Pathologic aspects of Polyomavirus (BK) nephropathy

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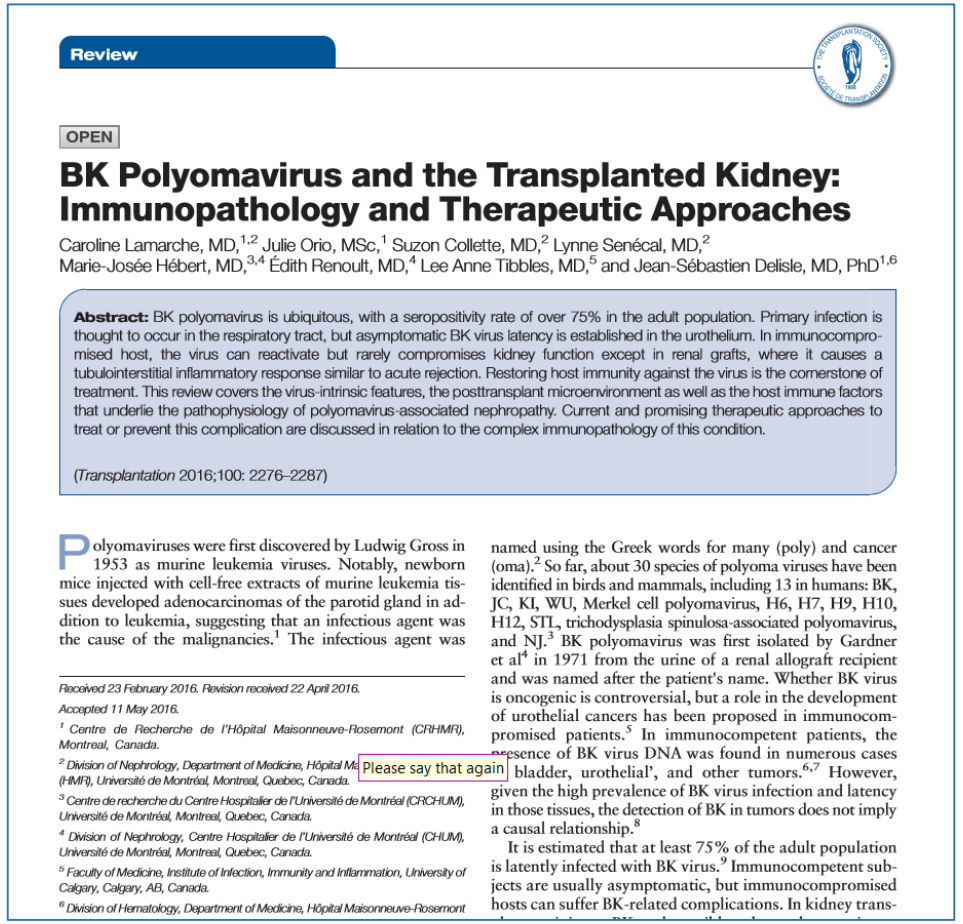
Polyomavirus Nephropathy

- First discovered by Ludwig Gross in 1953 as murine leukaemic viruses
- 1st isolated - urine of tx patient (BK) with ureteral stenosis (Gardner, Lancet 1:1253, 1971)
- 13 species in humans: BK, JC, KI, WU, merkel cells. Polyomavirus, edge six, edge seven, edge nine, edge 12, STL,...
- 75% of adult population has latent infection with BK virus.
  - Immunocompetent subjects: asymptomatic
  - immunocompromised hosts: complicated
    - kidney transplant recipients – nephropathy and ureteral stenosis(Reactivated in transplanted tissue)
    - haematopoietic stem cell transplant patients – haemorrhagic cystitis(Reactivated enhanced tissue)



Review

OPEN

BK Polyomavirus and the Transplanted Kidney: Immunopathology and Therapeutic Approaches

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Abstract: BK polyomavirus is ubiquitous, with a seropositivity rate of over 75% in the adult population. Primary infection is thought to occur in the respiratory tract, but asymptomatic BK virus latency is established in the urothelium. In immunocompromised host, the virus can reactivate but rarely compromises kidney function except in renal grafts, where it causes a tubulointerstitial inflammatory response similar to acute rejection. Restoring host immunity against the virus is the cornerstone of treatment. This review covers the virus-intrinsic features, the posttransplant microenvironment as well as the host immune factors that underlie the pathophysiology of polyomavirus-associated nephropathy. Current and promising therapeutic approaches to treat or prevent this complication are discussed in relation to the complex immunopathology of this condition.

(*Transplantation* 2016;100: 2276–2287)

Polyomaviruses were first discovered by Ludwig Gross in 1953 as murine leukemia viruses. Notably, newborn mice injected with cell-free extracts of murine leukemia tissues developed adenocarcinomas of the parotid gland in addition to leukemia, suggesting that an infectious agent was the cause of the malignancies.[1] The infectious agent was named using the Greek words for many (poly) and cancer (oma).[2] So far, about 30 species of polyoma viruses have been identified in birds and mammals, including 13 in humans: BK, JC, KI, WU, Merkel cell polyomavirus, H6, H7, H9, H10, H12, STL, trichodysplasia spinulosa-associated polyomavirus, and NJ.[3] BK polyomavirus was first isolated by Gardner et al[4] in 1971 from the urine of a renal allograft recipient and was named after the patient's name. Whether BK virus is oncogenic is controversial, but a role in the development of urothelial cancers has been proposed in immunocompromised patients.[5] In immunocompetent patients, the presence of BK virus DNA was found in numerous cases of bladder, urothelial', and other tumors.[6,7] However, given the high prevalence of BK virus infection and latency in those tissues, the detection of BK in tumors does not imply a causal relationship.[8]

It is estimated that at least 75% of the adult population is latently infected with BK virus.[9] Immunocompetent subjects are usually asymptomatic, but immunocompromised hosts can suffer BK-related complications. In kidney trans-

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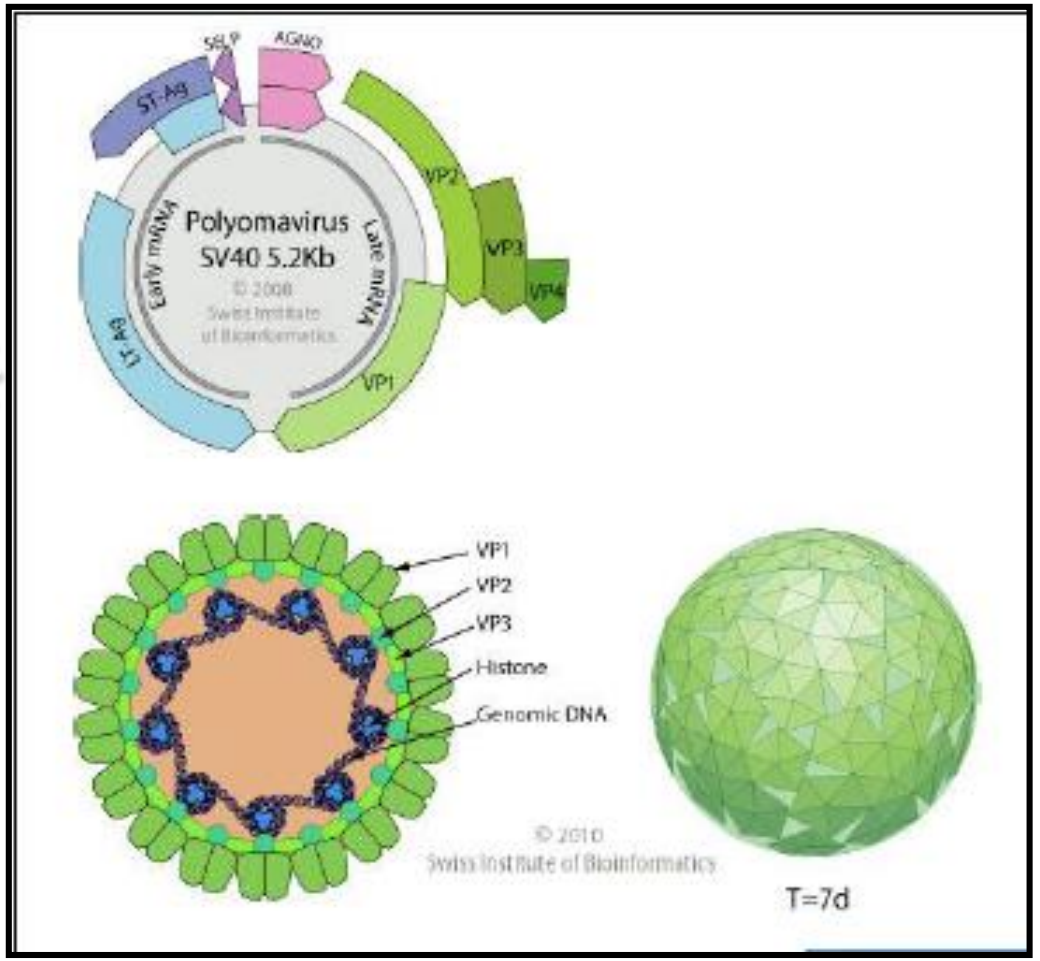
Polyomavirus Nephropathy

PV Basics:

- Double stranded DNA virus, Genus Orthopoly-omavirus of the family Polyomaviridae
- Natural transmission: oral or respiratory
- primary infection in early childhood (age of 4-5 years), mostly subclinical or “flu-like”
- Seroprevalence >75% in adults



The Banff Working Group Classification of Definitive Polyomavirus Nephropathy: Morphologic Definitions and Clinical Correlations

Volker Nickeleit,[1] Harsharan K. Singh,[1] Parmjeet Randhawa,[2] Cinthia B. Drachenberg,[3] Ramneesh Bhatnagar,[3] Erika Bracamonte,[4] Anthony Chang,[5] W. James Chon,[6] Darshana Dadhania,[7] Vicki G. Davis,[1] Helmut Hopfer,[8] Michael J. Mihatsch,[8] John C. Papadimitriou,[3] Stefan Schaub,[9] Michael B. Stokes,[10] Mohammad F. Tungekar,[11] and Surya V. Seshan,[12] on behalf of the Banff Working Group on Polyomavirus Nephropathy

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pathogens

MDPI

Review

BK Virus-Associated Nephropathy after Renal Transplantation

Yasuhito Funahashi

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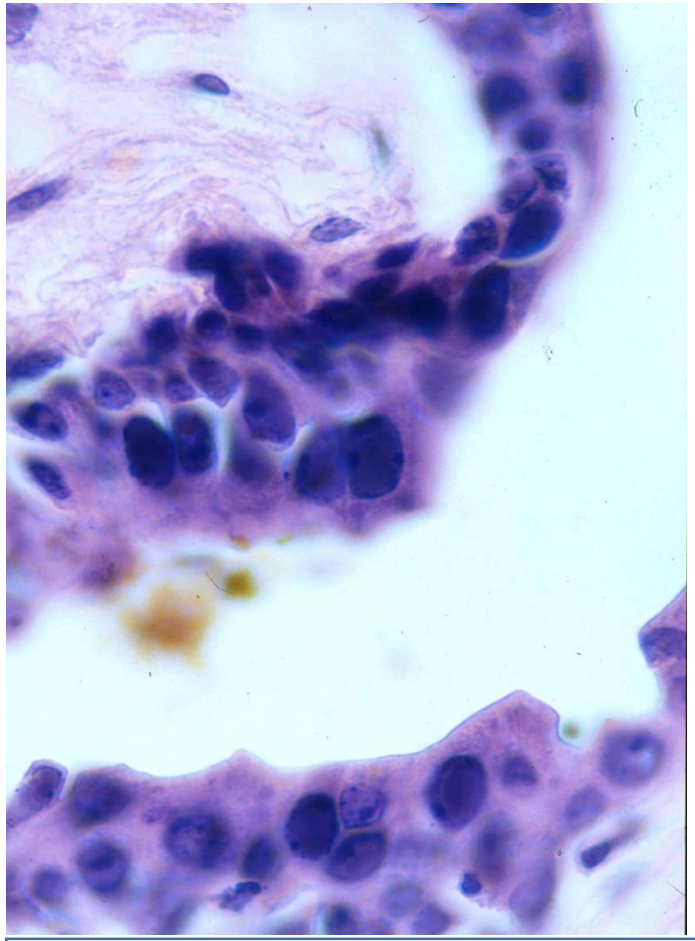
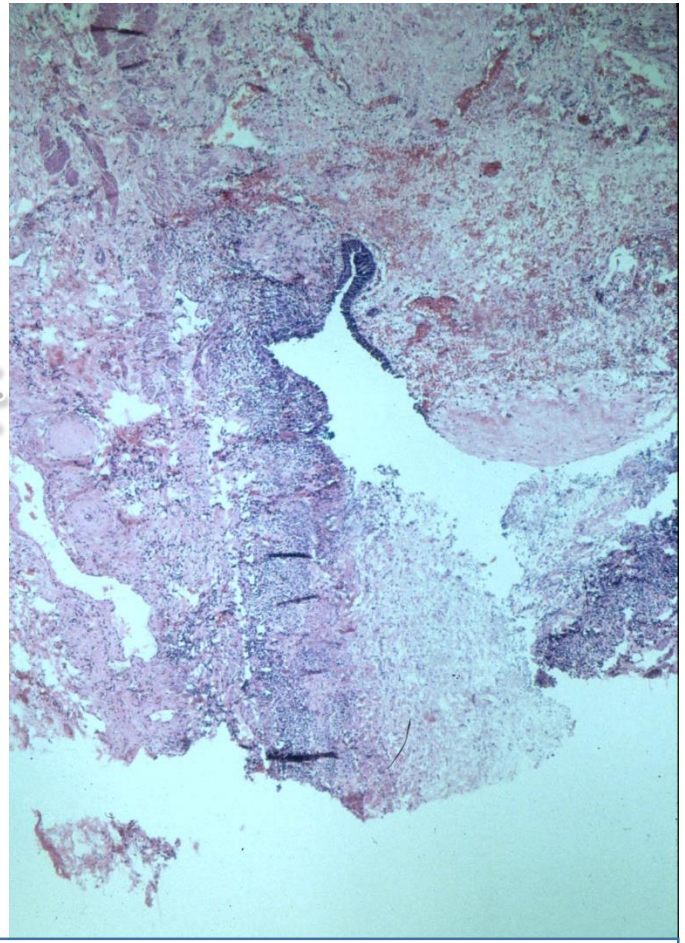
Abstract: Recent advances in immunosuppressive therapy have reduced the incidence of acute rejection and improved renal transplantation outcomes. Meanwhile, nephropathy caused by BK virus has become an important cause of acute or chronic graft dysfunction. The usual progression of infection begins with BK viruria and progresses to BK viremia, leading to BK virus associated nephropathy. To detect early signs of BK virus proliferation before the development of nephropathy, several screening tests are used including urinary cytology and urinary and plasma PCR. A definitive diagnosis of BK virus associated nephropathy can be achieved only histologically, typically by detecting tubulointerstitial inflammation associated with basophilic intranuclear inclusions in tubular and/or Bowman's epithelial cells, in addition to immunostaining with anti-Simian virus 40 large T-antigen. Several pathological classifications have been proposed to categorize the severity of the disease to allow treatment strategies to be determined and treatment success to be predicted. Since no specific drugs that directly suppress the proliferation of BKV are available, the main therapeutic approach is the reduction of immunosuppressive drugs. The diagnosis of subsequent acute rejection, the definition of remission, the protocol of resuming immunosuppression, and long-term follow-up remain controversial.

Keywords: BK virus; BK virus-associated nephropathy; renal transplantation

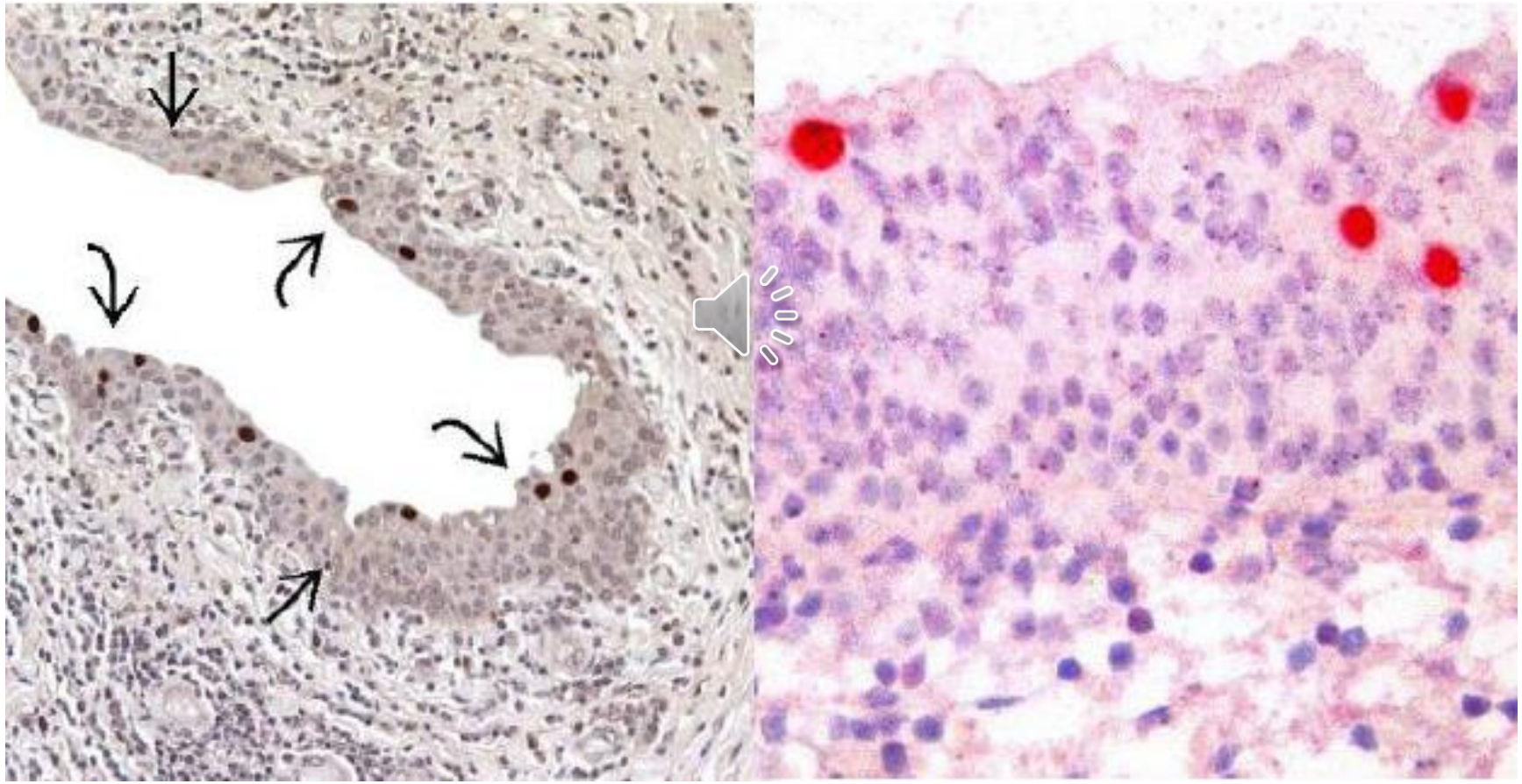
Polyomavirus Nephropathy





Biopsy from BK's ureter S. Gardner, St. Mary's Hosp, UK

Urothelium - Polyoma



A. Chang, in Colvin et al, *Diagnostic Pathology: Kidney Diseases*, 2011

Table 1 Polyomaviruses detected in humans and involved in the pathogenesis of polyomavirus-associated nephropathy

Virus	Host	Clinical diseases
BKV	Human	PVAN in renal transplantation Hemorrhagic cystitis in bone marrow transplantation
JCV	Human	Progressive multifocal leukoencephalopathy PVAN in renal transplantation
SV-40	Non-human primate	Unknown; PVAN in renal transplantation?

Costa C, Cavallo R. Polyomavirus-associated nephropathy. *World J Transplant* 2012; 2(6): 84-94

Associated Diseases

- Polyomavirus-associated nephropathy (PyVAN)
- Polyomavirus-associated hemorrhagic cystitis
- Ureteric stenosis
- «possibly carcinogenic to humans» (group 2B)
- CNS involvement
- Systemic vasculopathy with multiorgan failure
- Polyomavirus-associated pneumonia

BK Polyomavirus Nephropathy

Marked increase in reports >1995

Frequency of polyoma acute interstitial nephritis in large series: 2-7% of patients

Most patients have been on tacrolimus and/or mycophenolate mofetil (>95%)

Table 1. Reported risk factors for BKVAN.

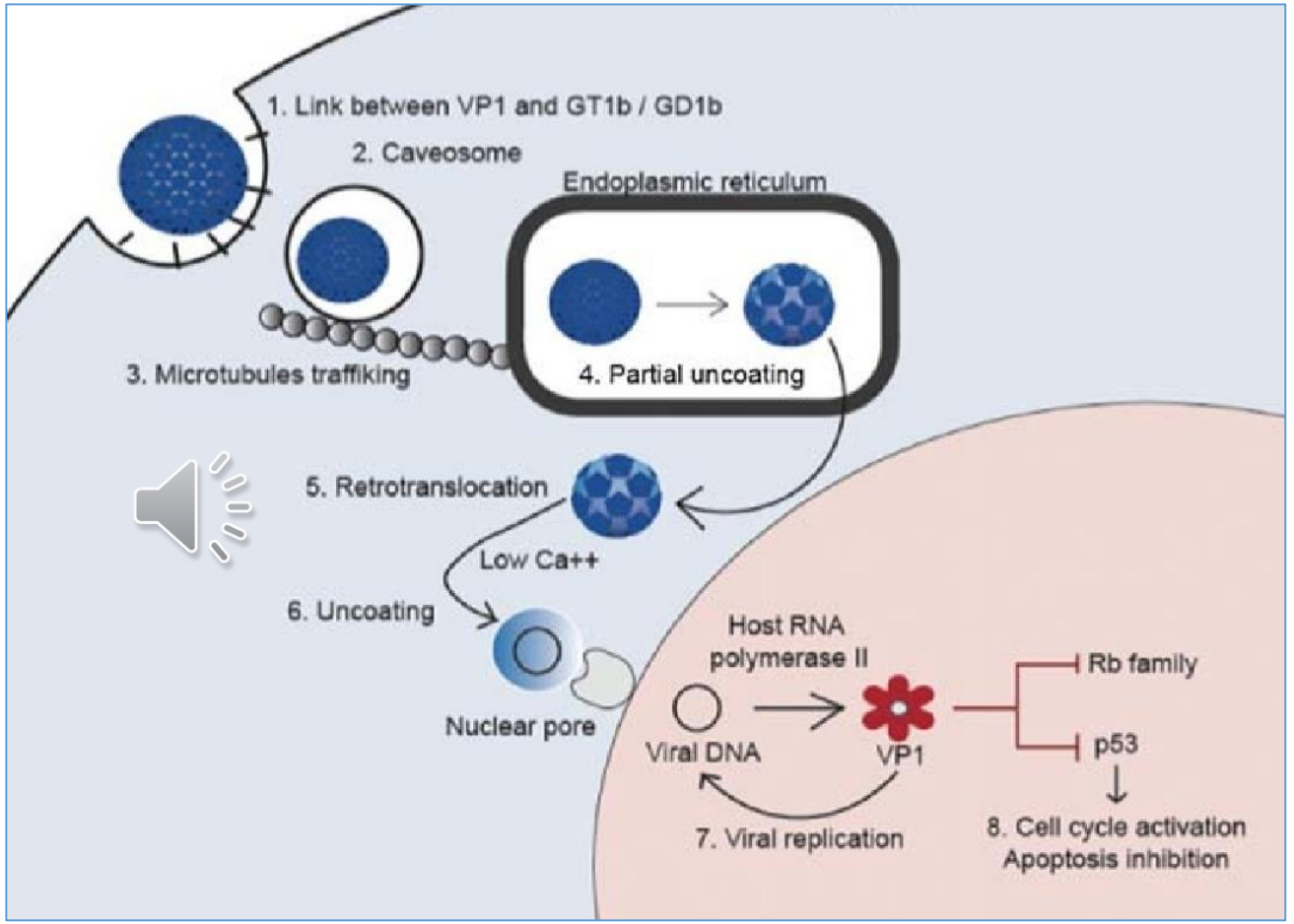
Donor factors	Deceased donor [21] BKV viruria [22] High BKV antibody titers [23,24] Female gender [21] Degree of HLA mismatches [21,25] Positivity of HLA A9 [26], G 3'UTR-4 [27] Negativity of HLA C7 [28,29]
Recipient factors	Older age [21] Male gender [21] ABO incompatibility [30] History of hemodialysis [31] Low BKV antibody titers [24] African American [32] Diabetes [21] Positivity of HLA A2 [26], G 3'UTR-4 [27] Negativity of HLA C7 [28], B51 [33]
Transplant factors	Acute rejection and antirejection treatment [25,34,35] Delayed graft function [36] Cold ischemia time [37] Steroid exposure [38] Tacrolimus levels [38] Tacrolimus and/or MMF-based maintenance immunosuppression [21,31,39] Ureteric stent replacement [40]

BK Polyomavirus cell entry and infection

- Binding to target cells through interaction with ganglia site receptors, endocytosis, partial uncoating of the virus, re-translocation to the cytosol, passage of viral DNA into the cell nucleus.

- Oncogenic effect: binding and interacting tumour suppressor proteins, including retinoblastoma family genes and p53

- viral replication, large T antigen expression and p53 accumulation associated with nuclear enlargement of infected cells and high expression of Ki 67.



Transplantation 2016; 100:2276-2287

Latency and Reactivation

in transplanted kidney:

virus initially replicates in the distal tubular epithelial cells

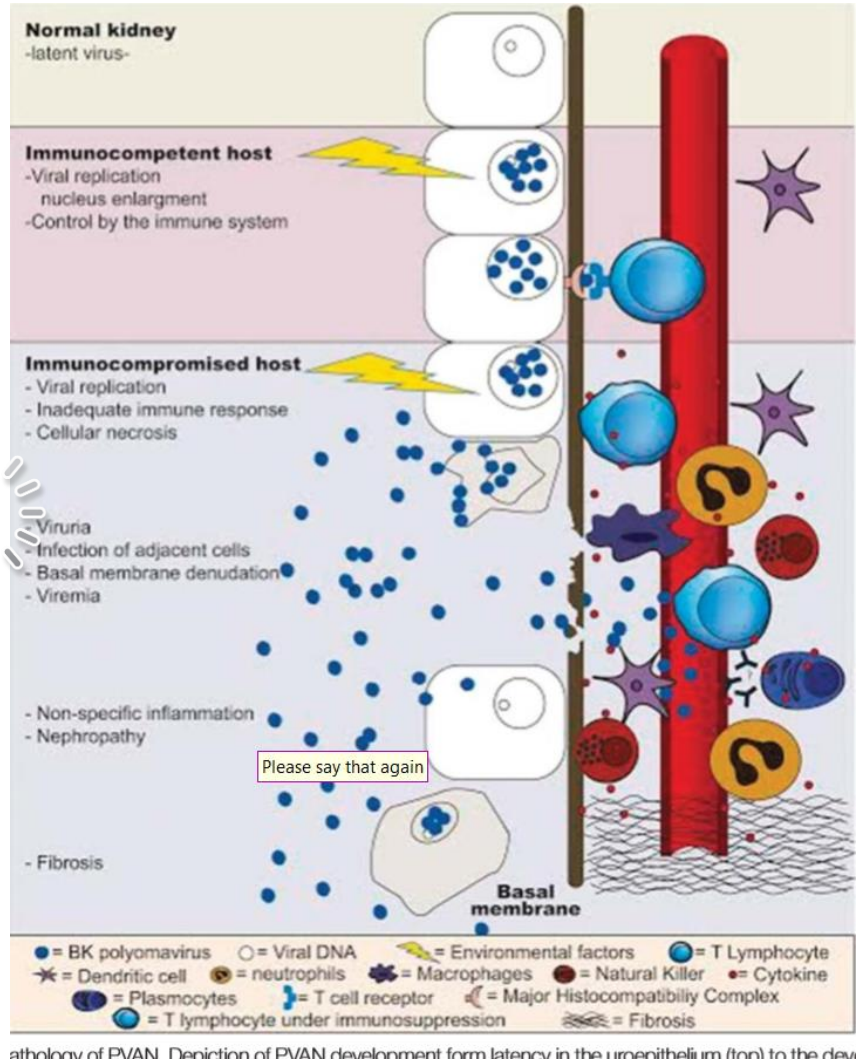
necrosis, local damage and inflammation

spread in the intra tubular space

by peritubular capillaries resulting viraemia

recruitment of inflammatory cells in the tubulointerstitial space

viral spread to proximal cells



athology of PVAN. Depiction of PVAN development form latency in the uroepithelium (top) to the dev

Transplantation 2016; 100:2276-2287

Diagnosis of Polyomavirus associated nephropathy(PVAN)

Decoy cells are virally infected uroithelial cells: a standard light microscopy (PPV: 11.7%)

Viraemia has a better positive predictive value for nephropathy than by viruria, especially if viral load is more than 10,000 copies/ml.

The diagnosis of PVN is highly suggested by the detection of viral inclusion bodies on kidney biopsy but confirmed with immunohistochemical staining for SV40.

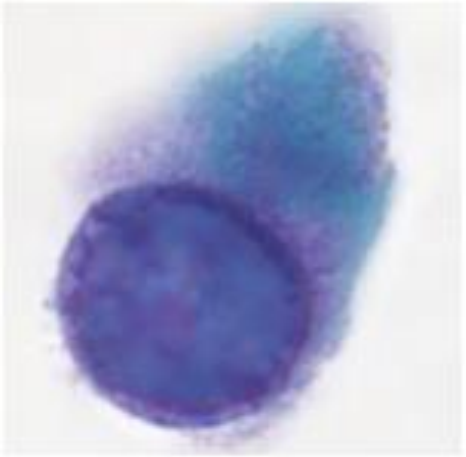
Other Biomarkers: urinary Polyomavirus-haufen test, urinary P1 messenger

(m) RNA, protease inhibitor-9 mRNA, plasminogen activator inhibitor-1 mRNA

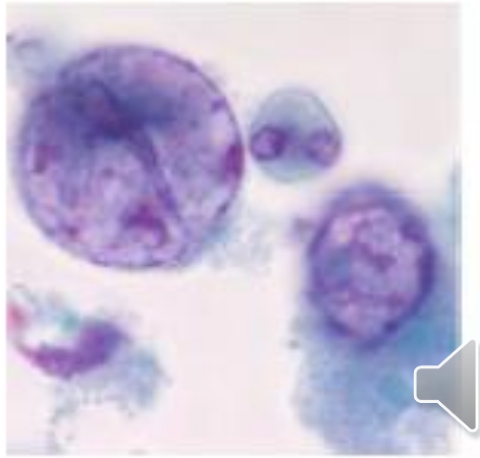
Decoy cells

- „Decoy cells“ in urinary tract (early 1960s), Andrew Ricci, Koss Laboratory: cells that may be mistaken for carcinoma cells
- Pregnancy 3%
- Diabetes mellitus 3%
- Cancer patients 13%
- Healthy renal Tx recipients 23%
- Healthy pulmonary Tx recipients 11%

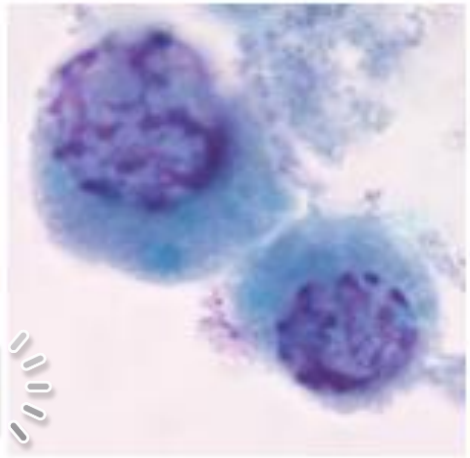
Morphology of decoy cells



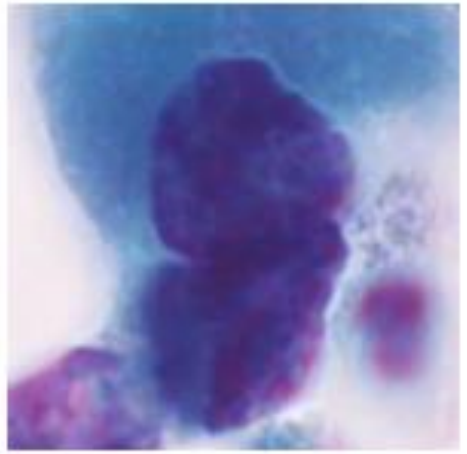
ground-glass (classic) type



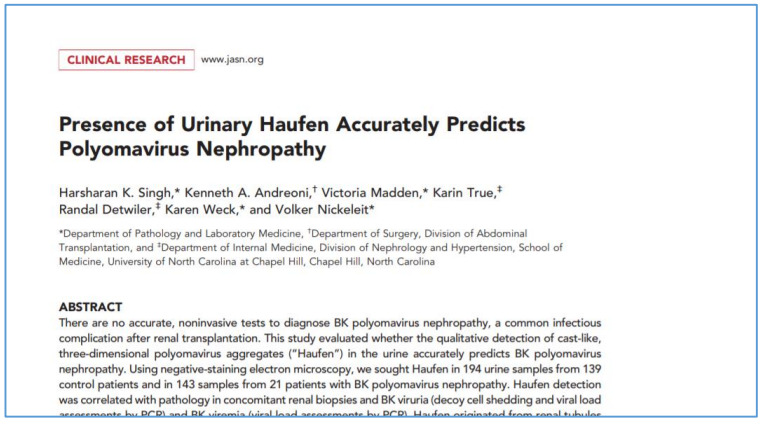
vesicular type



spider web-like type



carcinoma-like type



CLINICAL RESEARCH www.jasn.org

Presence of Urinary Haufen Accurately Predicts Polyomavirus Nephropathy

Harsharan K. Singh,* Kenneth A. Andreoni,† Victoria Madden,* Karin True,‡ Randal Detwiler,‡ Karen Weck,* and Volker Nickeleit*

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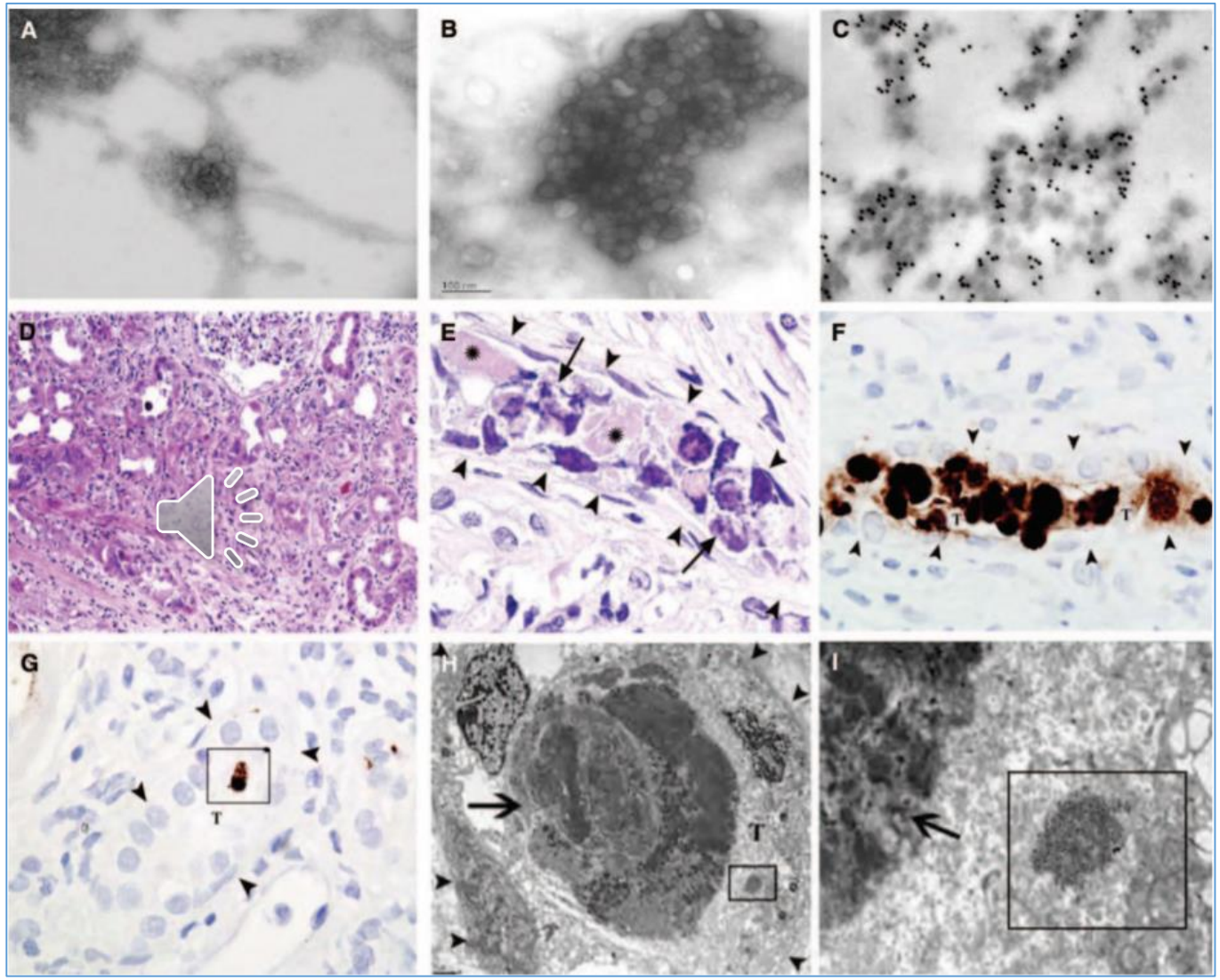
ABSTRACT

There are no accurate, noninvasive tests to diagnose BK polyomavirus nephropathy, a common infectious complication after renal transplantation. This study evaluated whether the qualitative detection of cast-like, three-dimensional polyomavirus aggregates ("Haufen") in the urine accurately predicts BK polyomavirus nephropathy. Using negative-staining electron microscopy, we sought Haufen in 194 urine samples from 139 control patients and in 143 samples from 21 patients with BK polyomavirus nephropathy. Haufen detection was correlated with pathology in concomitant renal biopsies and BK viruria (decoy cell shedding and viral load

haufen test

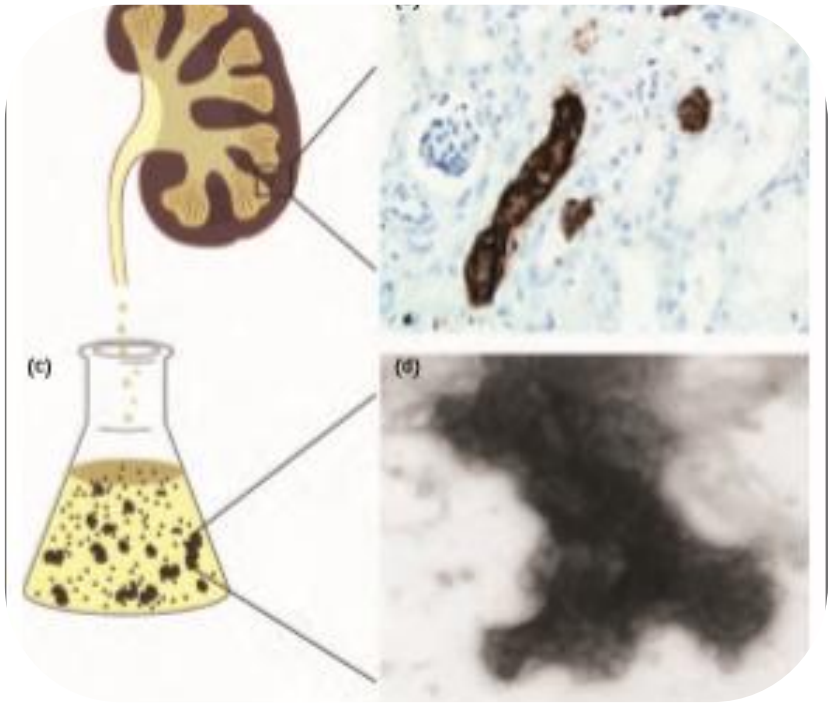
- Haufen Definition "Haufen" (after the German word for "**cluster or stack**") were defined as **three-dimensional, cast-like**, dense polyomavirus aggregates in urine samples analyzed **by EM**.

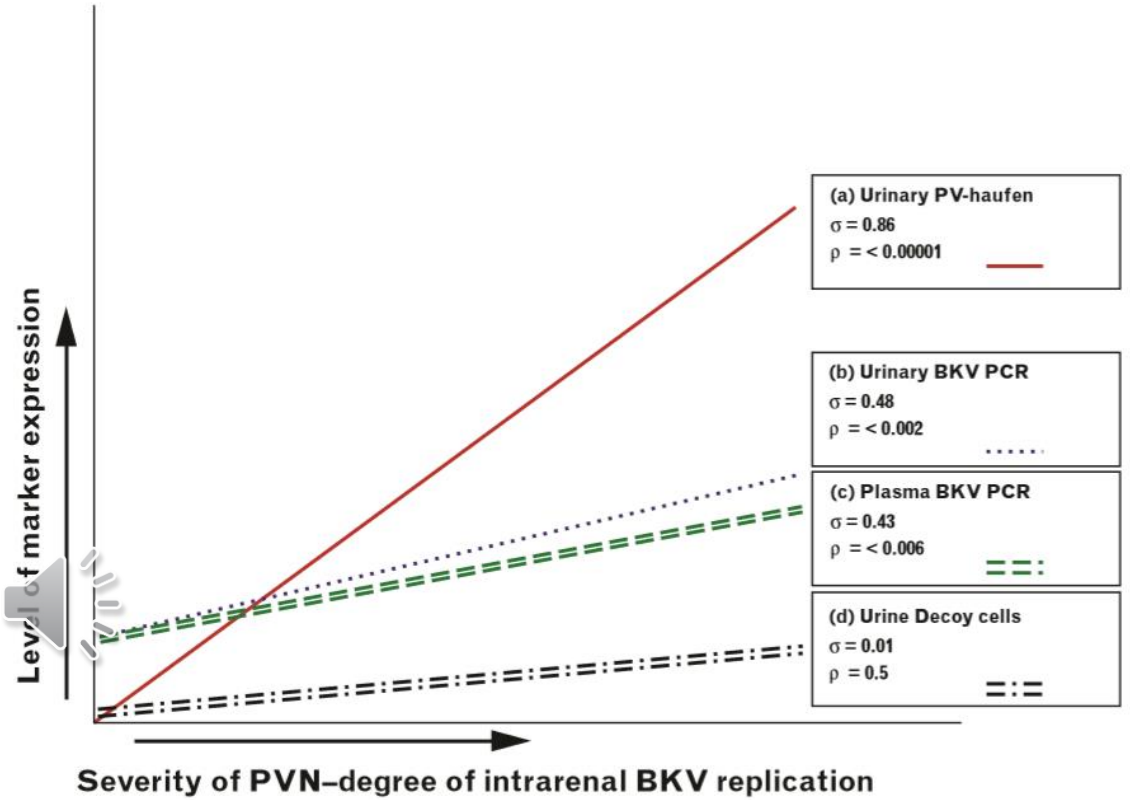
- Shedding of urinary Haufen and not BK viremia and viruria accurately mark BK polyomavirus nephropathy. It suggests that the ***detection of Haufen may serve as a noninvasive means to diagnose BK polyomavirus nephropathy in the urine.***

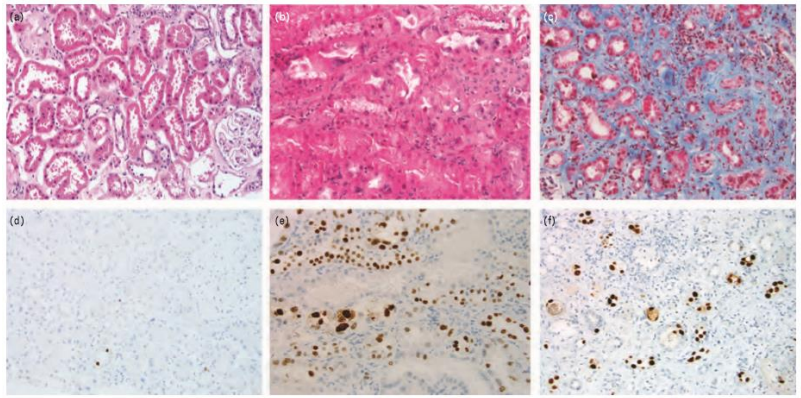


J Am Soc Nephrol 20: 416–427, 2009

haufen test

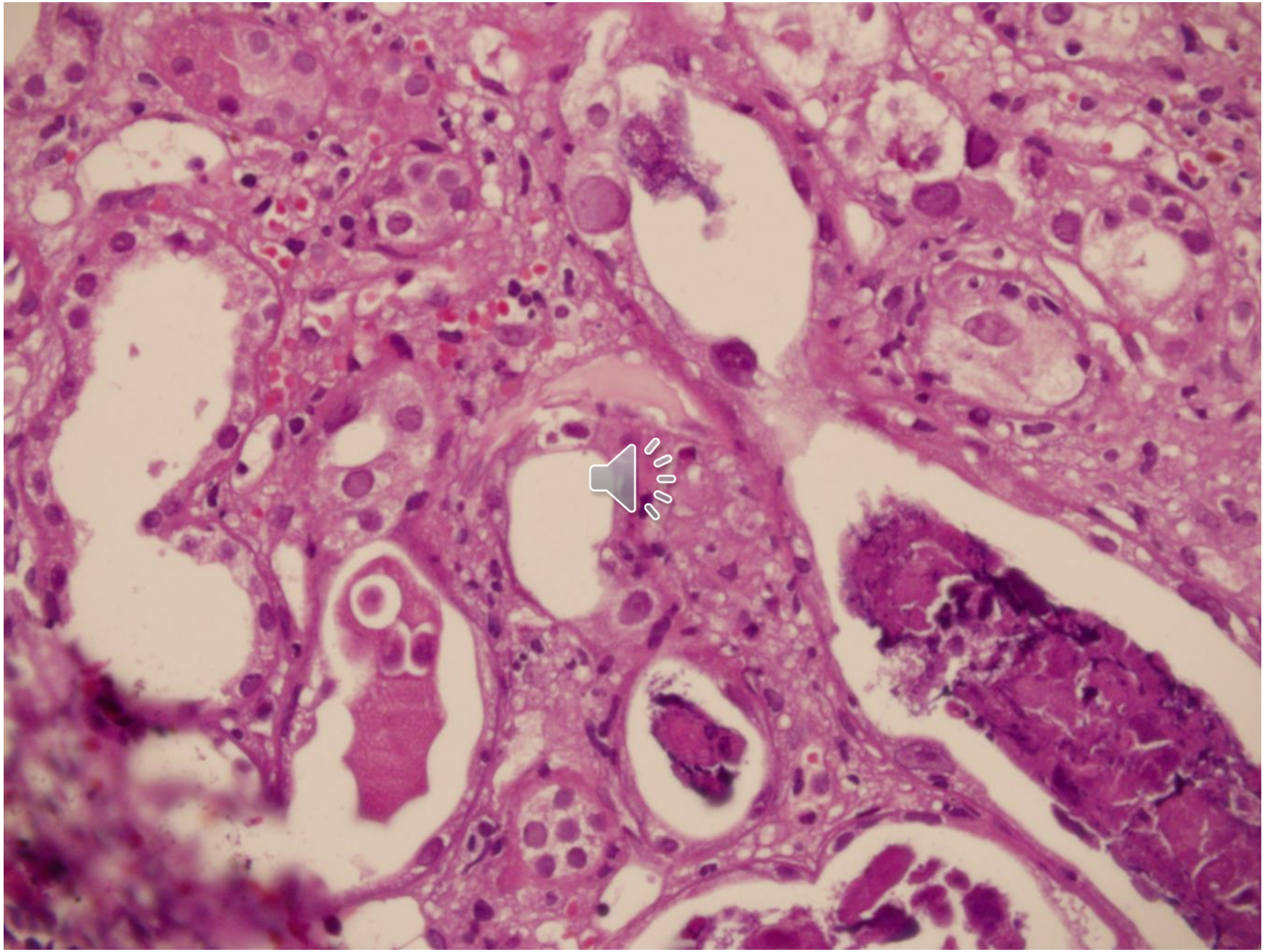


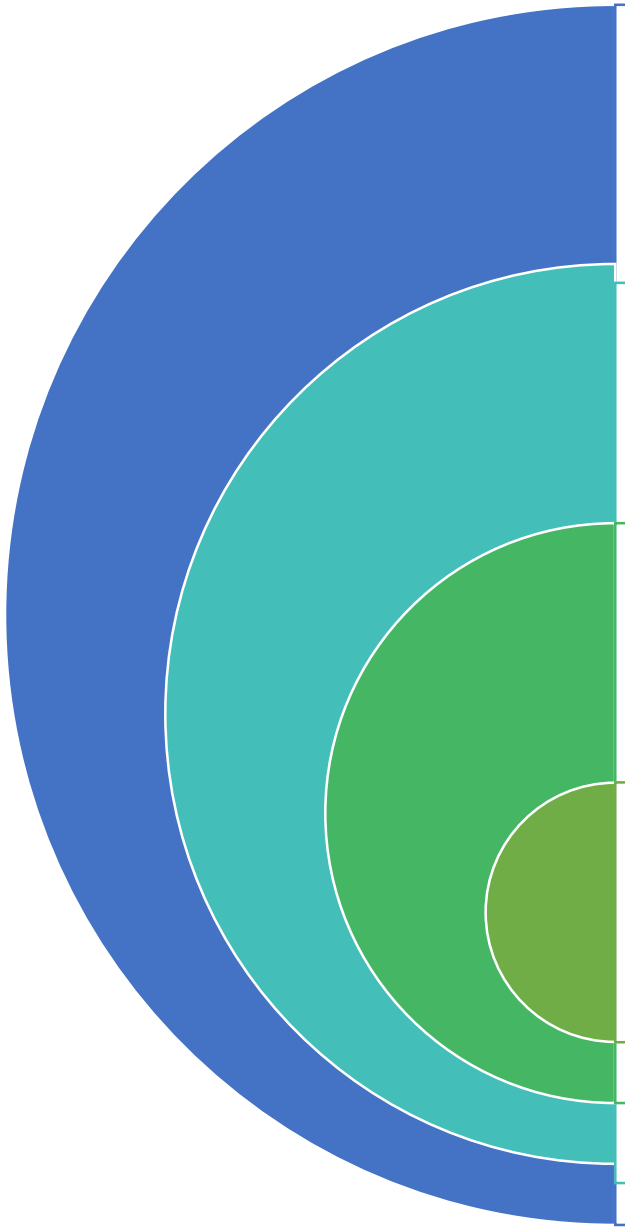




Quantitative urinary polyomavirus haufen testing can provide additional information on the severity of PVN that **is relevant for diagnosis and monitoring of disease resolution during the follow up**.

Organ transplantation. 2015 Jun;20(3):348-58





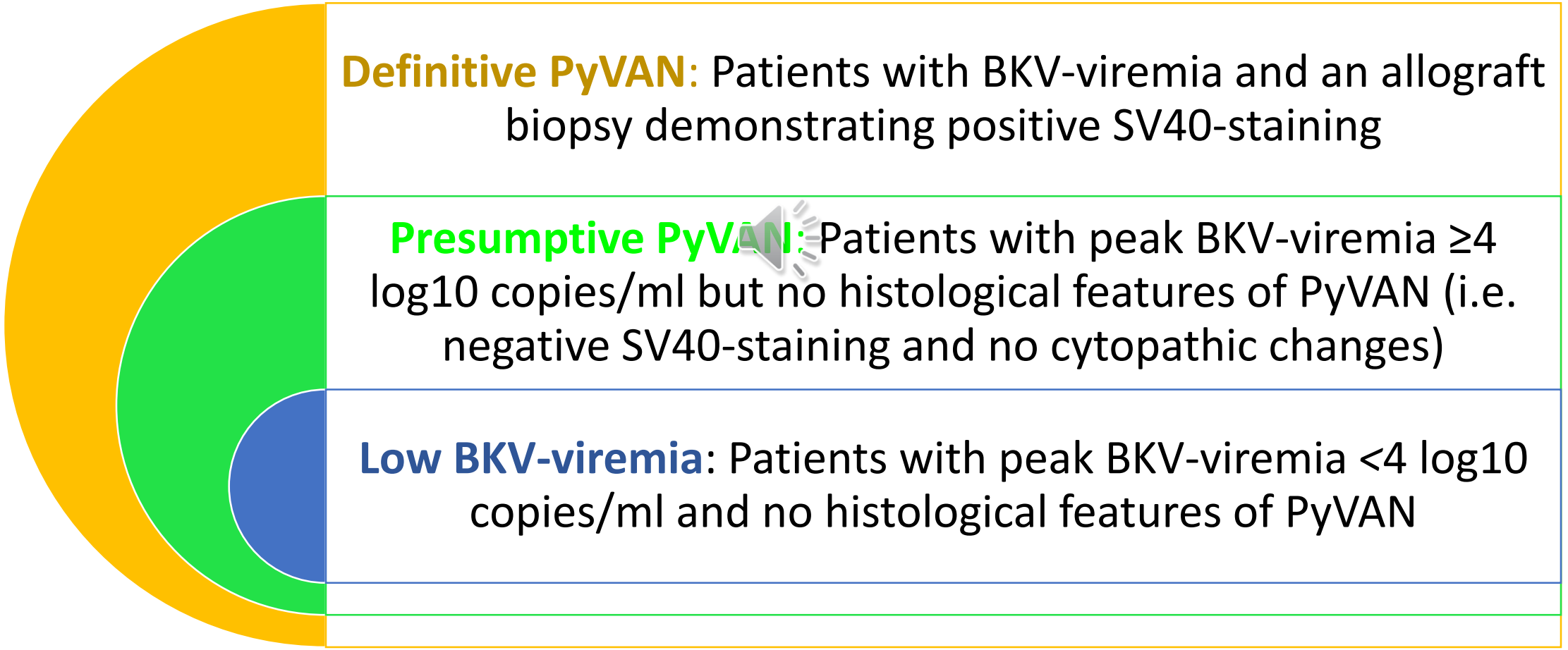
quantitative PCR tests to assess **BK viremia are not standardized**, and *BK viremia titers only imperfectly reflect the degree of viral renal injury*, thereby leaving diagnostic uncertainty.

Definitive PVN can also be unexpectedly observed in surveillance biopsies of stable grafts or occasionally, in patients with polyomavirus infections other than BK virus.

In developed countries, the incidence of biopsy confirmed definitive PVN is approximately 5%–6%, with broad transplant center variations.

The highest incidence of definitive PVN is found in **ABO-incompatible grafts (18%)** and highly **sensitized allograft recipients** after desensitization (20%).

Definitions



pvl scoring

A tubule with intranuclear viral inclusion bodies (type 1 or 2) and/or a positive IHC reaction for SV40-T antigen in one or more cells per tubular cross-section is considered “a positive tubule.”

The overall percentage of positive tubular cross-sections is estimated in the entire biopsy sample (all available cores, cortex, and medulla):

pvl 1: ≤1% of all tubules/ducts with viral replication.

pvl 2: >1% to ≤10% of all tubules/ducts with viral replication.

pvl 3: > 10% of all tubules/ducts with viral replication.

In PVN classes 1–3, interstitial inflammation and tubulitis can vary from Banff scores ti 0 to ti 3/t 0 to t 3.

PVN class 1 often lacks a significant inflammatory reaction.

To adequately establish or exclude a diagnosis of definitive PVN, two biopsy cores including portions of medulla in at least one of the two cores are required

PyVAN Stages

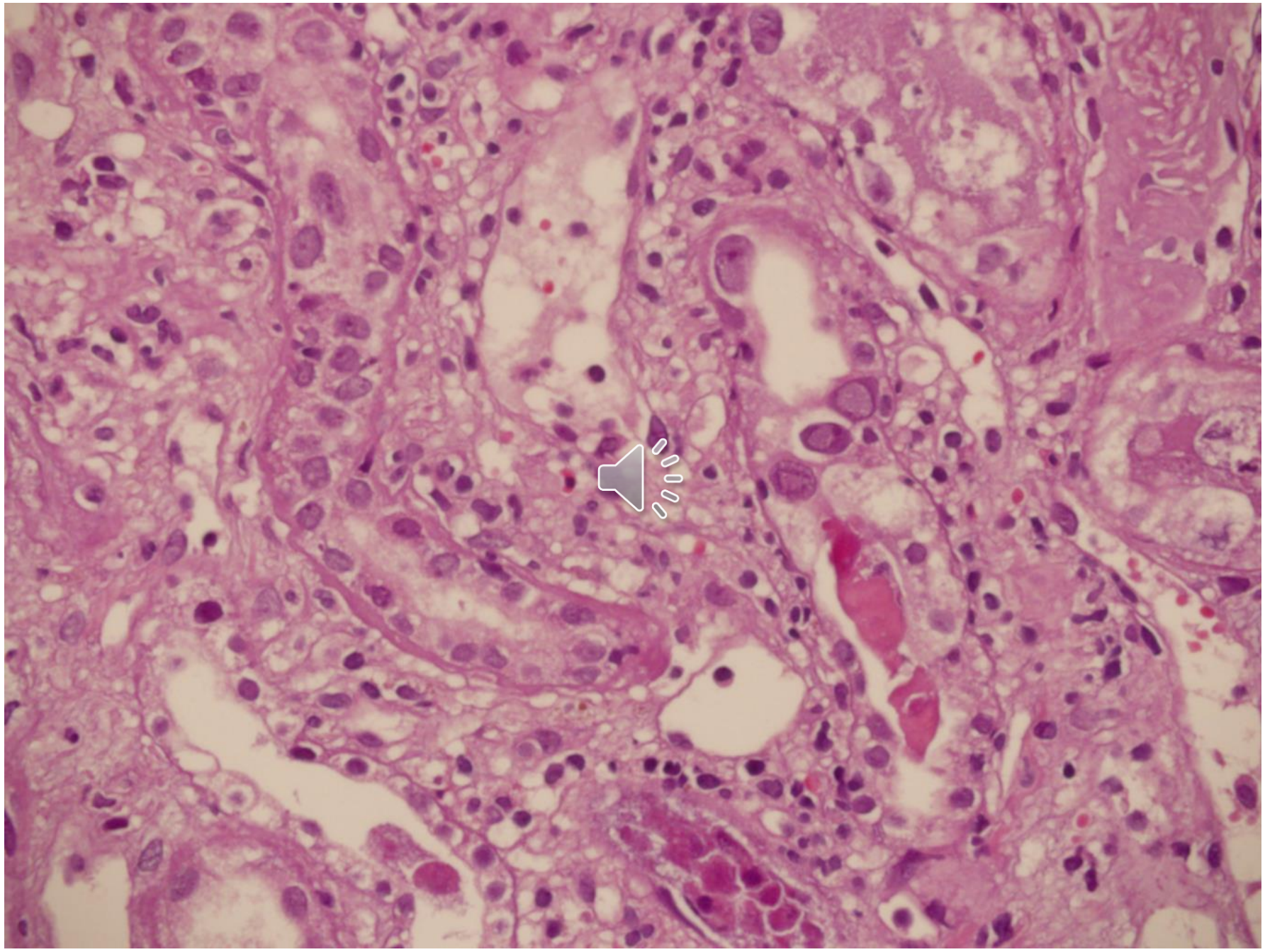
Stage A: early mild	- mild cytopathic change (≤ 25% of tubules) (mostly medulla) - no extensive necrosis - no/minimal interstitial changes
Stage B: florid	- marked cytopathic changes - marked tubular epithelial necrosis - interstitial changes with “some” inflammation and minimal fibrosis
Stage C: sclerosing	- rare cytopathic changes, “late sclerosed” - marked interstitial fibrosis with tubular atrophy

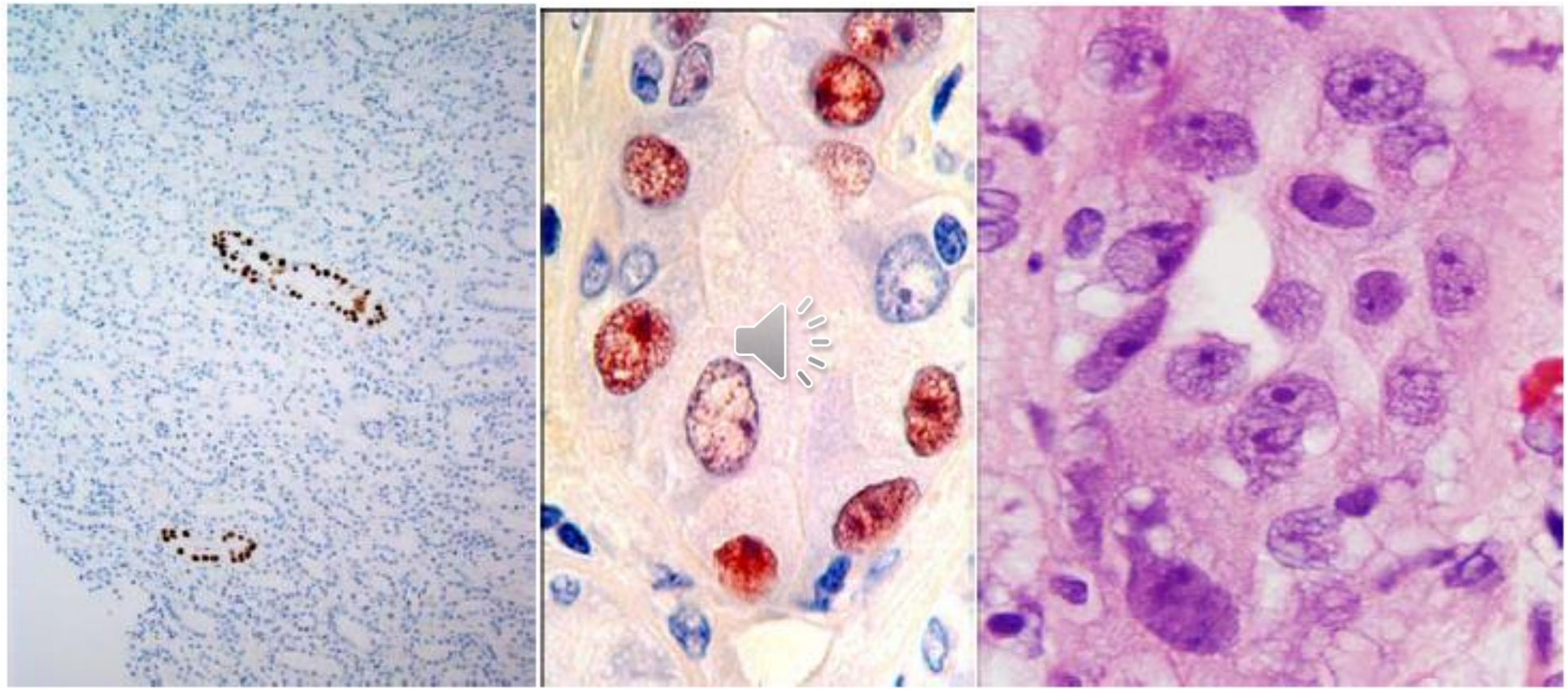
Table 2. Histological grading of BKVAN–2013 AST classification.

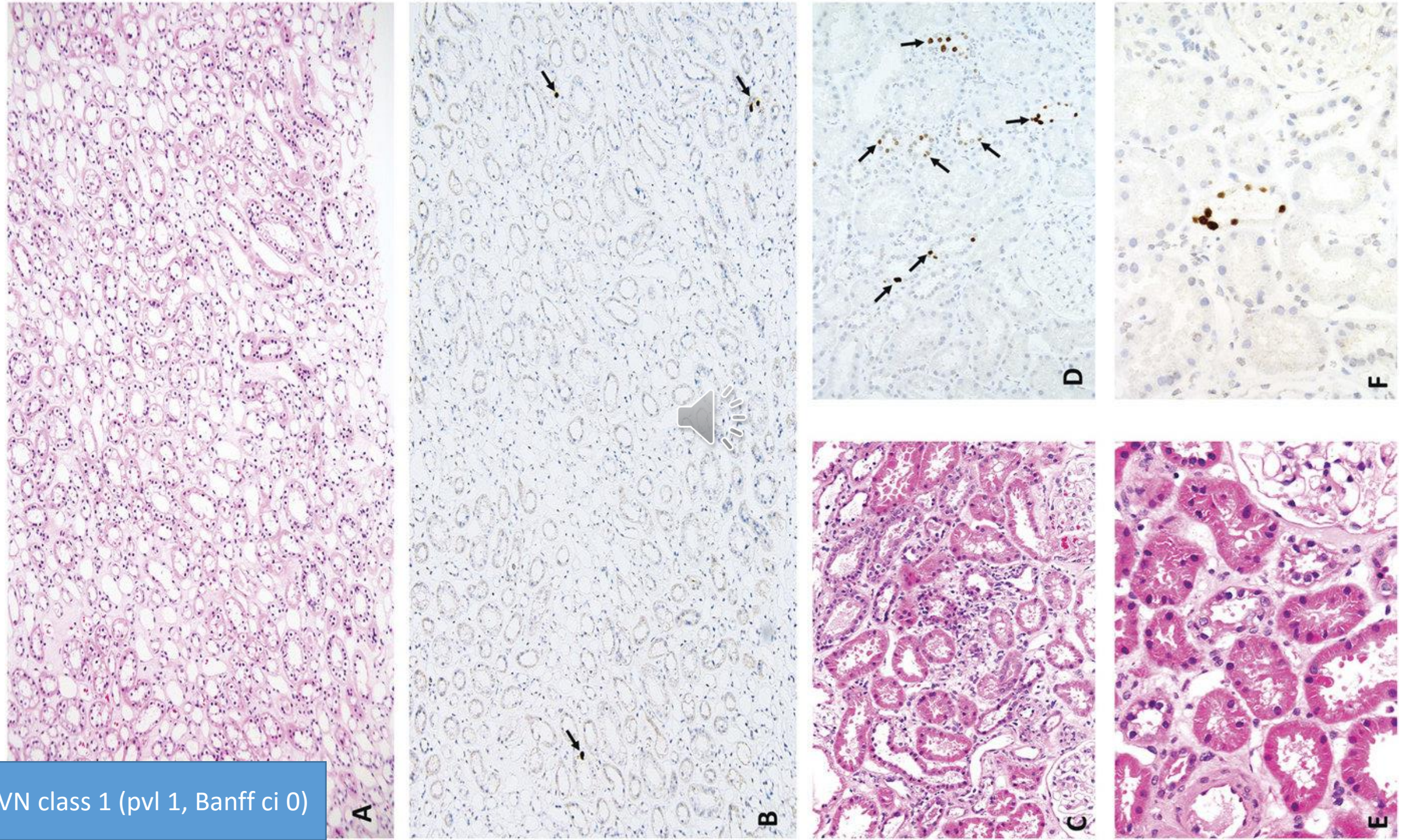
	Pattern A	Pattern B	Pattern C
Viral cytopathic changes	≤25%	11–>50%	variable
Interstitial inflammation	≤10%	B1; 11–25% B2; 26–50% B3; >50%	variable
Tubular atrophy	≤10%	<50%	>50%
Interstitial fibrosis	≤10%	<50%	>50%

Table 2. Histologic classification system of PVN: Definitions

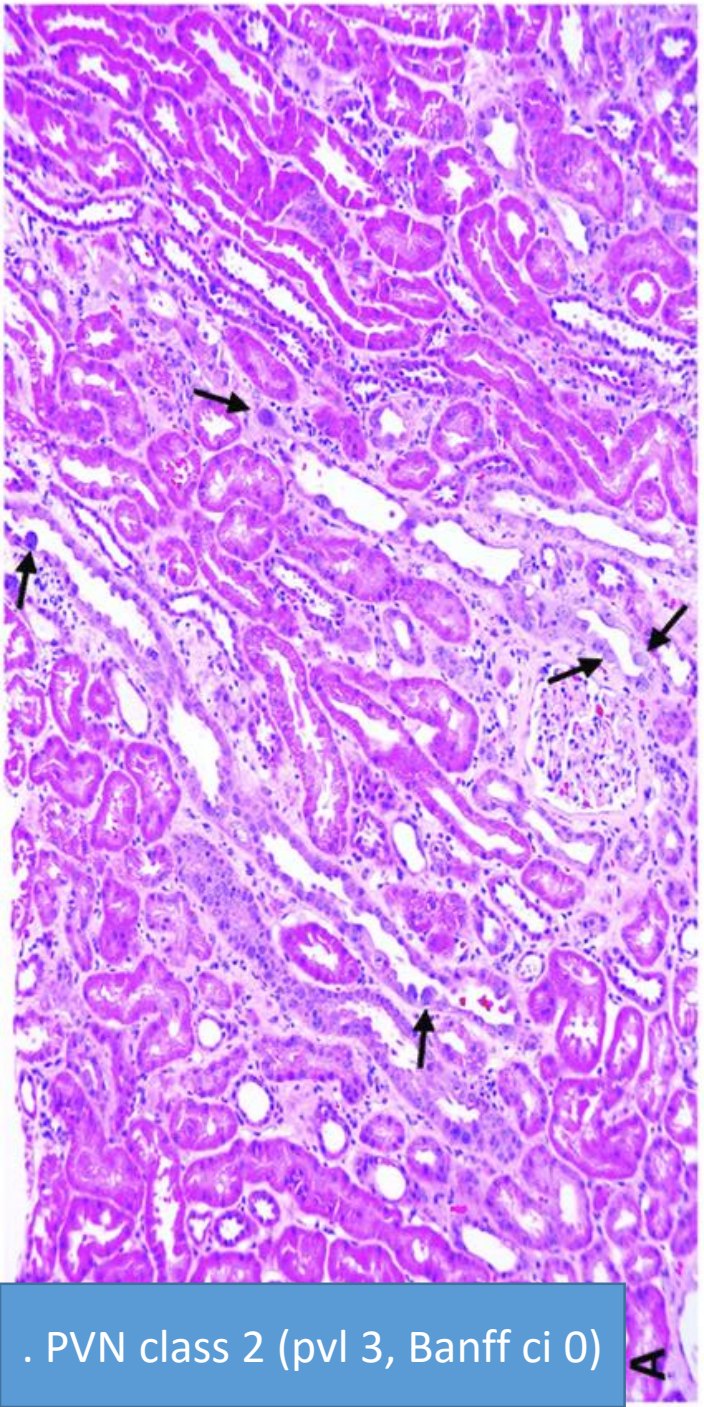
Biopsy-Proven PVN[a] Class 1		Biopsy-Proven PVN[a] Class 2		Biopsy-Proven PVN[a] Class 3	
pvl	Banff ci Score	pvl	Banff ci Score	pvl	Banff ci Score
1	0–1	1	2–3	—	—
—	—	2	0–3	—	—
—	—	3	0–1	3	2–3

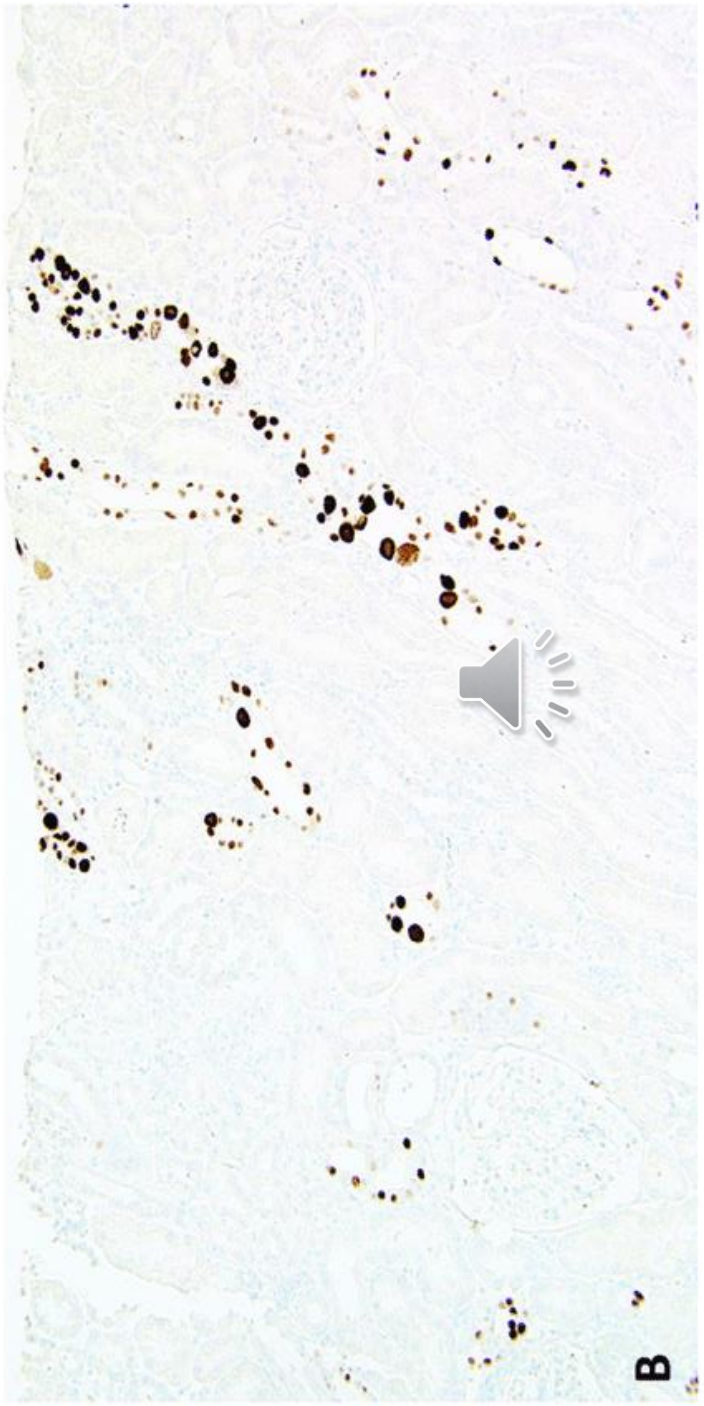


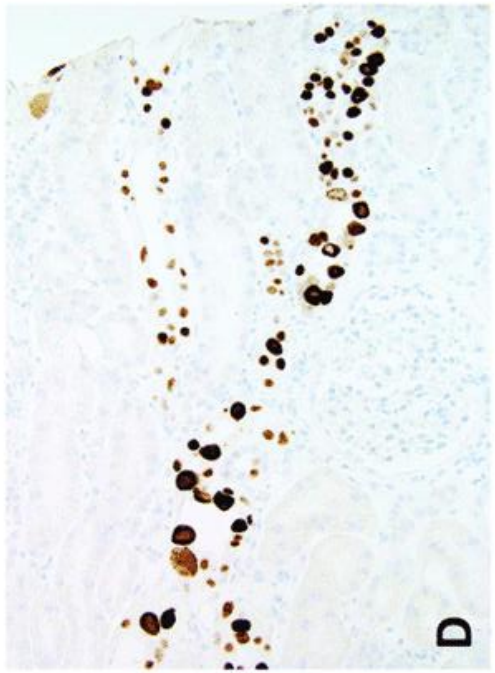


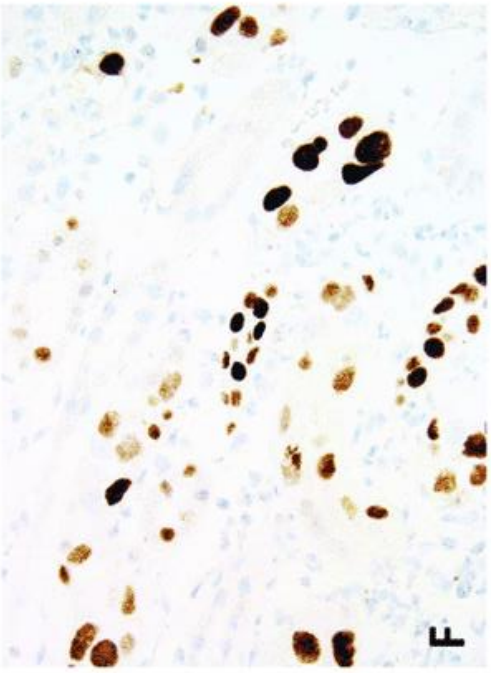


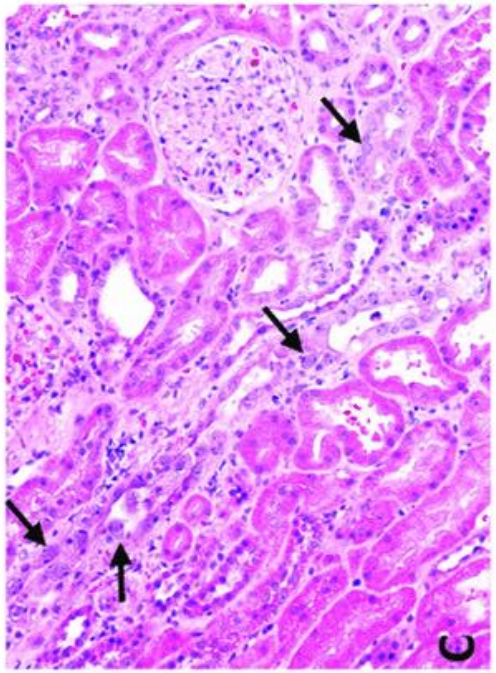
PVN class 1 (pvl 1, Banff ci 0)

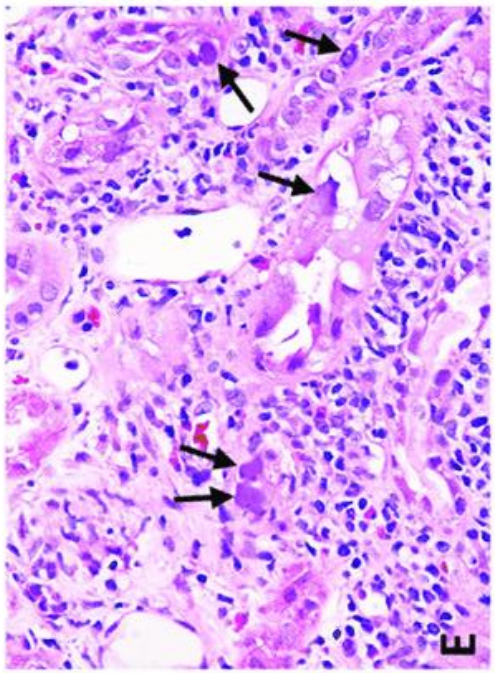




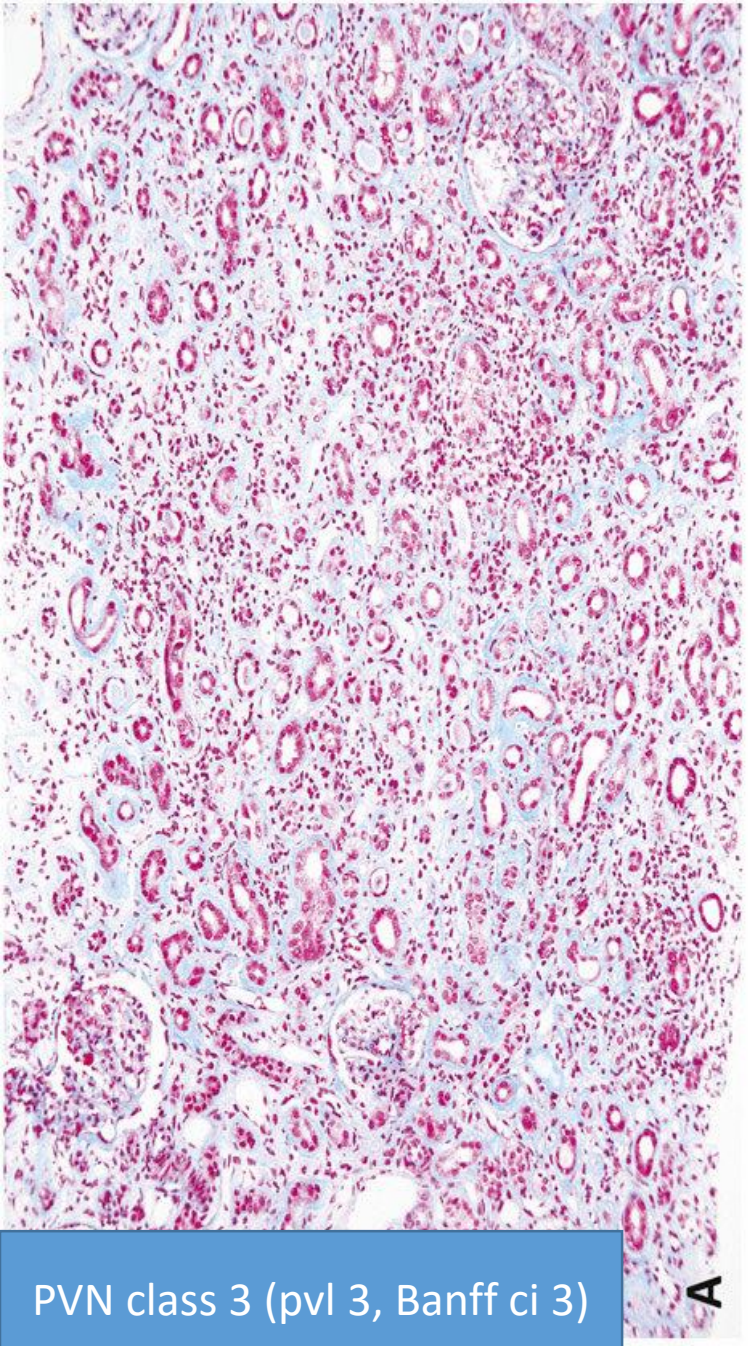


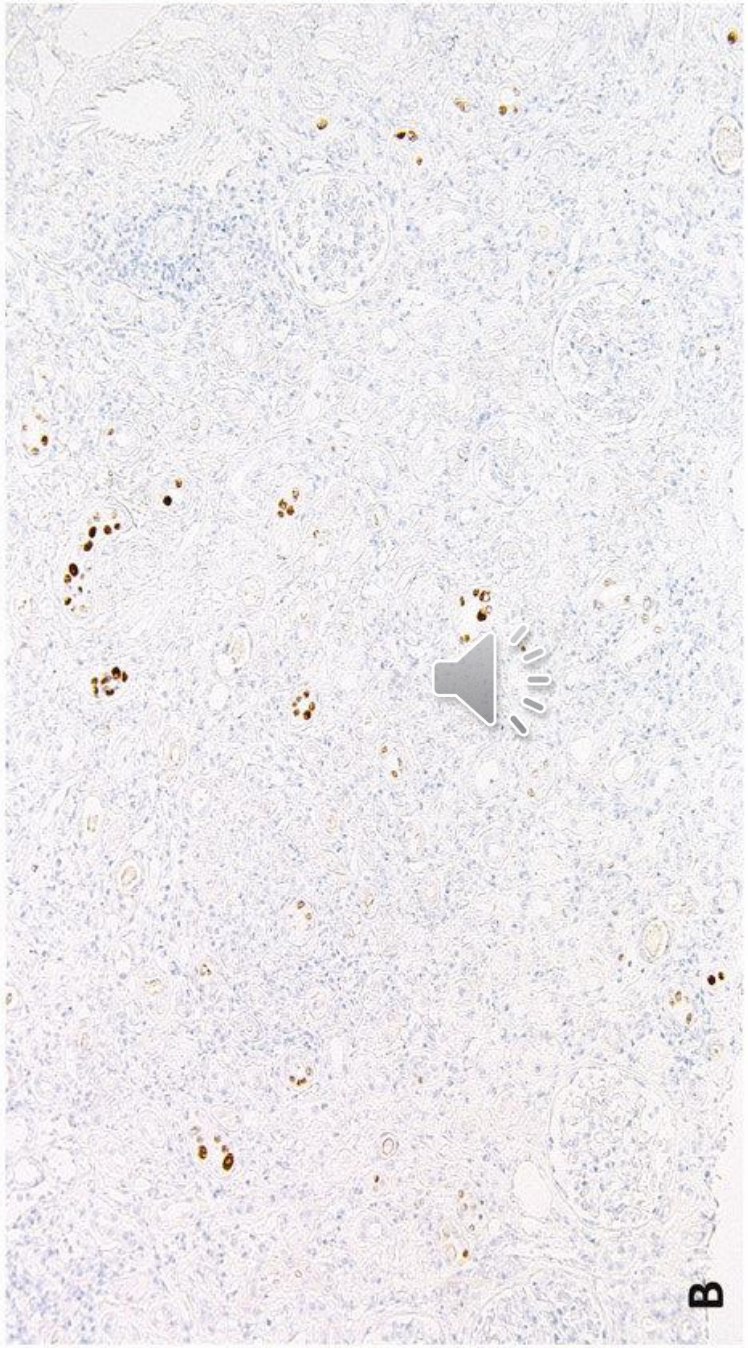


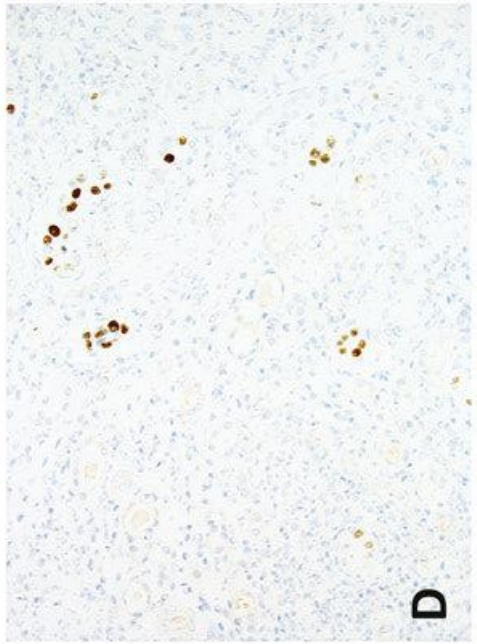


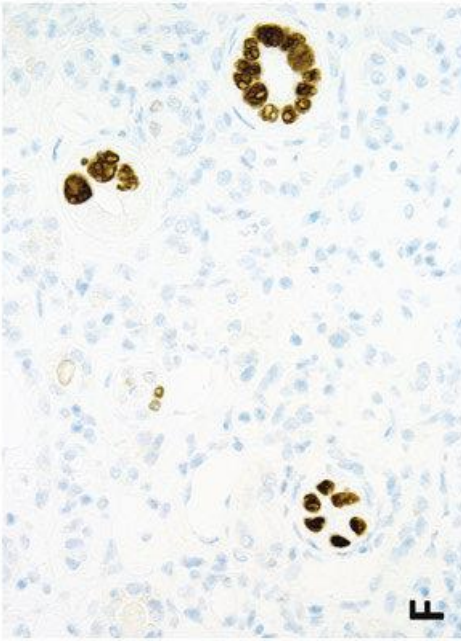


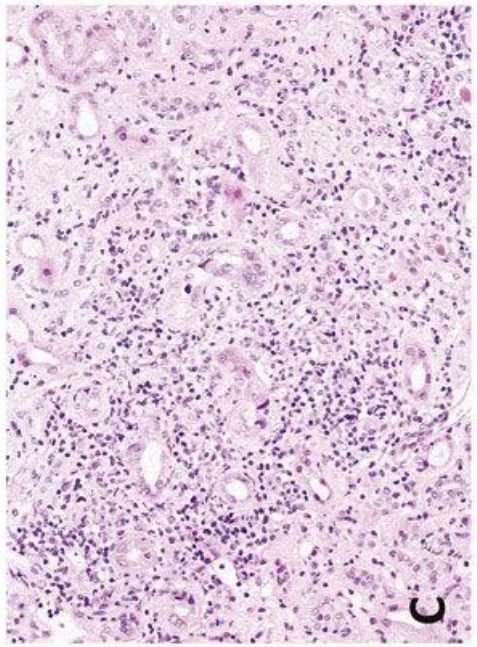
. PVN class 2 (pvl 3, Banff ci 0)

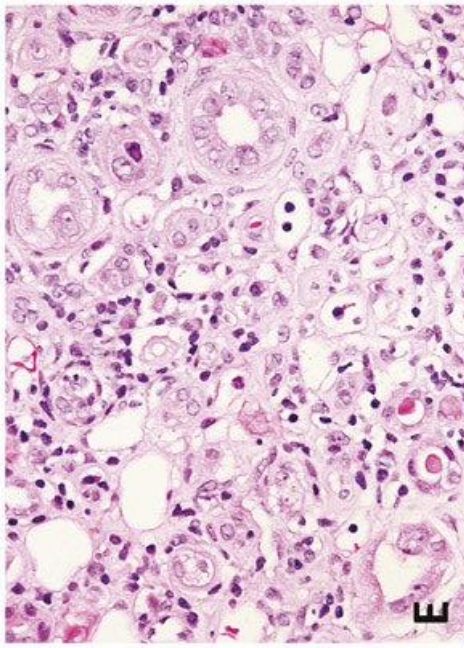












PVN class 3 (pvl 3, Banff ci 3)

Rejection or PVN

May be hard to distinguish PVN from rejection

Clear indicators of rejection

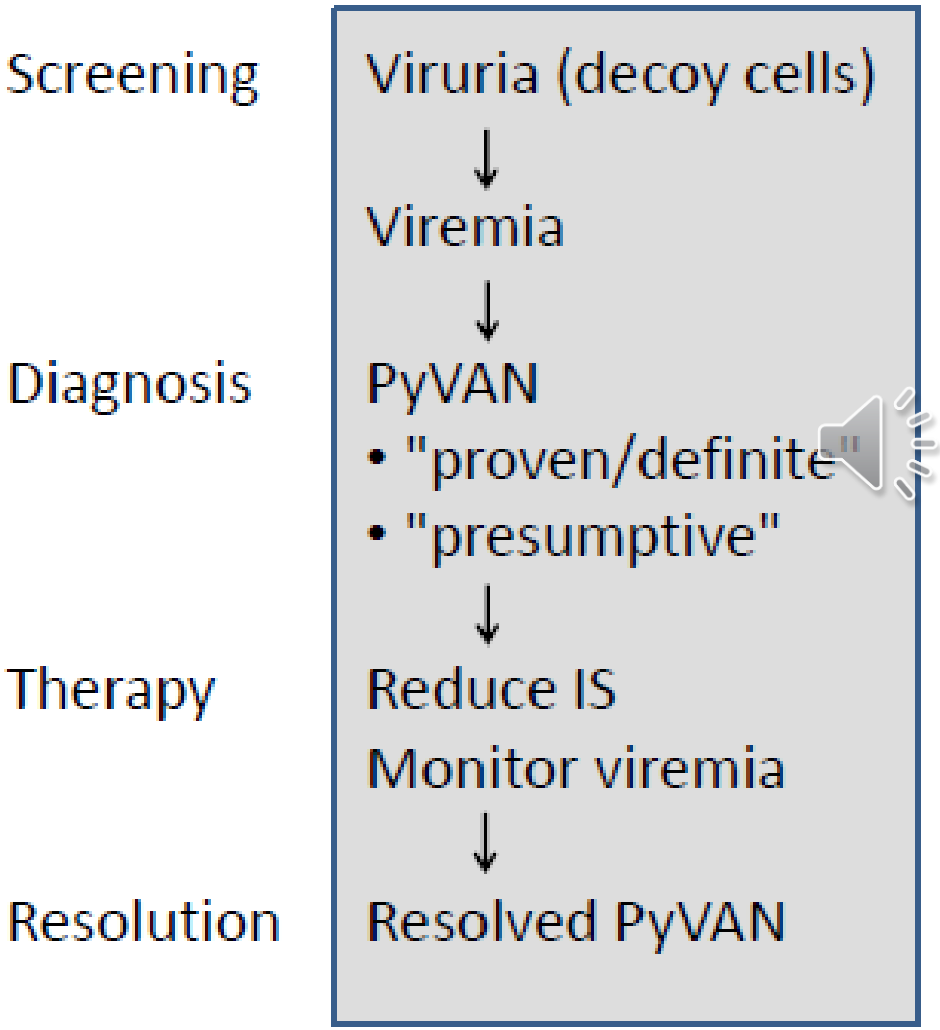
- Endothelialitis
- C4d+

Clear indicator of viral pathogenesis

- Widespread viral Ag

Extensive inflammation with rare viral Ag favors rejection

Guidelines for screening and therapy



Therapy

- **reduction of immuno-suppression**
- cidofovir? ☠☠☠
- leflunomide?

Hirsch et al., Am J Transplant 9:S136-S146,2009; 13:S179-188,2013