IMPACT OF BK INFECTION IN PANCREAS TRANSPLANT RECIPIENTS

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I HAVE NO CONFLICT OF INTEREST TO DISCLOSE

LEARNING OBJECTIVES

- To describe the incidence, outcomes and treatment for BK Virus Nephropathy in simultaneous pancreas and kidney transplants (SPK).

. To analyze the clinical impact of BK Virus infections in SPKT recipients.

. To evaluate the clinical value of performing pancreas and kidney biopsies in BKV infections.

BK INFECTION IN SPK TRANSPLATS

- Infections have increased in simultaneous pancreas-kidney recipients (SPKTR) with BK polyomavirus associated nephropathy (BKVN) being the most important infections cause of allograft loss.

- Polyomaviruses are common in the adult population with more than 80-90% of adults demostrating serologic evidence of past exposure.

- In healthy individuals, latent polyomavirus infection does not appear to result in any health consequences as the virus can establish latency in the uroepithelium, renal tubular cells, oligodendrocytes and mononuclear cells

Schachtner, T et al. Simultaneous páncreas/kidney transplant recipients present with late-onset BK polyomavirus-associated nephropathy. Nephrol Dial Transplantation 2016; 31: 1174-1182


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BK VIRUS IN SPK TRANSPLANTS

- Polyomavirus – associated nephropathy has been increasingly recognized as a significant potentially reversible cause of graft failure in kidney transplant recipients and is mainly attributed to immunosuppresion

- BK virus is frequently associated with interstitial nephritis and uretral stenosis , potentially leading to kidney allograft loss.

- Althogh very well described in the isolated kidney transplant literature, the incidence, outcomes and treatment strategies for BKVN, in the SPK populations is less well studied.

Ramos E , Drachember CG et al. Clinical course of Polyoma virus nephropathy in 67 renal transplants patients. J Am Soc Nephrol 2002: 13: 2145

BK INFECTION IN SPK TRANSPLANTS

. Solid organ pancreas transplantation offers the potential for euglycemia in patients with type I diabetes and is most frequently performed in association with kidney transplantation in patients with end-stage diabetic nephropathy.

- This procedure can either be performed as a simultaneous pancreas and kidney transplant (SPK) or as two separate operations with a pancreas transplant following a kidney transplant

- In our institution we usually perform SPK transplants.

Mujitaba M et al. BK virus nephropathy in simultaneous páncreas kidney transplant: a potentially preventable cause of kidney allograft loss. Clin Transplant 2012; 26: 87-93


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BK INFECTION IN SPK TRASNPLANTS

. Previous work on the clinical relevance of BKVN in SPKT recipients suggested that BKVN represented the leading cause of **kidney allograft loss in SPKT** while the pancreas was not directly vulnerable to BKV and did not lead to an increased risk of rejection.

. However, this data was published a couple of years ago, and little is known about the clinical course of BKVN in SPKT under modern immunosuppressive agents.

Lipschutz GS et al. BKV in a simultaneous kidney and pancreas recipients: a leading cause of renal graft loss in first two years post transplant. Am J Transplant 2005; 5: 366-373

Mujitaba M et al. BK virus nephropathy in simultaneous páncreas-kidney transplant: a potentially preventable cause of kidney allograft loss. Clin Transplant 2012: 2012; 26: 87-93

BK INFECTION IN SPK TRANSPLANT

. In particular, potent immunosuppressive regimens containing tracolimus and /or mycophenolate mofetil have been suggested to stimulate BKV replication and to lead to the current hight prevalence of BKVN.

. The incidence of BKVN in previous publications range between 2.9 (Gupta G, 2006) to 7,5 (Lipschutz GS, 2005). These studies were done in the era of cyclosporine based mainteinance immunosupression.

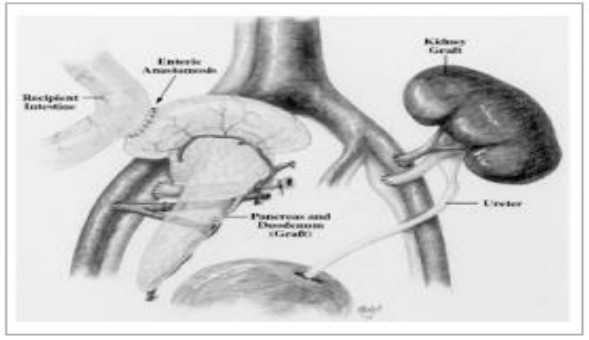
Brennan DC et al. Incidence of BK with tacrolimus versus ciclosporine and impact of preemptive immunosuppression redction. Am J Transp 2005; 5: 582-594

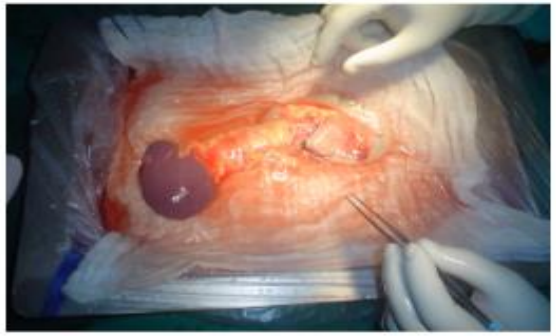
COMPARISON WITH OTHER PUBLISHED DATA

Parameter	IUSM[a]	UCSF[b]	NMH[c]	UPMC[d]
BK cases/no. SKPT (%)	6/138 (4.3)	9/146 (6.2)	9/205 (4.4)	7/243 (2.9)
Mean age at transplant (yr)	42 ± 5	38 ± 6	48 ± 5	40 ± 11
Male sex (%)	84	89	78	57
Follow-up (months)	43 (25–55)	35 (11–60)	36 (7–72)	43 (10–109)
Time to BK virus nephropathy (BKVN) diagnosis (months)	11 (9–17)	12 (4–28)	20 (7–37)	19 (9–40)
Baseline serum creatinine (mg/dL)	1.4 ± 0.3	1.5 ± 0.4	1.1 ± 0.3	1.4 ± 0.4
Serum creatinine at BKVN diagnosis (mg/dL)	2.1 ± 0.5	3.5 ± 1.2	2.6 ± 0.4	2.4 ± 0.7
Kidney loss from BKVN (%)	0	55	89	43
Serum creatinine at last F/U (mg/dL)	1.7 ± 0.6	3.5 ± 1.2	ND	1.9 ± 0.3
Pancreatic rejection/allograft loss (%)	0	0	0	0
Use of cidofovir/leflunamide	0	44%	78%	86%

MATERIAL

- We examined 133 SPK transplants at our center between 2012 and 2016 for development of BKVN.
- Donor pancreas/kidney were procured from young deceased donors with no evidence of pancreatic or renal dysfunction.
- Pancreas were placed in the recipient´s right iliac fossa with enteric dranaige to exocrine secretions and anastomosis to the iliac vasculature. Kidneys were placed in the recipient´s left iliac fossa with vascular anastomosis to the iliac vessels.






ARG
5299
DRA
8852
My Way

BK VIRUS SCREENING

- At our center, we routinely screen SPK patients for BK V in plasma by q PCR (real time polymerase chain reaction with cuantification of viral loads in plasma).

- Screening is carried out every three months in the first two years. After that, every six moths.

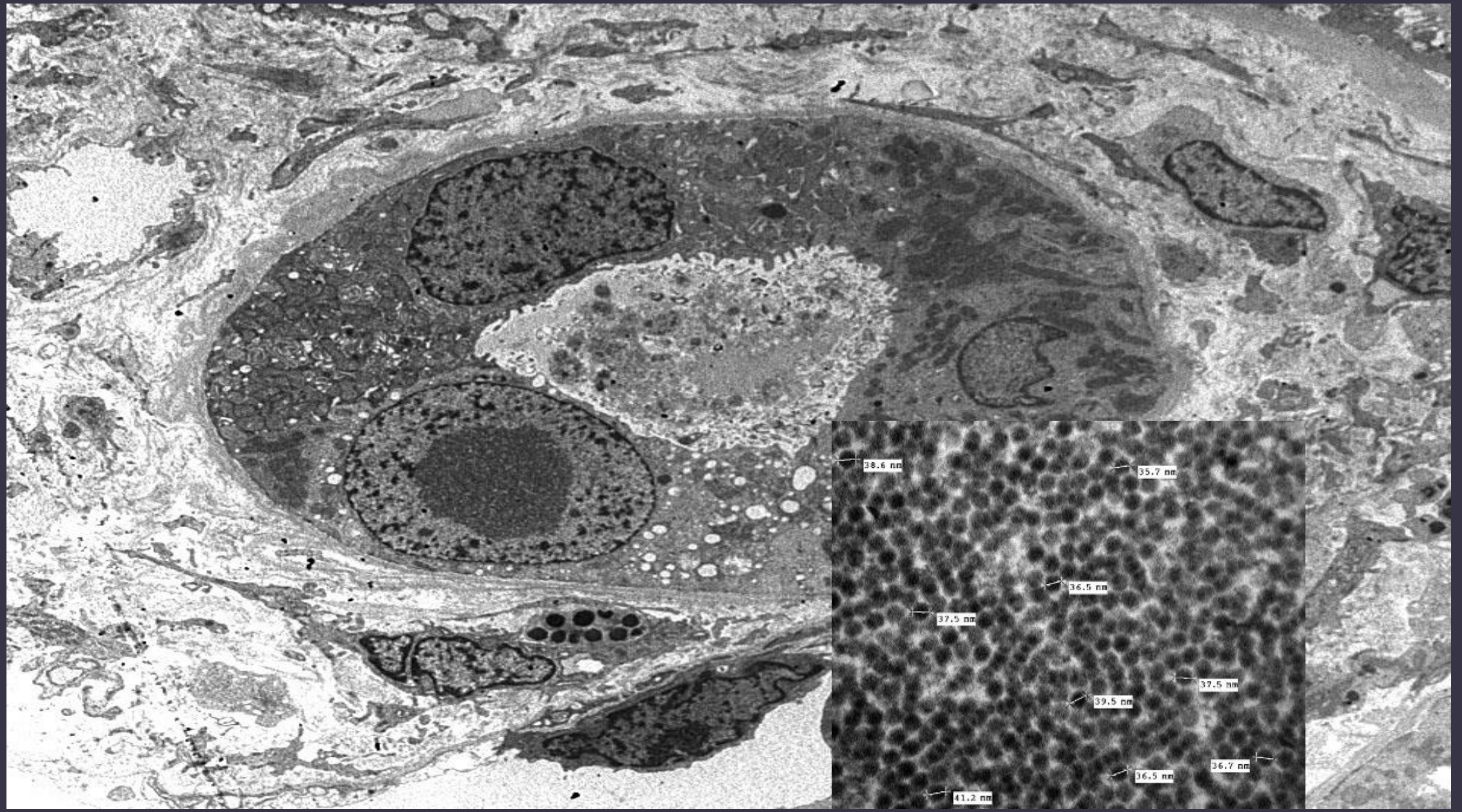
-In addition to the above, screening serum BKV is part of the evaluation process for any patient with an unexplained deterioration in kidney function.

BK VIRUS DIAGNOSIS

- The gold standard for BKVN is renal biopsy.

- All the patients with positive qPCR underwent kidney and pancreas allograft biopsy

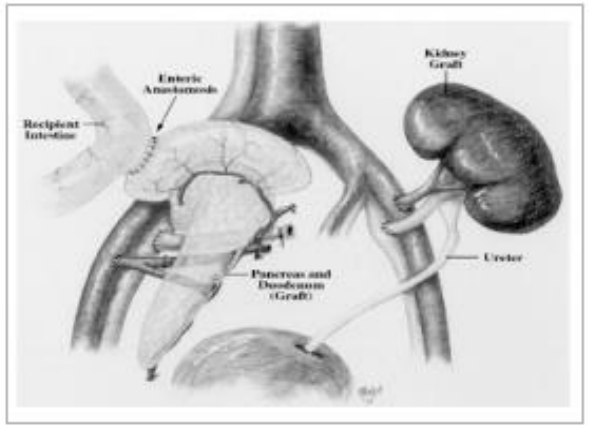
- Pancreatic biopsies were performed by laparoscopy. The tail was dissected and tissue was taken using scissors and a cautery. Kidney biopsies were performed by core biopsy needle (16G) under direct visualization.

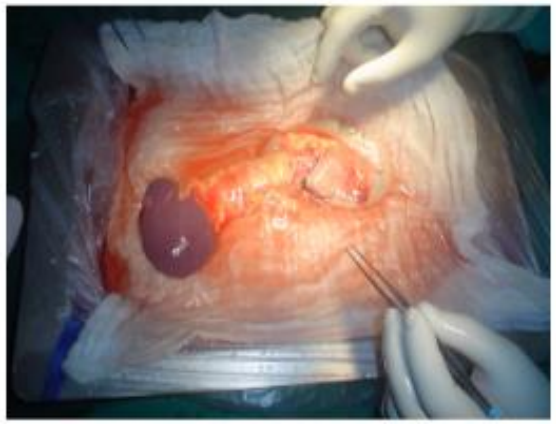

38.6 nm
35.7 nm
36.5 nm
37.5 nm
37.5 nm
39.5 nm
36.5 nm
36.7 nm
41.2 nm

DEMOGRAPHICS

. Eleven SPK T recipients with BKV viremia were indentified.

- All patients were caucasian.
- Eight of eleven were male.
- Mean age at transplant was 42 years (range 25-62)
- None had circulating antibodies.

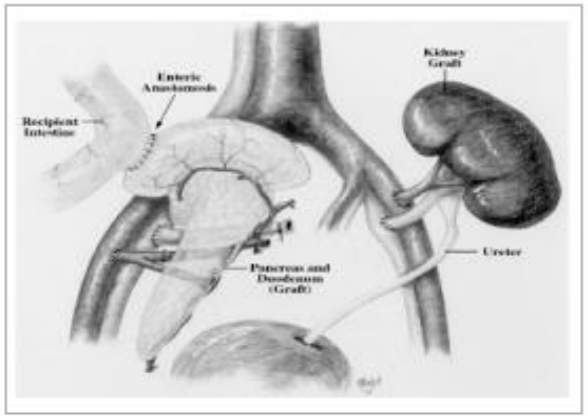


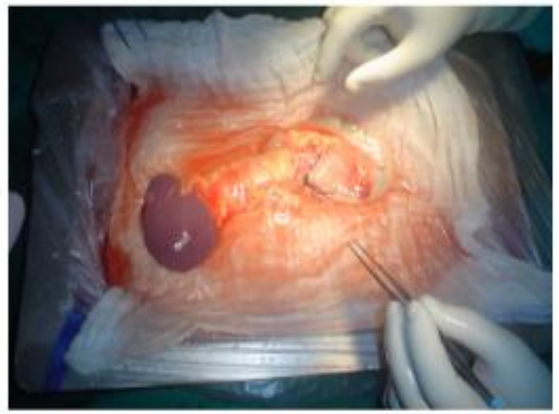


DEMOGRAPHICS

- The median time to BKVN diagnosis was 12 months (4-60)
- Four patients had prior episodes of Acute Cellular Rejection: Two cases were Type IA and two cases Type IB according to Banff Classification. They were treated with Steroids and Tymoglobulin.

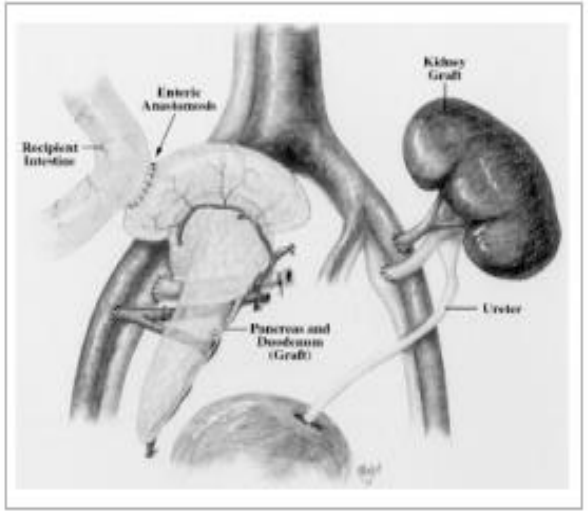
. Pancreas rejection ocurred in one patient.

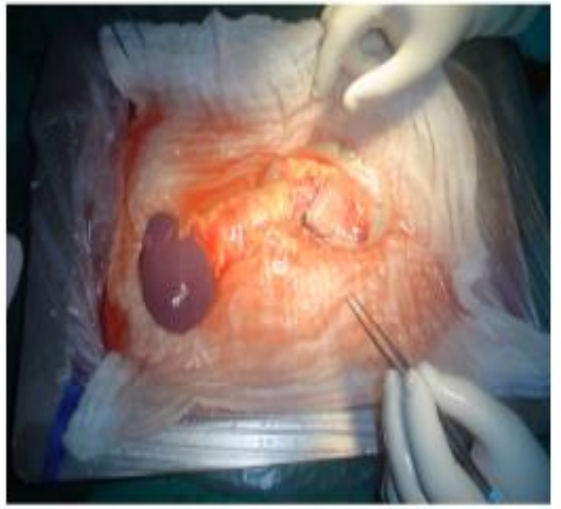




DEMOGRAPHICS

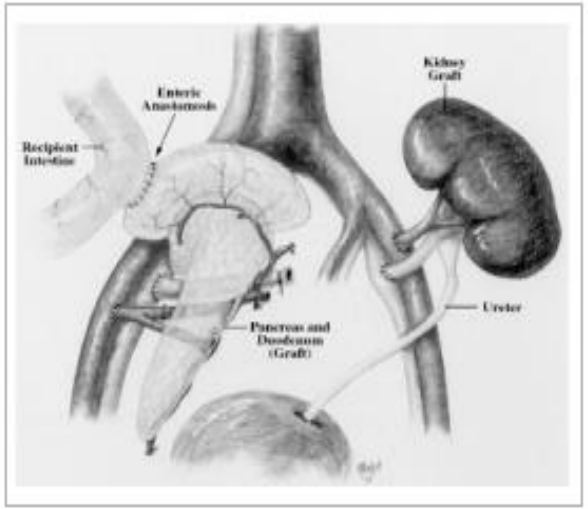
- All SPKT recipients received induction with a lymphocyte-depleting agent.
- Delay in initial graft function (DGF) were not identified in this group of patients
- Time on dyalisis before transplant was 36 months (range 12-60).

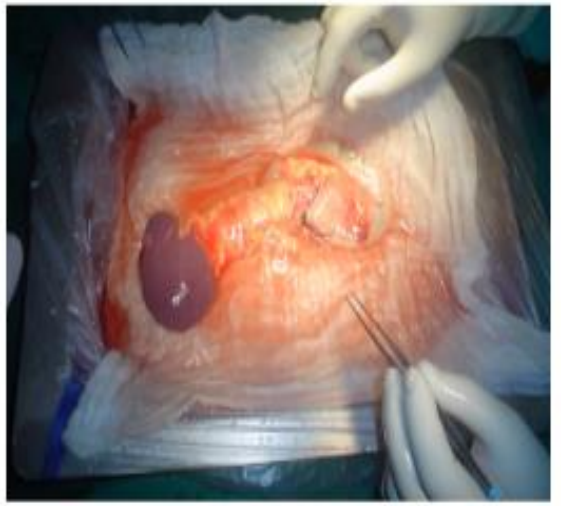




INMUNOSUPPRESSIVE THERAPY

- Primary inmunosuppression was a triple drug regimen with a calcineurin inhibitor, mycophenolate and steroid.
- All patients received routine perioperative antibiotics, a prophylaxis with vancyclovir against CMV and prophylaxis against Pneumocystis pneumonia with trimethoprim- sulfamethoxazole. Patients also received oral fluconazole.





BK VIRUS NEPHROPATHY

- BKVN is defined morphologically and pathology plays a crucial role in patient management
- A diagnosis requires histologic evidence of an intrarrenal, productive polyomavirus infection in the medulla and/or cortex.
- Polyomavirus replication can be identified by standard light microscopy
- A definitive diagnosis of BKVN is not established by laboratory tests such as the level of viremia but rather requires a Renal Biopsy.

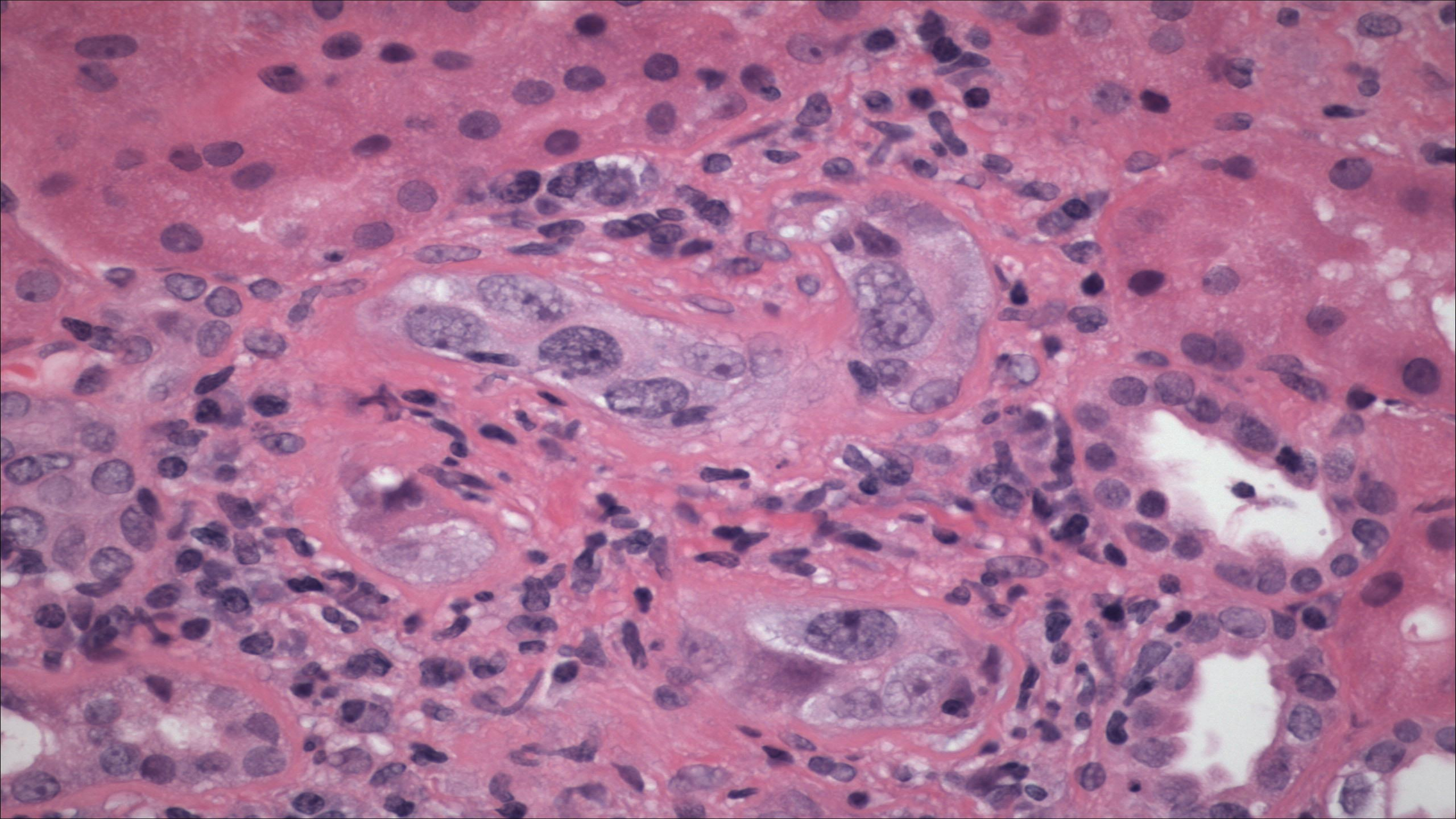
Nickeleit V. The pathology of kidney transplantation . In Ruiz P, ed.Transplantation Pathology. New York : Cambridge Univ Press; 2009; 45-110.

BK VIRUS NEPHROPATHY

. Renal Tissue was processed for Light Microscopy and Inmunoflurescence. For all biopsies there were usually 2 PAS section , 2 Tricrome, 2 Silver Methenamine and 2 H&E section. In two cases we also processed tissue for EM.

. Pancreatic tissue was also processed for Light Microscopy and, 2 H&E, 2 PAS and 2 Tricrome section were examined. All biopsies were examined by 1 transplant pathologist.C4d was performed on formalin-fixed paraffin tissue

. Biopsies were classified according to Banff Criteria.



BK VIRUS NEPHROPATHY

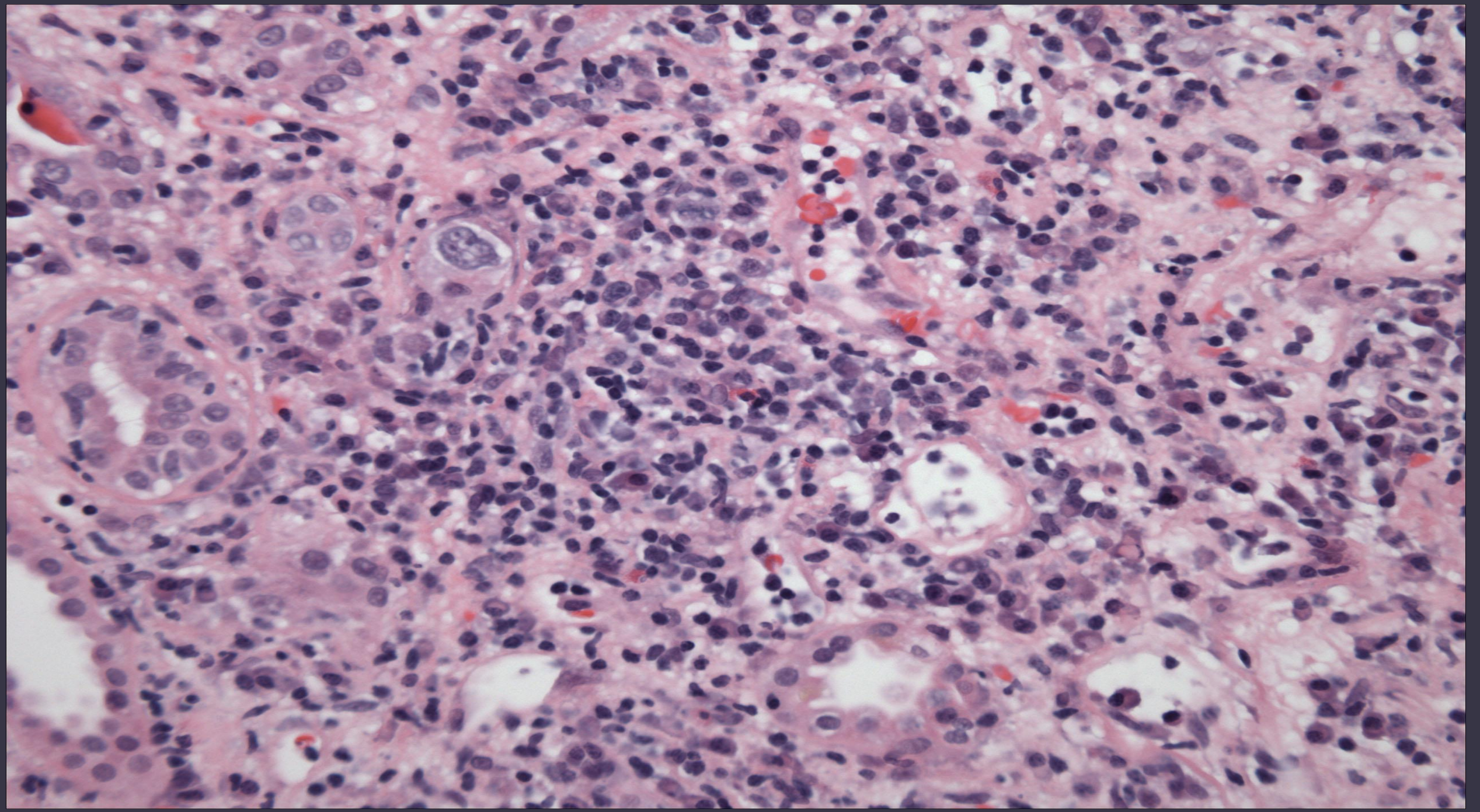
. Two histological features **were found in the biopsies**:

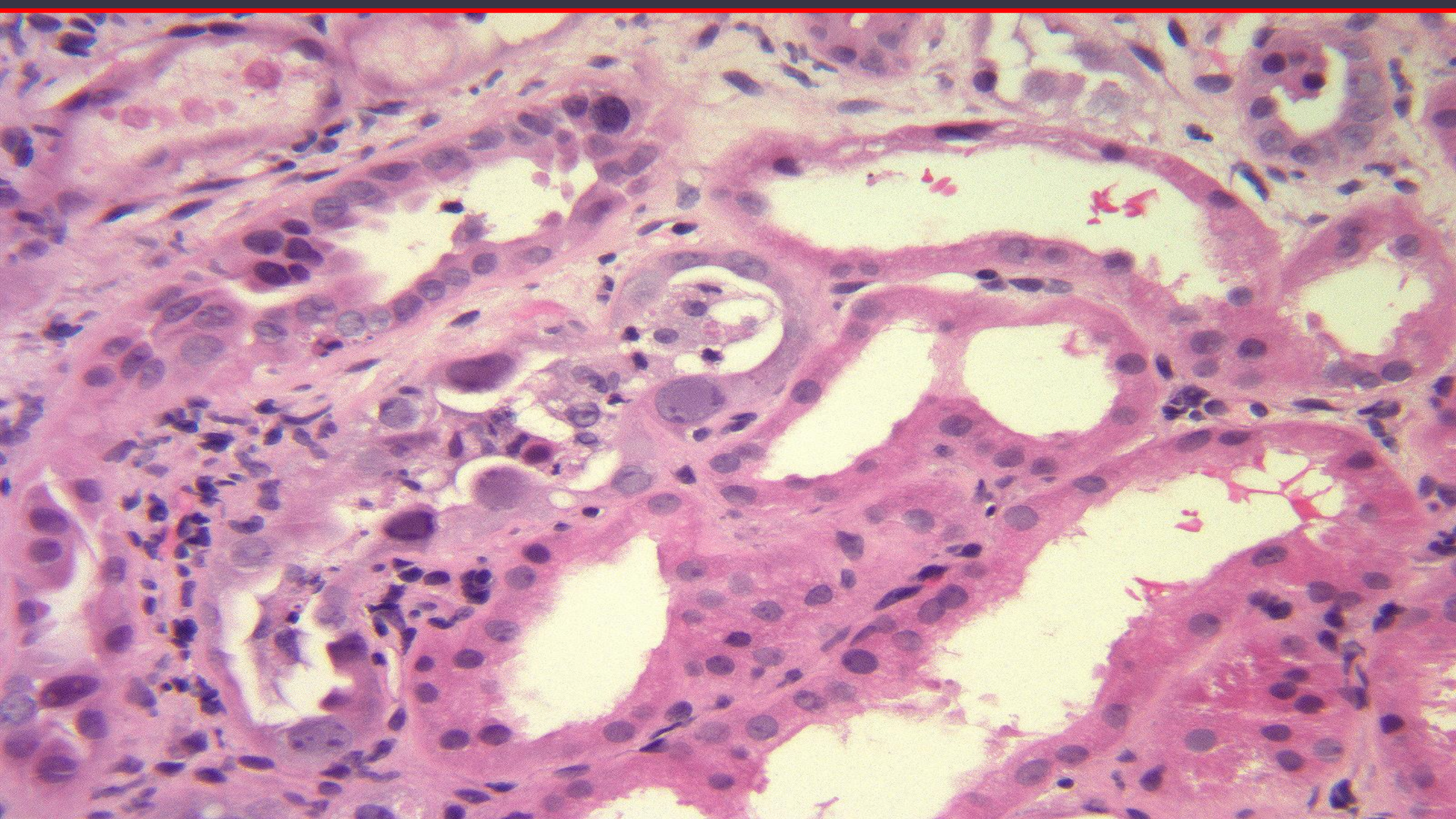
- Intranuclear viral inclusion bodies in tubular epithelial cells
- Virally induced tubular epithelial cells injury and lysis

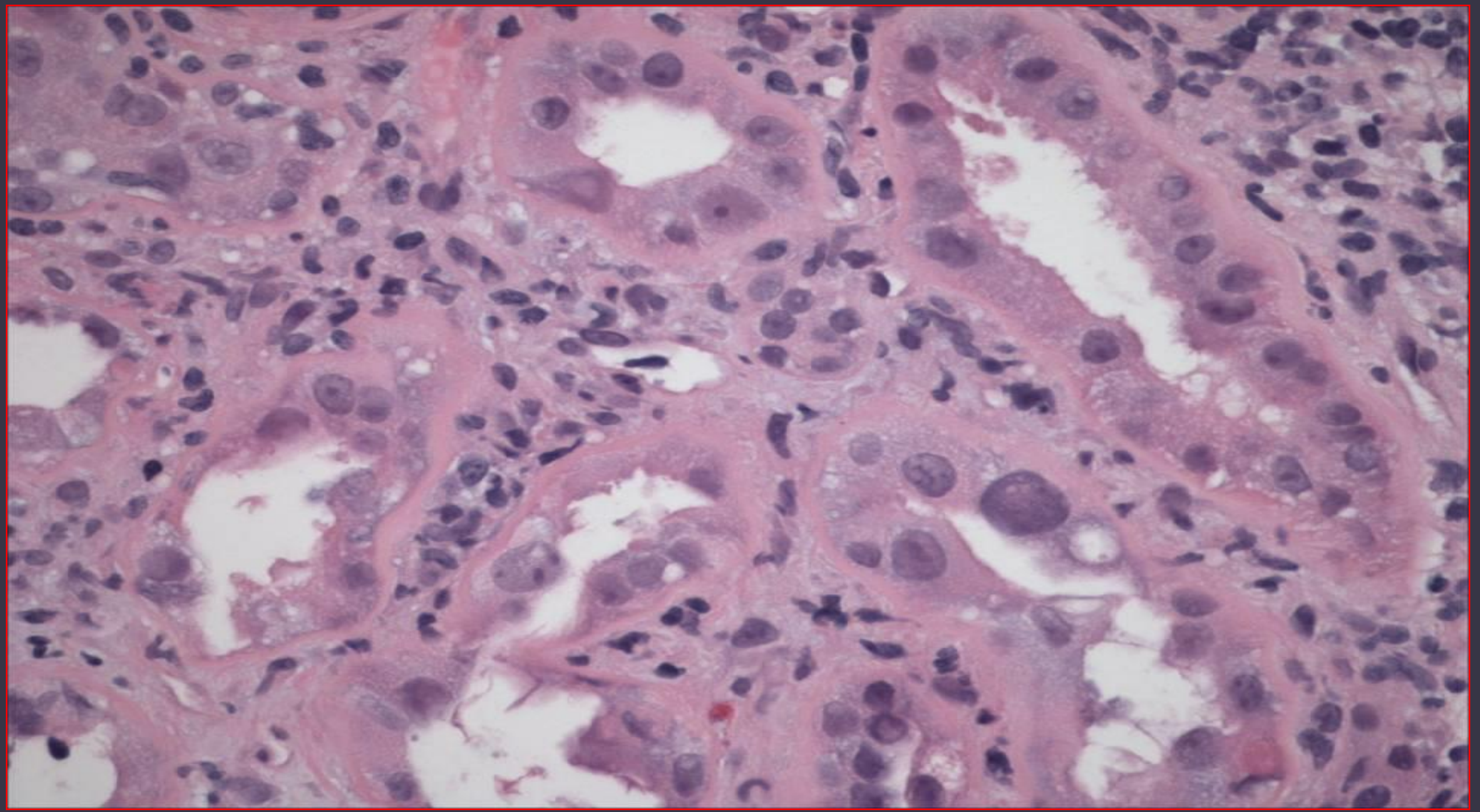
. Cortex was more afected than medulla in all cases.

. Twenty-eigth percent of biopises (four cases) with multiples cores had cores discordant with virus expression further underscoring the focal distribution pattern of BKVN

Drachemberg DC at al. Histological patterns of polyoma virus nephropathy: correlations with graf toutcome and viral load.Am J Transp 2004; 4 (12) : 2082-2092

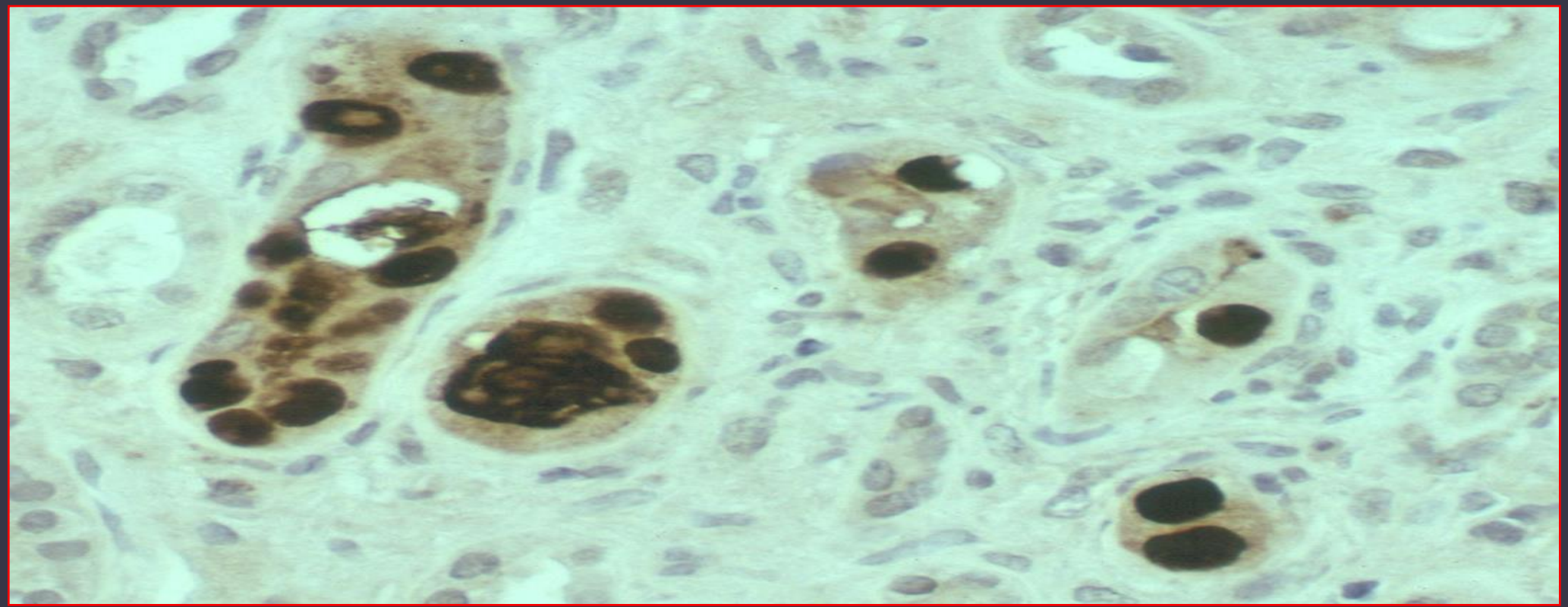


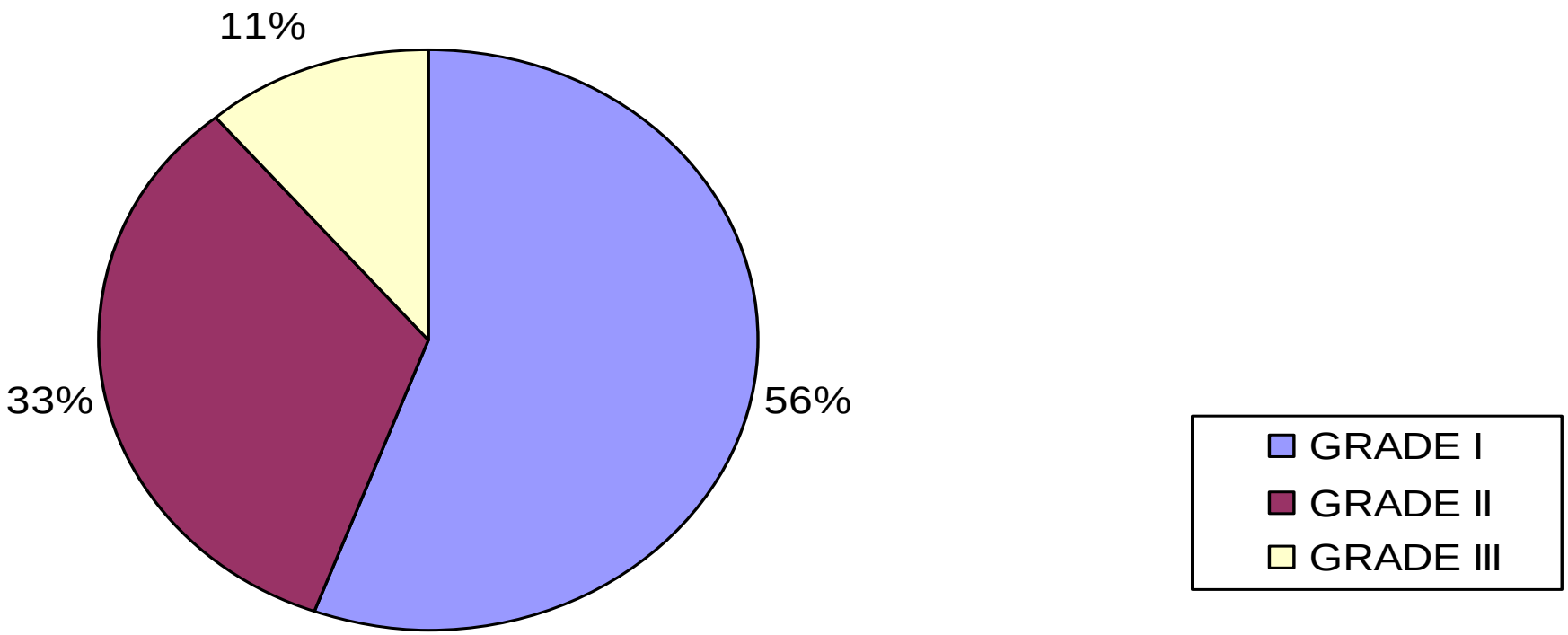




BK VIRUS NEPHROPATHY

- Polyomavirus replication were detected with antibodies to the SV 40 T antigen , that cross- reacts with all polyomaviruses pathogenic in humans (BK, JC and SV40) and works in paraffin sections.




11%
33%
56%
GRADE I
GRADE II
GRADE III

RENAL BIOPSY FINDINGS

- Inflammation of the interstitium was present in all patients and it was graded in : mild (+), moderate (++) and severe (+++).

- Plasma cells was the more common cell in the infiltrate. Lymphocytes, and polymorphonuclear cells were also present but in less proportion

. Tubulits was also present in almost all the cases, but the severity of tubulitis did not parallel the intensity of inflammation of the interstitium. (Trofe J-2003)

RENAL BIOPSY FINDINGS

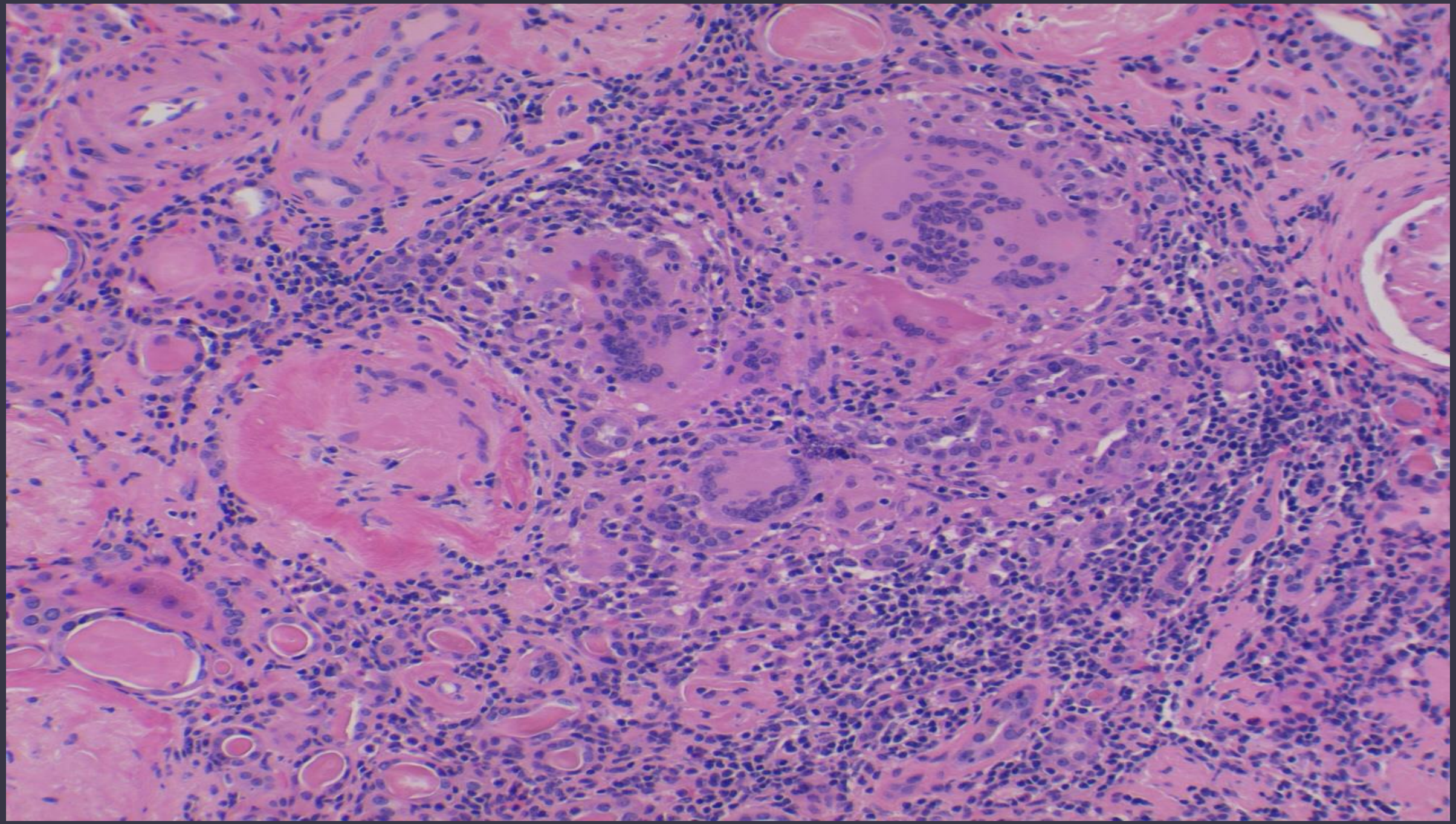
	INTERSTITIUM	TUBULITIS	GLOMERULI	VESSELS
1	MILD	-	FSGS	Hyaline arteriolopathy
2	MODERATE	+	FSGS	Hyaline arteriolopathy
3	MILD	+	NORMAL	NORMAL
4	MODERATE	++	FSGS	NORMAL
5	SEVERE	+	NORMAL	Hyaline arteriolopathy
6	GRANULOMAS	+	NORMAL	NORMAL
7	MODERATE	+	FSGS	Hyaline arteriolopathy
8	MILD	++	NORMAL	NORMAL
9	MILD	++	NORMAL	Hyaline arteriolopathy

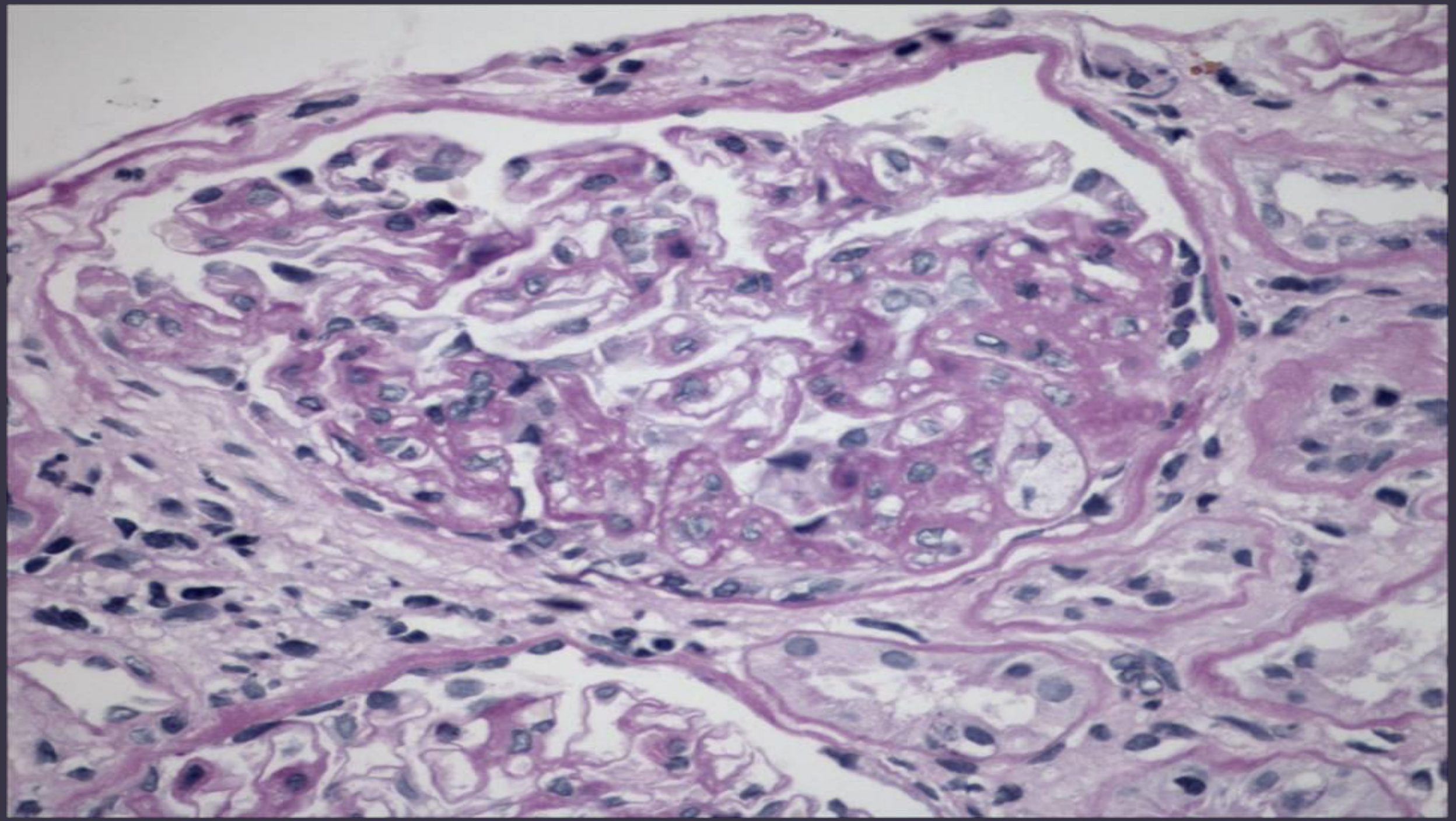
RENAL BIOPSY FINDINGS

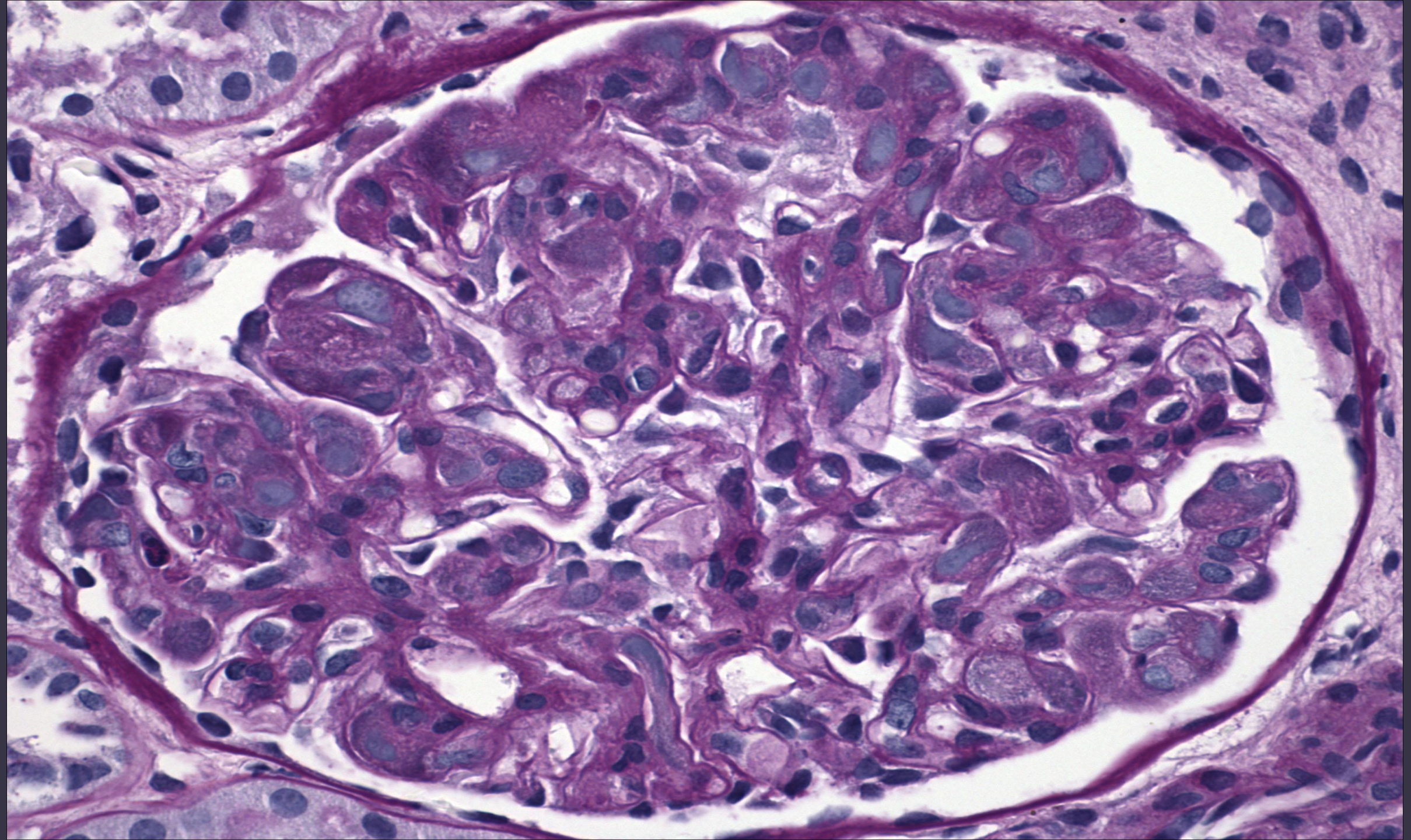
- One patient showed non-necrotizing granulomas in the interstitium . Extravasation of Tamm-Horsfall protein was also found in the biopsy. Ziehl-Nielsen Stain, Grocott and PAS did not show microorganisms.

- Arteriolar lessions were present in 5 patients. These included hyaline arteriolopathy and fibromuscular proliferation.

- Focal Glomeruloesclerosis was diagnosed in 4 biopsies. And we also found reactive atypia en some glomerular epitelial cells however viral inclusions were not identified in the glomeruli (Trofe-2003)





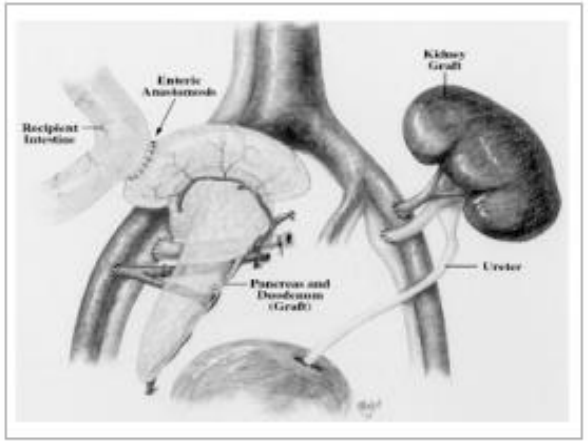


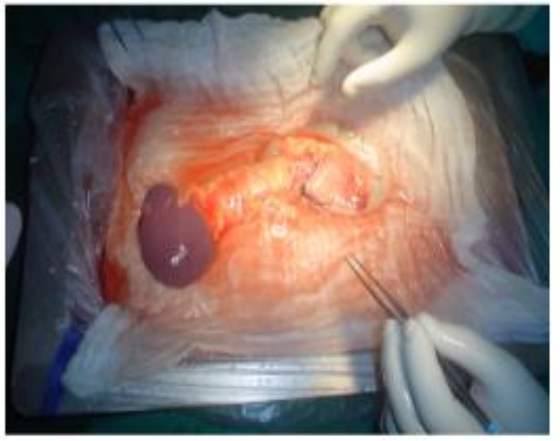
RESULTS

- All patients were manegement with immmunosuppresion reduction with close monitoring of the serum BK load and serum chemistries

. Tacrolimus levels were reduced and mycophenolate was switched to leflunomide.

. Additionaly seven patients received 2g/kg of IVIG.





RESULTS

- After treatment all patients had negative viremia in less than six months and remained negative until last visit.

- Four patient had graft dysfunction at 1, 6, 9 and 26 months after BKVN treatment. Pancreas and kidney biopsies were performed in all cases.

- Patients were treated with steroids (kidney rejection) and steroids and Thymoglobulin (kidney and pancreas rejection)

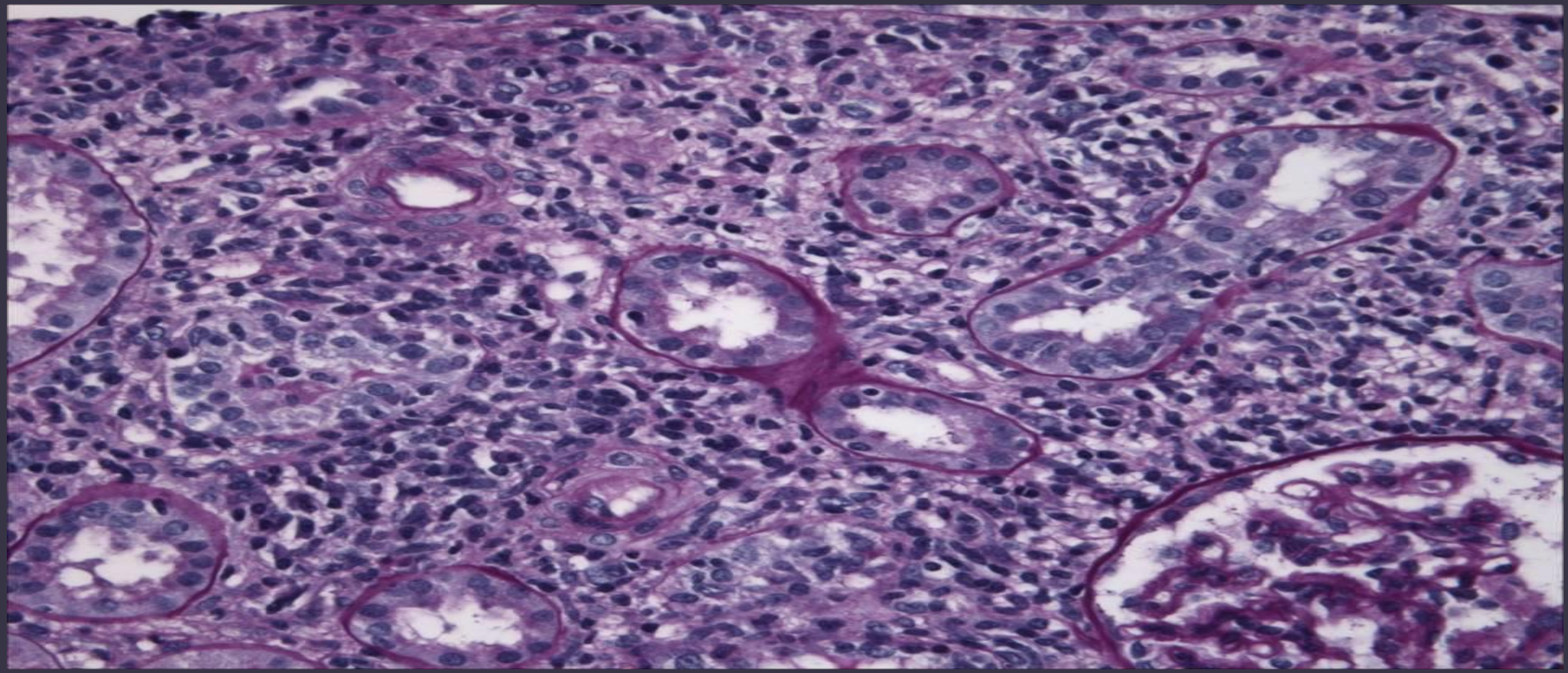
REJECTION POST BK TREATMENT

	KIDNEY	PANCREAS	TREATMENT	Serum Cr after treatment
1	CELLULAR REJECTION, IA	NORMAL	STEROIDS	1,65
2	CELLULAR REJECTION, IA	MILD REJECTION	STEROIDS	1,48
3	CELLULAR REJECTION IB	MILD REJECTION	STEROIDS TIMOGLOBULYN	2,04
4	NORMAL	MILD REJECTION	STEROIDS.	1,05

PATIENT 1 (7 MONTHS POST BKVN DIAGNOSIS)

KIDNEY: ACUTE CELULAR REJECTION, TYPE IA , BANFF CATEGORY. C4D NEGATIVE.

PANCREAS : NORMAL FEATURES.

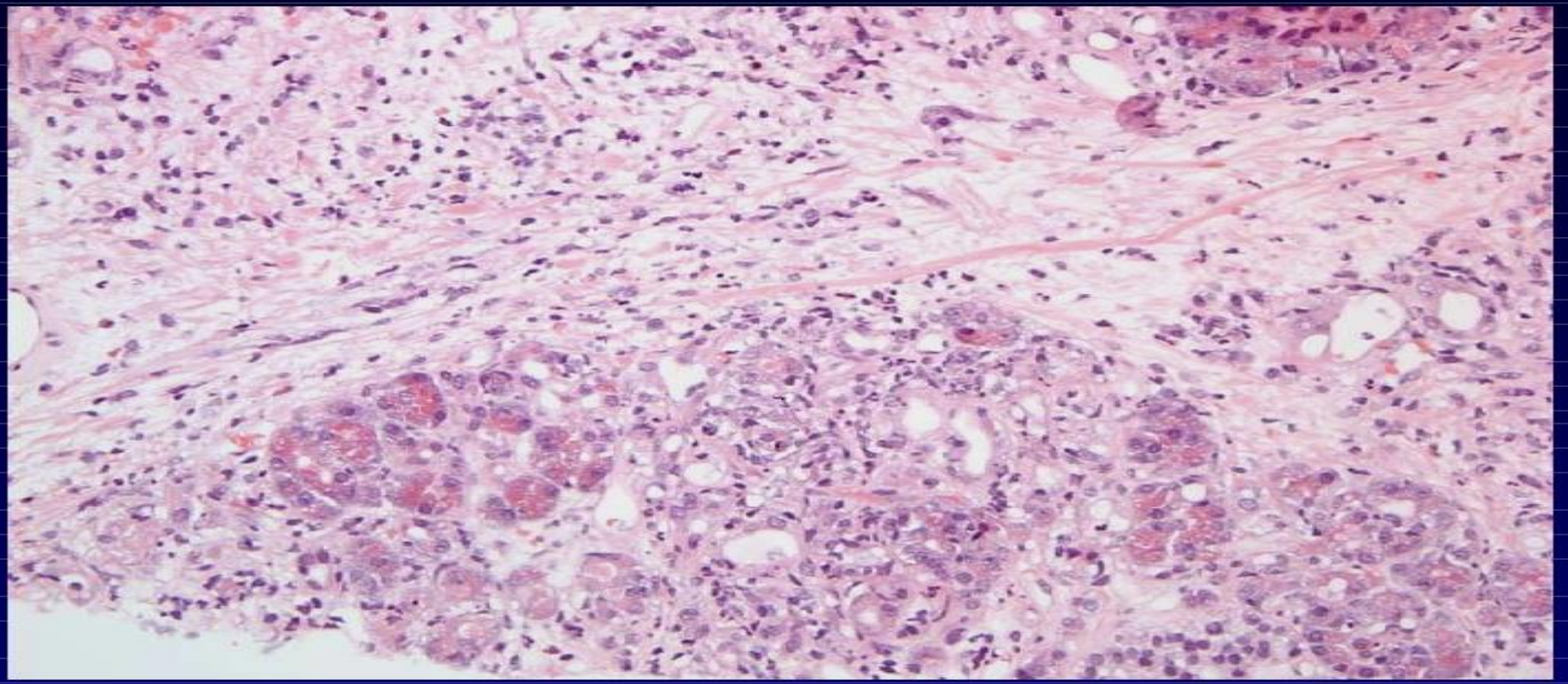


PATIENT 2 (9 MONTH POST DIAGNOSIS)

KIDNEY: ACUTE CELULAR REJECTION, TYPE IA , BANFF CATEGORY.

PANCREAS: ACUTE CELULAR REJECTION, GRADE I, BANFF CATEGORY

BOTH C4D WERE NEGATIVE

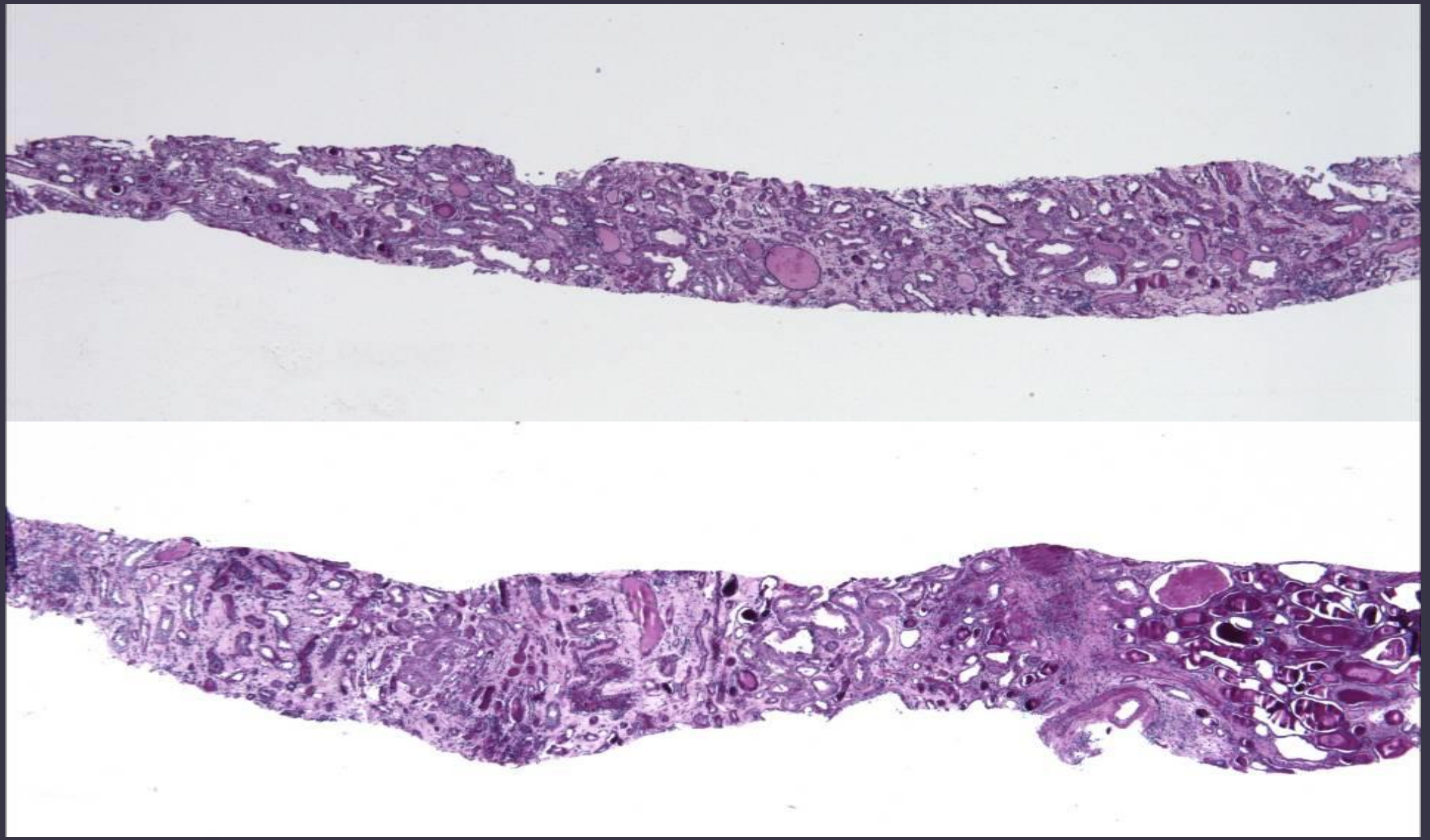


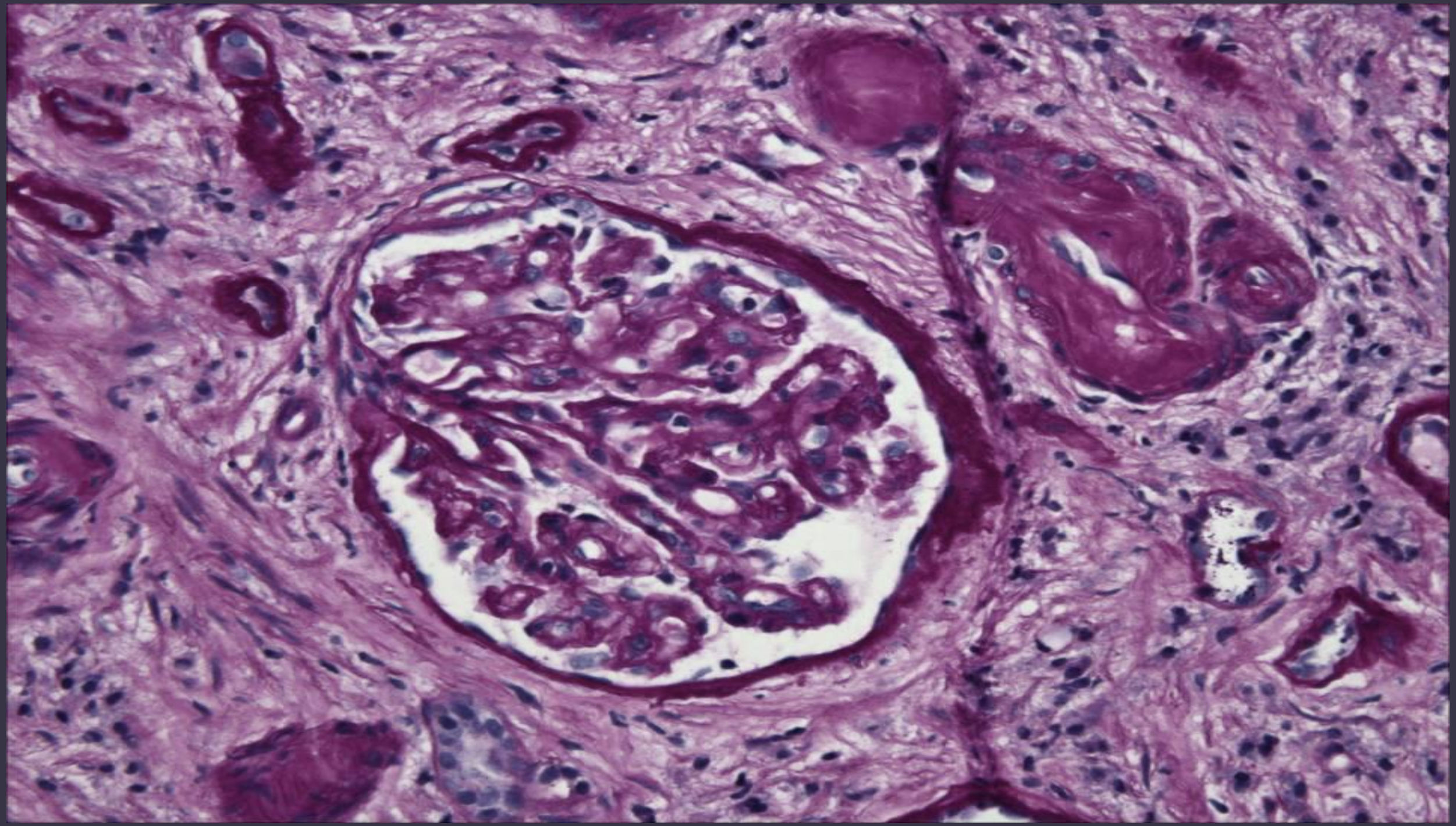
RENAL BIOPSY POST BKVN TREATMENT

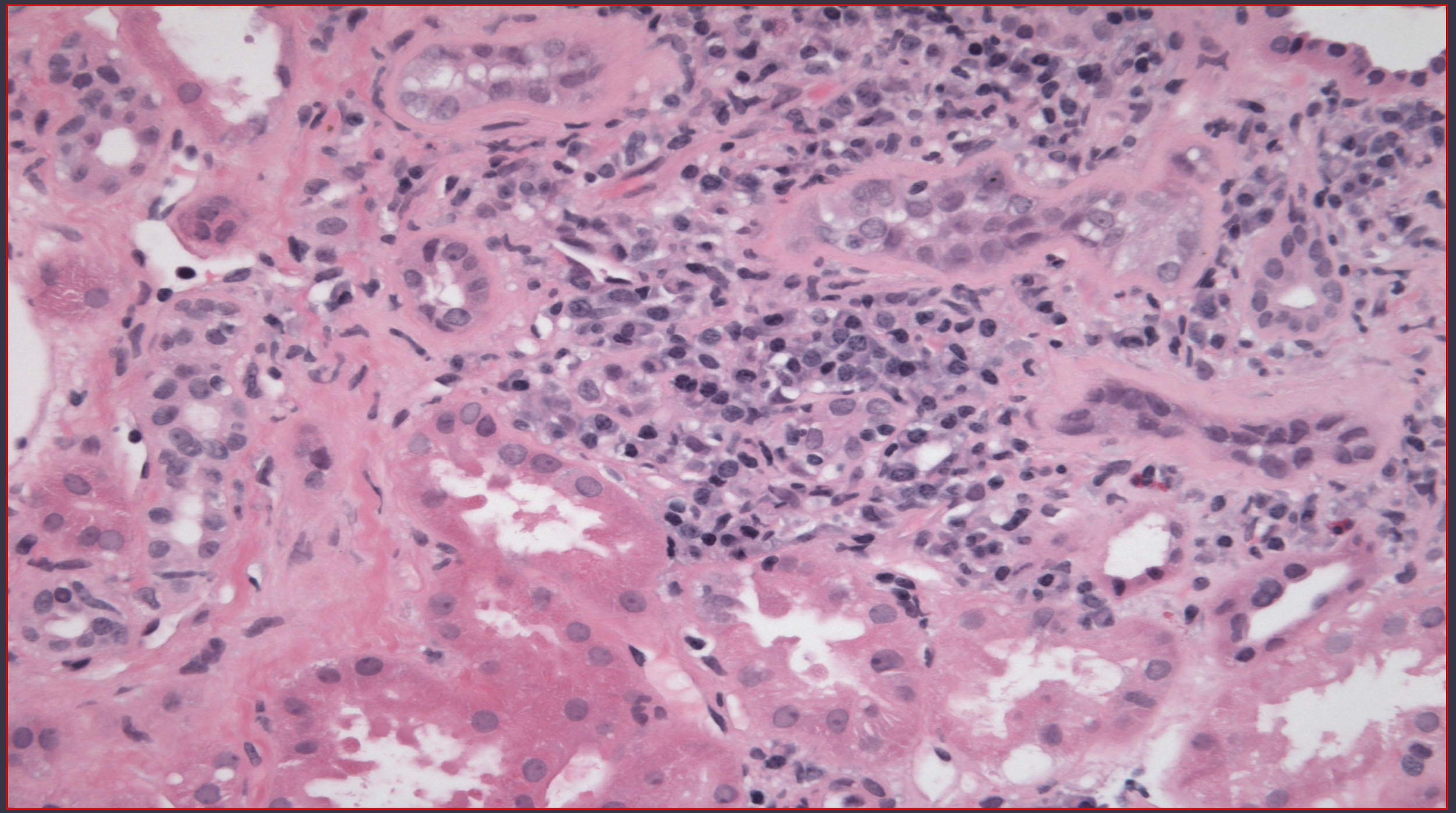
- We performed renal biopsies on five patients (45 %) after BKVN treatment.
- Four biopsies showed an increased of interstitial inflammation and tubular atrophy, between 10 and 20%, respect to the prior biopsy.

Glomeruloesclerosis was also higher in three biopsies.

BKV infections was not found in any biopsy (SV 40 was negative in all cases)







DISCUSSION

- SPK presents a unique scenario where the diagnosis and therapy of BKVN can be a challenging problem.
- The corner stone of BKVN is **reduction** in maintenance immunosuppression
- This strategy is specially challenging in SPK patients as there is a risk for pancreatic allograft rejection, wich can have significant mortality.

Trofe J et al. Polyomavirus in kidney and kidney-pancreas recipients. Transpl Infect Dis 2003; 5-21

SmithF et al. Screening to prevent Polyoma Virus nephropathy in kidney trasnplantation: a cost analysis. Am J Transplant 2009: 9 : 2177

DISCUSSION

- This fear of pancreatic allograft rejection indirectly may contribute to inadequate treatment of BKVN that can lead a very hight rate (43-89%)of kidney allograft loss.

- Very little is currently know about the clinical course of SPK recipients although the pancreas allograft is not thought to be vulnerable directly to BK virus infections, like we seemed in our cases.

Lipshutz GS et al. BK virus in simultaneous páncreas-kidney recipients: a leading cause of renal graft loss in first two years post-transplants. Am J Transplant 2005: 5: 366

DISCUSSION

- Our results suggest a high incidence of biopsy proven BKVN in SPKT recipients. (6,7%). This observation is in the line of previous works suggest an incresased incedence of 7,5 and 6,2 % (Lipshutz GS and Al-Jedai AH) for BK in SPKT.

- Our data also suggest a late onset of BKVN in SPKT recipients compared with early onset of BKVN in Kidney transplants patients. (12 months).

- The use of lymphocyte-depleting induction has been associated with an increased incedence of BKV replication most likely do to an elimination of protective BK specific celular inmunity

DISCUSSION

. However, additional risk factors seem to be decisive for the development of BKV replication and progression at BKVN : acute cellular rejection episodes and Systemic CMV recativation-

.Pre-existing diabetes has been also suggested to be a posible risk factor for BKVN and at least in part explain the increased incidence of BKVN in SPKT recipients.

Schachtner T at al. Inflammatory activation and recovering BKV- specific immunity correlate with self-limited BKV replication after renal transplantation.Transpl Int 2014; 27: 290-301

SUMMARY

SPKT recipients present late onset BKVN wich may be atributed to a greater risk of overimmunosuppresion du to the higher rejection risk presented to the pancreas allograft.

BKVN in SPKT recipients is also a potentially preventable cause of allograft loss. Screening for BK virus in SPK patients permits early detection and timely intevention that it turn may results in improved Kidney allograft survival.

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