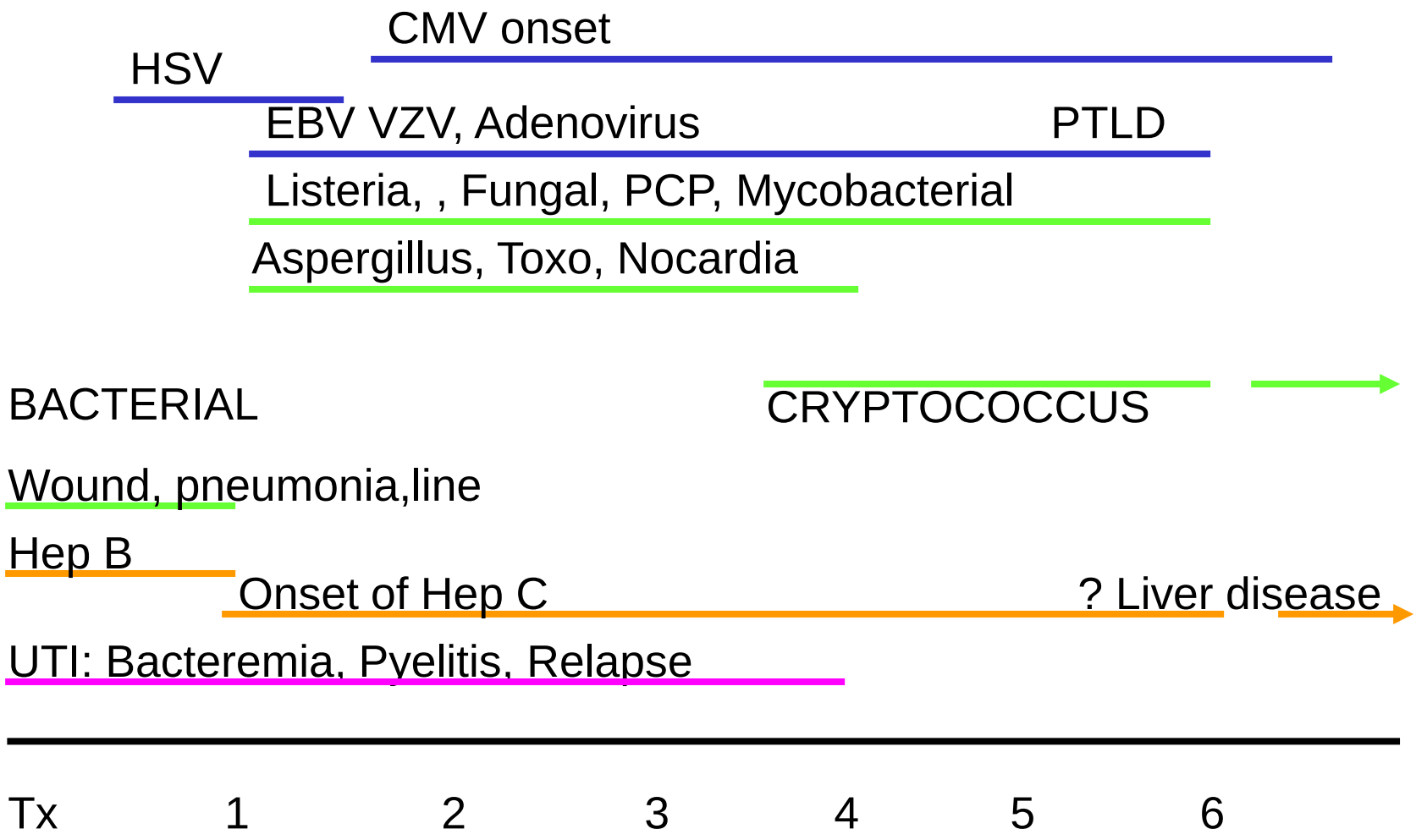
A CMV negative recipient receives a 0MM kidney from a CMV positive donor and is prophylaxed with valganciclovir. 2 weeks post transplant she develops a fever. Which is least likely source?

A. CMV
B. Wound infection
C. UTI
D. Common cold
E. Pneumonia

A CMV negative recipient receives a 0MM kidney from a CMV positive donor and is prophylaxed with valganciclovir. 2 weeks post transplant she develops a fever. Which is least likely source?

A. CMV
B. Wound infection
C. UTI
D. Common cold
E. Pneumonia

Infections in the Post Transplant Period



Which of the following is not a common side effect of tacrolimus?

A. Neurotoxicity - tremors

B. Hypertrichosis

C. Islet cell toxicity

D. Hyperkalemia

E. Hypertension

Which of the following is not a common side effect of tacrolimus?

A. Neurotoxicity - tremors

B. Hypertrichosis

C. Islet cell toxicity

D. Hyperkalemia

E. Hypertension

	Cyclosporine	Tacrolimus
Post Tx DM	+	+++
Neurotoxic	+	++
Hirsutism	+++	+
Hair loss	+	++
Gum Hyperplasia	+++	-
Immunosupp. effects	++	+++
Nephrotoxic	+	+
Hypertension and Na retention	++	+
Hypercholes-terolemia	++	+
Drug interactions	Similar	Similar

56 yr old female patient is 8 days post deceased donor Tx has slow graft function -Cr 3.8. On Tacrolimus and Mycophenolate. Mild hypomagnesemic and is hypertensive (170/90). Presents to the ED via EMT with generalized tonic clonic seizures.

Which of the following is false?

A. Antiepileptic meds are indicated

B. Mg repletion is necessary

C. Tacrolimus should be discontinued

D. Treatment includes increasing her tacrolimus dose

E. MRI may show white matter changes

56 yr old female patient is 8 days post deceased donor Tx has slow graft function -Cr 3.8. On Tacrolimus and Mycophenolate. Mild hypomagnesemic and is hypertensive (170/90). Presents to the ED via EMT with generalized tonic clonic seizures.

Which of the following is false?

A. Antiepileptic meds are indicated

B. Mg repletion is necessary

C. Tacrolimus should be discontinued

D. Treatment includes increasing her tacrolimus dose

E. MRI may show white matter changes

Reversible Posterior Leukoencephalopathy Syndrome (aka PRES)

- Disordered cerebral autoregulation
- Endothelial dysfunction
- HypoMg, HTN, renal dysfunction
- Seen with immunosuppression in transplant patients
- Also seen with sepsis, pre-eclampsia, cisplatin,
- MRI: symmetrical white matter edema in the posterior cerebral hemispheres, particularly the parieto-occipital regions
- Clinical and radiologic findings are reversible with treatment of exacerbating factors
- Treatment is targeted to the precipitating cause, with use of antihypertensive agents or withdrawal of offending drugs, short-term treatment with antiepileptic drugs

HLA molecules normally:

A. Present foreign antigen to T cells

B. Present foreign antigen to B cells

C. Present foreign antigen to both T and B cells

D. Have nothing to do with antigen presentation

HLA molecules normally:

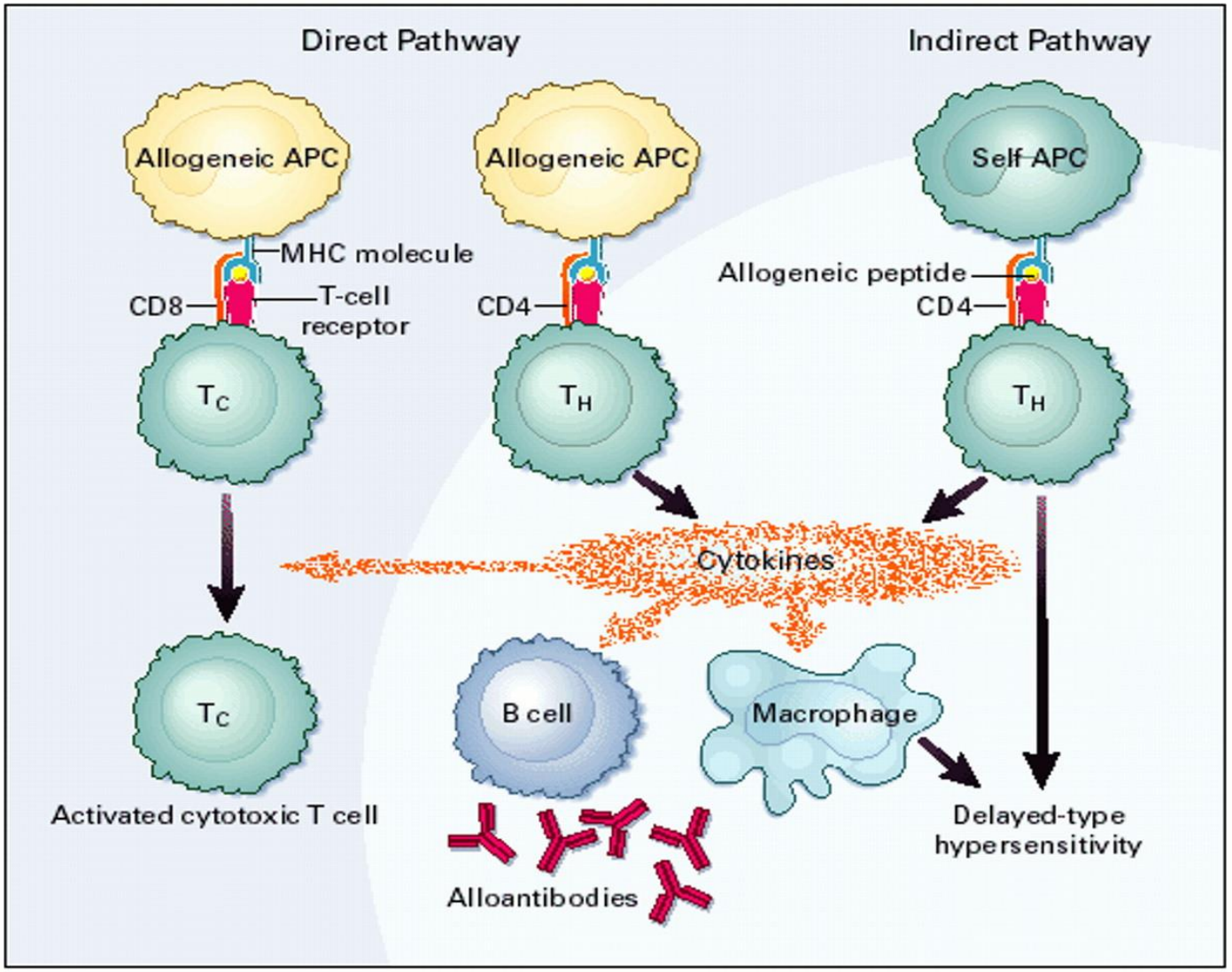
A. Present foreign antigen to T cells

B. Present foreign antigen to B cells

C. Present foreign antigen to both T and B cells

D. Have nothing to do with antigen presentation

Recognizing Foreign Antigens



Sayegh and Turka. N Engl J Med 1998;338:1813-1821

The NEW ENGLAND JOURNAL of MEDICINE

Case 2

- 51 yr old AA female had an uncomplicated living donor kidney transplant. Donor was husband APOL1 G1/G0.
- Historic DSA had been positive but pretransplant crossmatch negative.
- Diagnosed with FSGS and APOL1 G2/G2 phenotype
- Immunosuppression: thymoglobulin, MMF, prednisone, tacrolimus
- Cr fell quickly to 1.2mg/dL
- Medical Hx: History of SLE, hypertension, PVD

Case 2 cont'd

- 3 months posttransplant, admitted with a serum Cr 1.9
- Meds included MMF 1g BID, prednisone 5mg QD, tacrolimus, valganciclovir 450mg QOD
- Exam: P 100, BP 180/95, no papilledema; allograft non-tender; otherwise unremarkable
- US: no hydronephrosis, RI – 0.6
- Cr 1.9 → 2.3; tacrolimus 11.2
- Urinalysis: neg blood, neg WBC, +1 protein
- WBC 1.0-2.2 (eosinophils 4-15% but absolute # normal), Hgb 9.1, platelets 223

Which one of the following is not in the differential diagnosis?

a) Acute antibody mediated rejection (AMR)

b) Acute cellular rejection (ACR)

c) Recurrent APOL1 related kidney disease

d) Atheroembolism

e) Renal artery stenosis

Which one of the following is not in the differential diagnosis?

a) Acute antibody mediated rejection (AMR)

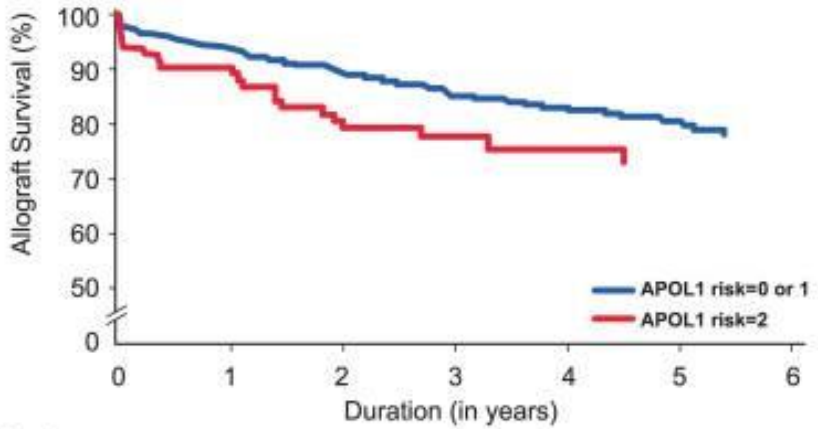
b) Acute cellular rejection (ACR)

c) Recurrent APOL1 related kidney disease

d) Atheroembolism

e) Renal artery stenosis

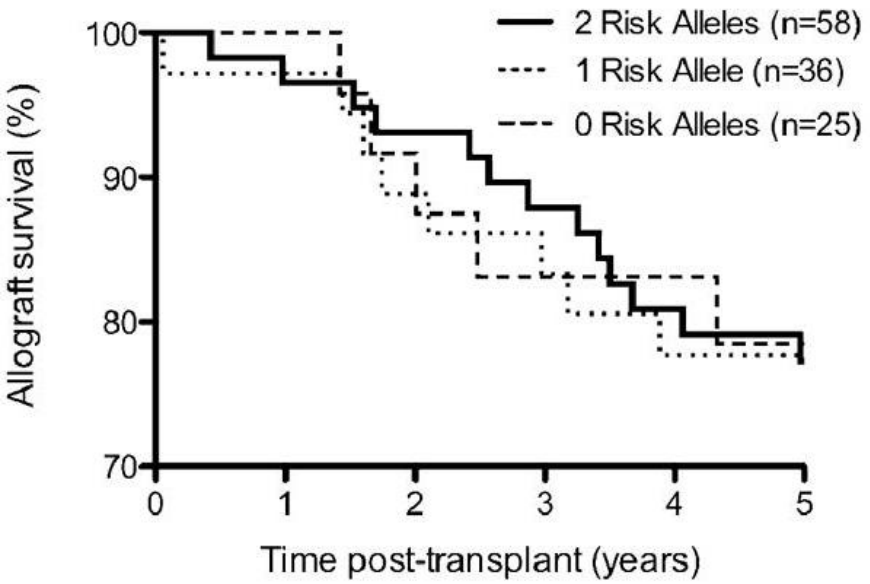
Risk of Allograft Failure in APOL1 High Risk Deceased Donors



APOL1 risk=0 or 1							
No. at risk	575	486	387	306	213	151	101
No. of graft losses	1	34	53	68	73	78	81
Failure rate	0.2%	6.2%	10.6%	14.8%	16.7%	19.4%	21.7%
No. censored	0	56	136	202	290	347	394
APOL1 risk=2							
No. at risk	99	86	63	45	35	29	29
No. of graft losses	2	9	18	19	20	21	21
Failure rate	2.0%	9.4%	20.6%	22.3%	24.5%	27.0%	27.0%
No. censored	0	4	18	35	44	49	49

Freedman BI et al. Apolipoprotein L1 gene variants in deceased organ donors are associated with renal allograft failure. *Am J Transplant.* 2015;15:1615–22

Transplant Recipients with High Risk APOL1 Genotypes do not have Increased Risk of Early Allograft Failure



Lee BT…Chandraker A. The APOL1 genotype of African American kidney transplant recipients does not impact 5-year allograft survival. *Am J Transplant*. 2012;12:1924-1928

The next best test to determine the etiology of her acute allograft dysfunction is:

a) Flow cytometry crossmatch against donor cells

b) Kidney biopsy

c) CT angiography of iliac and transplant renal arteries

d) Blood CMV viral load

e) Serum C3, C4

The next best test to determine the etiology of her acute allograft dysfunction is:

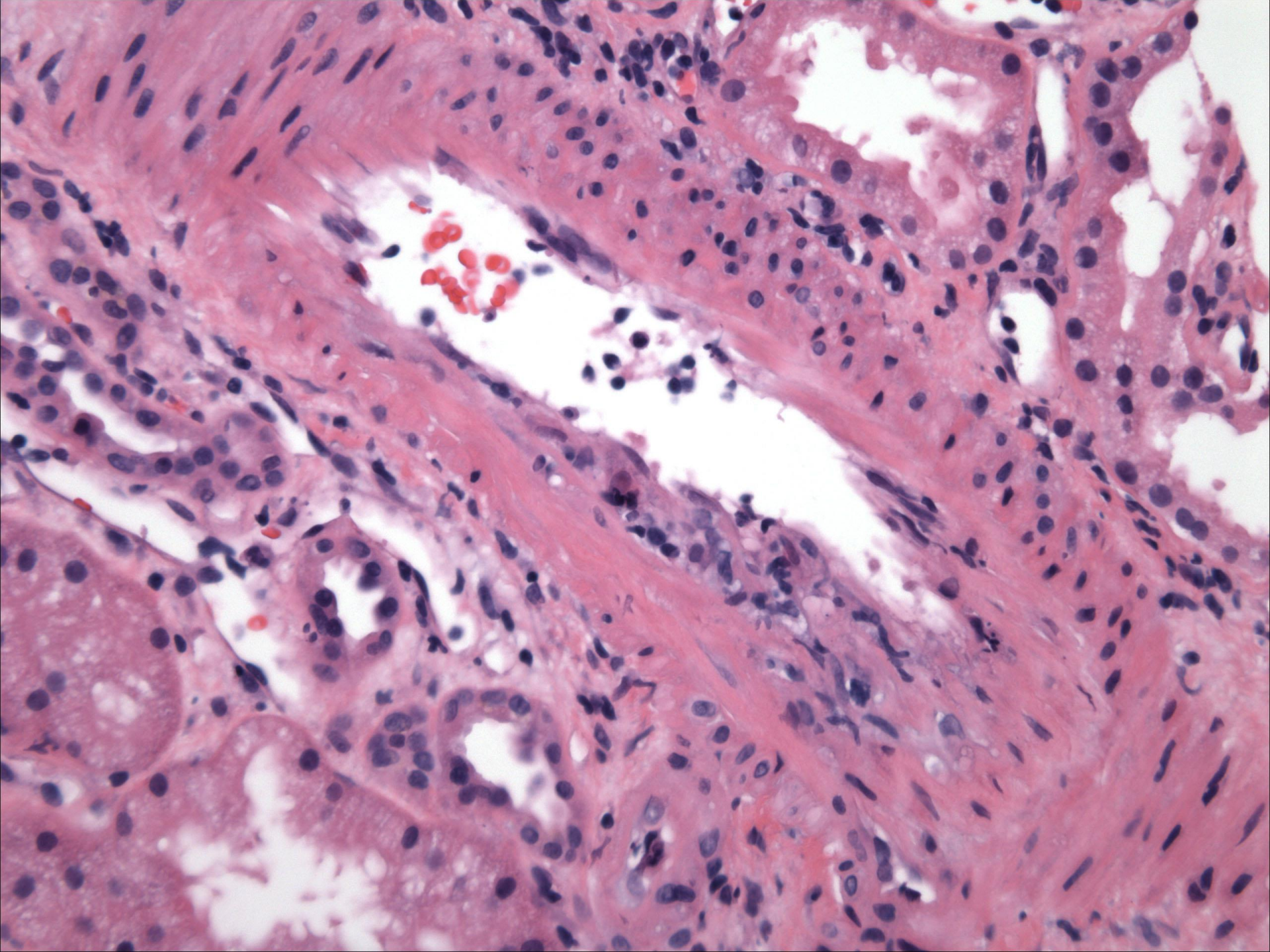
a) Flow cytometry crossmatch against donor cells

b) Kidney biopsy

c) CT angiography of iliac and transplant renal arteries

d) Blood CMV viral load

e) Serum C3, C4



The mononuclear cells undermining the endothelium of the small artery are most consistent with:

a) Acute AMR

b) Mild acute ACR

c) Polyoma (BK-virus) nephritis

d) Severe ACR

e) Atheroembolism

The mononuclear cells undermining the endothelium of the small artery are most consistent with:

a) Acute AMR

b) Mild acute ACR

c) Polyoma (BK-virus) nephritis

d) Moderate-Severe ACR

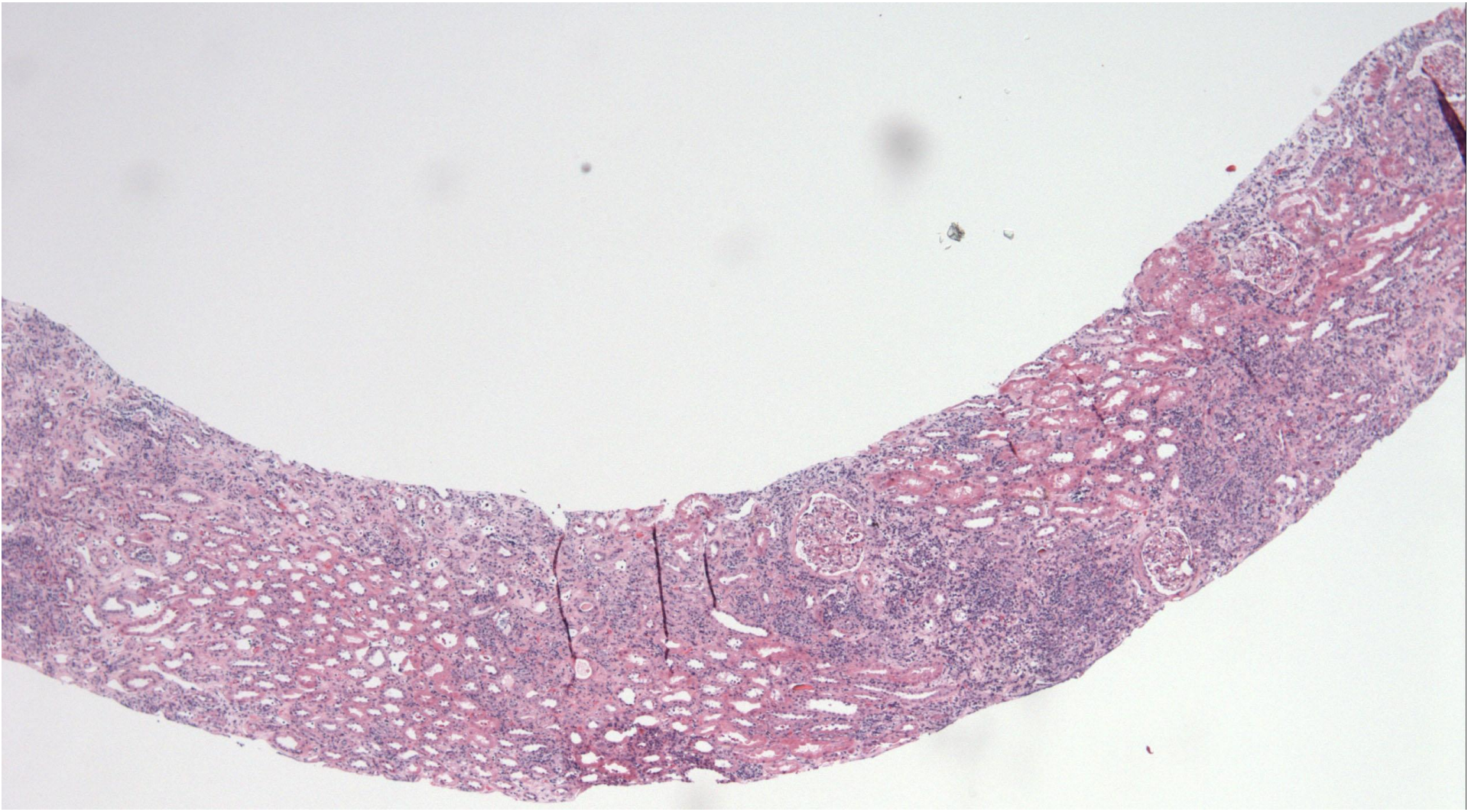
e) Atheroembolism

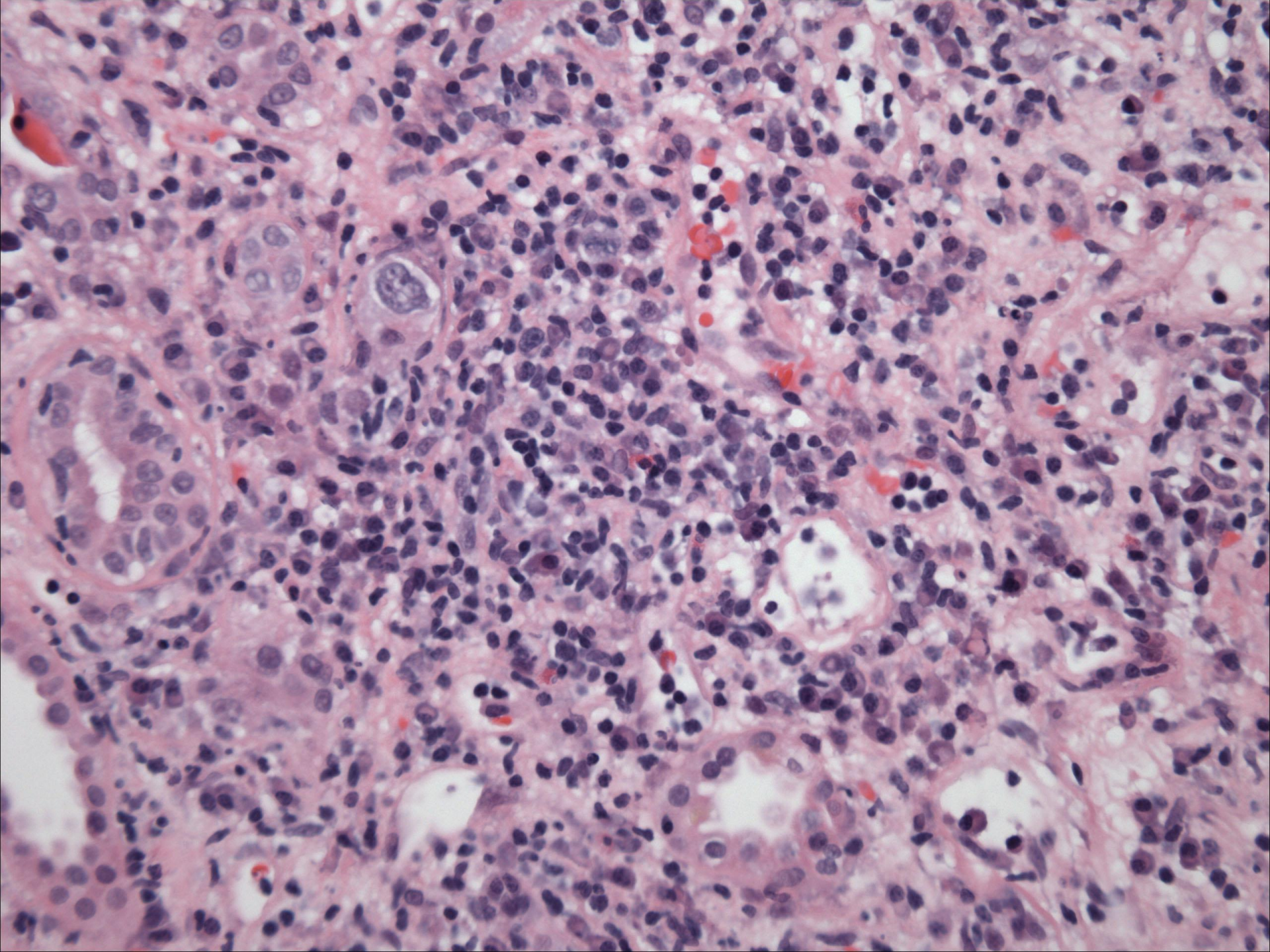
Case cont’d

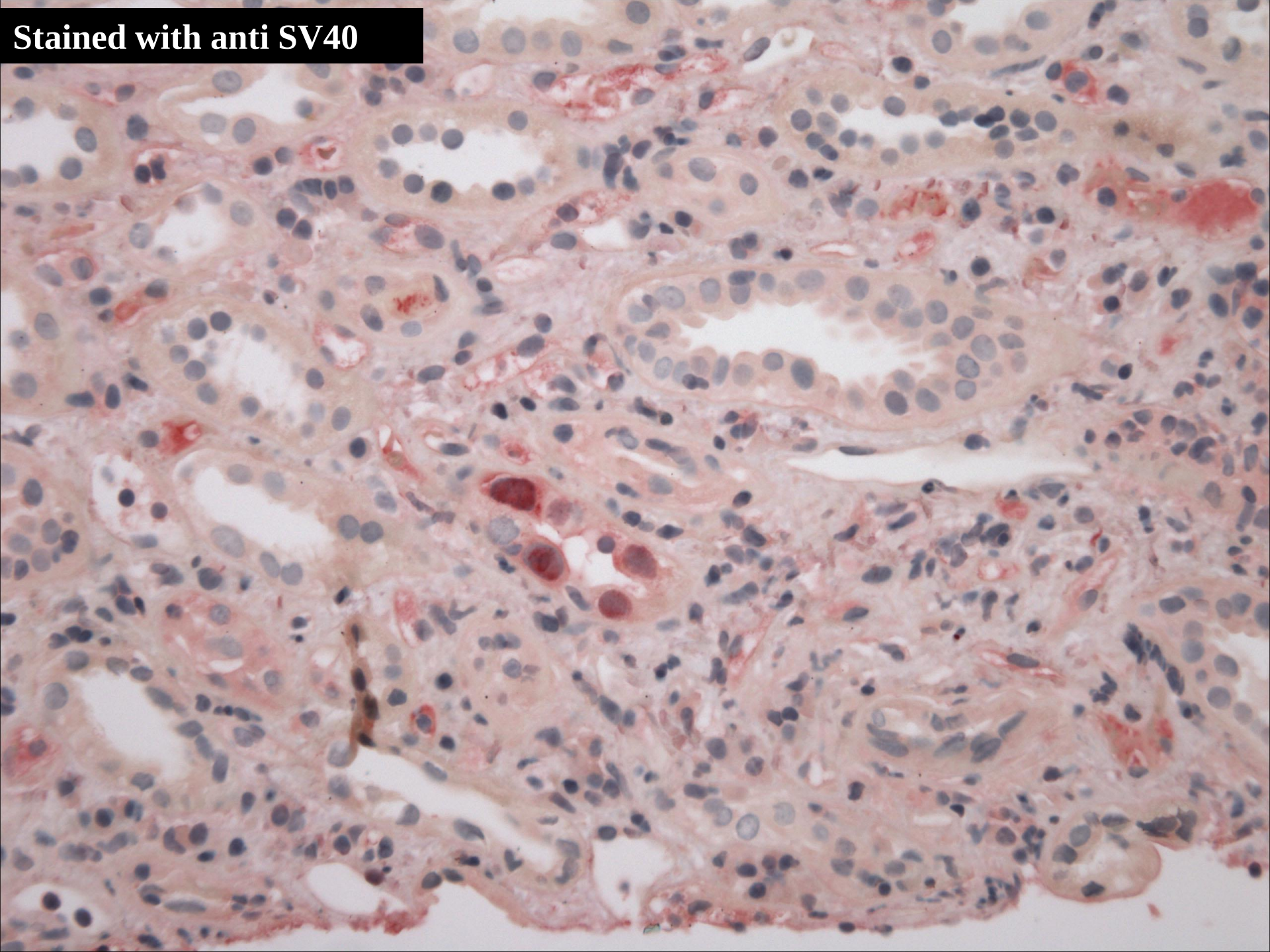
- Biopsy: ACR (IIA); C4d neg
- Crossmatch against donor T and B cells: neg
- LDH, haptoglobin, smear for schistocytes: neg for HUS / TTP
- MRA: plaques in aorta but no stenosis of common iliac or transplant renal artery
- Steroids then thymoglobulin

Case cont’d

- 3 months later, presents with increase in Cr from 1.8 to 2.5
- Meds: MMF, tacrolimus, pred
- Kidney bx is performed
- C4d stain neg






Stained with anti SV40

The biopsy findings are most consistent with:

a) Acute AMR

b) ACR + acute AMR

c) BK-virus nephritis

d) CMV infection

e) Atheroembolism

The biopsy findings are most consistent with:

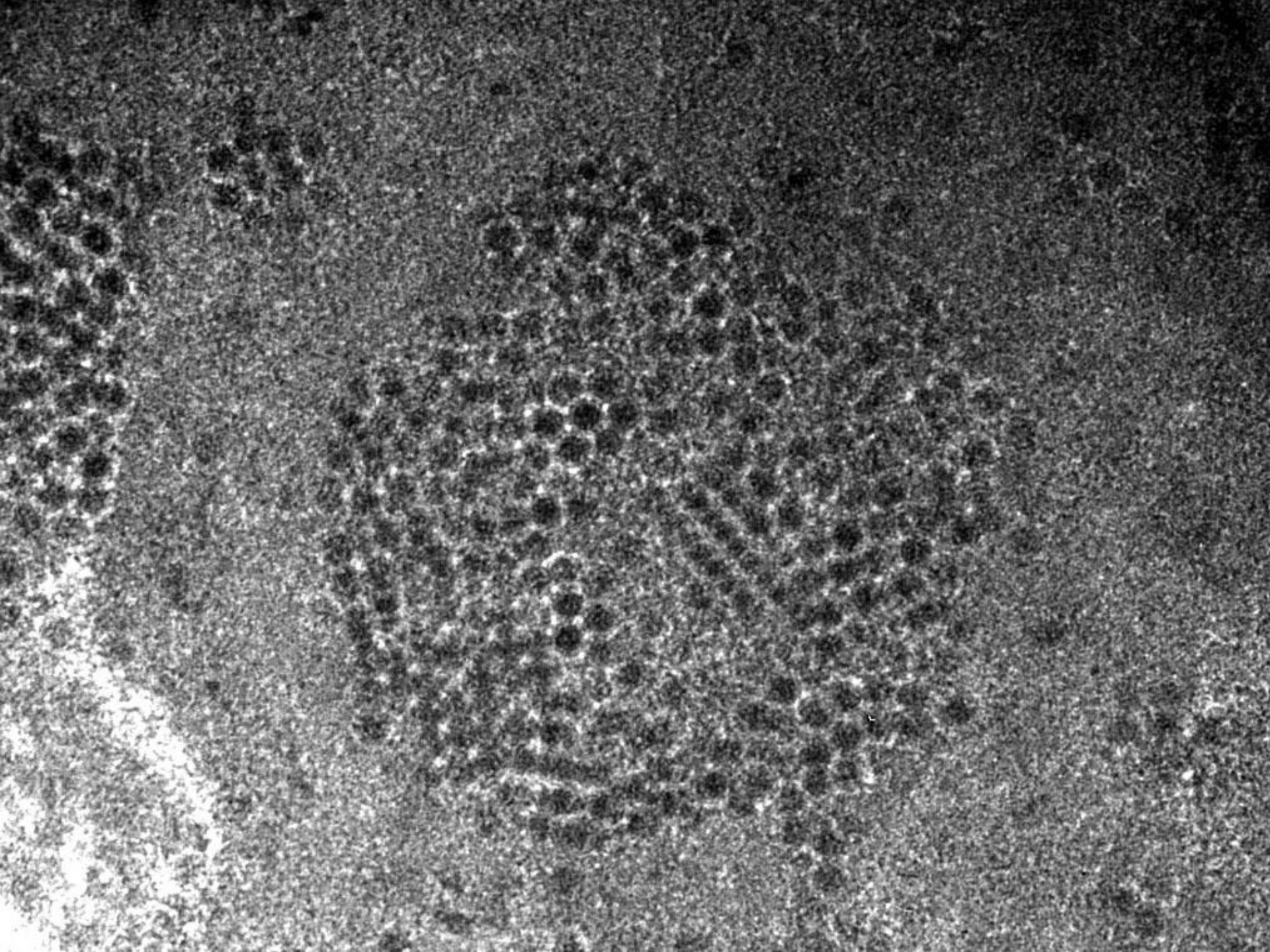
a) Acute AMR

b) ACR + acute AMR

c) BK-virus nephritis

d) CMV infection

e) Atheroembolism



BK Nephropathy

- Reactivation of BK virus that is dominant in the uroepithelial cells from immunosuppression and ischemia
- Most likely to occur 4 weeks to 1 year post transplant
- Diagnosis is by screening serum (sometimes urine)
- BK nephropathy – SV40 on biopsy
- Treatment is primarily reduction of immunosuppression but IVIG, and mTor inhibitors maybe useful
- Cytotoxic T cell lines and BK specific Ig being tested
- Graft loss due to BK is declining and is not a contraindication to re-transplantation

All of the following factors are included in calculating the Kidney Donor Profile Index (KDPI) except for:

a) Race

b) History of Diabetes

c) Serum Creatinine

d) Smoking History

e) Age

All of the following factors are included in calculating the Kidney Donor Profile Index (KDPI) except for:

a) Race

b) History of Diabetes

c) Serum Creatinine

d) Smoking History

e) Age

KDPI is calculated from 10 factors:

- Age
- Height
- Weight
- Ethnicity
- Hypertension
- Diabetes
- Cause of Death
- Serum Cr
- Hep C status
- Cardiac Death

It is a measure of organ quality and is used to allocate deceased donor organs. The lower the KDPI the better the quality of the organ. Younger, healthy patients are allocated low KDPI kidneys. Older, frailer patients have an option to be list for a high KDPI kidney.