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SUMMARY

This report describes a man in his late 50s who underwent donation-after-circulatory-death kidney transplantation in 2012, due to end-stage kidney disease of unknown origin. More than a decade post-transplant, he presented with a progressive decline in graft function after maintenance immunosuppression had been reduced due to multiple skin carcinomas and the prolonged time since transplantation. Kidney biopsy revealed chronic-active tubulointerstitial nephritis with positive immunohistochemical staining for SV40, initially raising suspicion for BK polyomavirus-associated nephropathy. However, quantitative PCR (qPCR) analysis for BKPyV in both plasma and tissue was negative. In contrast, qPCR for JC polyomavirus (JCPyV) was positive in both plasma and biopsy tissue, leading to the diagnosis of JC polyomavirus nephropathy. Despite the reduction of immunosuppressive therapy, the patient experienced ongoing deterioration of graft function. Our report adds to the limited but growing body of literature on JCPyV and emphasises the need for increased clinical awareness and further research into its prevalence, pathogenesis and optimal management in kidney transplant recipients.

BACKGROUND

The JC polyomavirus (JCPyV) is a small, non-enveloped virus with a circular double-stranded DNA genome, belonging to the Polyomaviridae family. Closely related to BK polyomavirus (BKPyV), JCPyV shares many structural and genetic features, including a genome that consists of three main regions: an early region encoding regulatory proteins such as the Large Tumour Antigen (LTag), a late region encoding capsid proteins, and a non-coding control region (NCCR) that governs viral replication and transcription.[1 2]

Primary infection with JCPyV usually occurs in early childhood, likely through respiratory or oral transmission. This initial infection is typically asymptomatic. Seroprevalence estimates range from 39% to 60% in the general population.[3 4] Following primary infection, the virus is believed to establish a latent or low level persistent infection in various tissues, including renal tissue and urothelium.[1 5]

In immunocompromised hosts, JCPyV is most often associated with progressive multifocal leukoencephalopathy (PML), a severe demyelinating disease of the central nervous system, marked by white matter lesions and high morbidity and mortality.[6] In contrast, BKPyV infection is a well-recognised complication in kidney transplant recipients (KTRs), where it can cause BK polyomavirus-associated nephropathy (BKPyVAN). This condition typically presents as tubulointerstitial nephritis (TIN) with detection of SV40 LTag in kidney biopsy. However, this immunohistochemical marker, while indicative of a polyomavirus infection, does not distinguish between BKPyV, JCPyV or SV40, as they all belong to the Betapolyomavirus genus.[7] In this report, we describe a KTR in whom JCPyV, rather than BKPyV, was the underlying cause of polyomavirus associated nephropathy.

CASE PRESENTATION

A man in his late 50s with renal failure of unknown origin underwent a kidney transplant from a donor after circulatory death in 2012 and was jointly followed up at both the Leiden University Medical Center and the Groene Hart Hospital in Gouda. His medical history post-transplantation was notable for basal cell carcinoma and squamous cell carcinoma of the skin. Due to the occurrence of these skin carcinomas and the extended period since transplantation, his maintenance immunosuppression regimen was reduced in March 2023, from prednisone, everolimus (EVL; trough levels ranged from 4.8 to 7.1 µg/L, with a 12 hours whole blood concentration-time curve of 82 µg*h/L, measured in 2023), and enteric-coated mycophenolate sodium (EC-MPS; was given two times a day 540 mg, with a 12 hours plasma concentration-time curve of 47 mg*h/L, measured in 2021) to prednisone and EVL.

At the time of immunosuppression reduction, there was already a slight decline in kidney function, with serum creatinine rising from approximately 1.3 mg/dL in January 2023 (estimated glomerular filtration rate (eGFR) of 60 mL/min/m^2) to 1.56 mg/dL (eGFR 48 mL/min/m^2). By November 2023, serum creatinine had further increased to 2.08 mg/dL, with an eGFR of 34 mL/min/m^2. Urine analysis revealed no proteinuria or erythrocyturia, and an ultrasound of the transplanted kidney showed no abnormalities. Luminex screening and single antigen assays detected no de novo donor-specific antibodies. A renal biopsy was performed, revealing a chronic-active TIN, with positive staining for SV40, consistent with BKPyVAN (figure 1). However, BKPyV PCR in the serum was negative. Since T cell-mediated rejection (TCMR) Banff1B following reduction of immunosuppression could not be excluded, and given the absence of detectable BKPyV viremia, the patient was treated under the working diagnosis of TCMR. The patient received

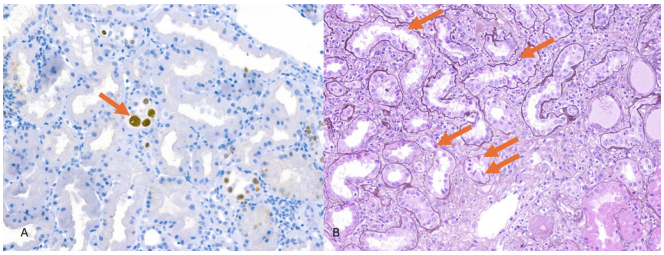

Figure 1 (A) Kidney biopsy showing positive nuclear staining for SV40 large T antigen in tubular epithelial cells, brown nuclear signal (indicated by red arrow), consistent with polyomavirus infection (×200). (B) H&E staining of the same biopsy reveals tubular epithelial cells with irregular, somewhat flattened nuclei (indicated by red arrows), suggestive of viral cytopathic changes (×200).

methylprednisolone 1000 mg/day for 3 days, and EC-MPS was reintroduced to his maintenance immunosuppression regimen.

Despite this treatment, his kidney function continued to deteriorate, with serum creatinine rising to 3.39 mg/dL and an eGFR of 19 mL/min/m^2. We reconsidered the diagnosis and decided to perform a real-time (qPCR) testing for JCPyV on both plasma and biopsy samples, which returned positive with a cycle threshold value of 28 and 17, respectively (figure 2). An additional BKPyV PCR on the kidney biopsy was negative, leading to the diagnosis of JCPyV-associated nephropathy (JCPyVAN). Following this diagnosis, EC-MPS was discontinued.

The patient exhibited no symptoms or signs of neurological involvement, and an MRI cerebrum showed no abnormalities concordant with PML. However, over the subsequent months, his graft function has continued to deteriorate.

OUTCOME AND FOLLOW-UP

As of the latest follow-up in May 2025—approximately 1 year after the diagnosis of JCPyVAN—his renal graft function has progressively declined, with a serum creatinine of 4.01 mg/dL and an eGFR of 15 mL/min/1.73 m^2. The patient reports increased fatigue compared with earlier, but he remains able to pursue his hobbies and continues to work full-time. He is currently being evaluated for a second kidney transplantation. Before proceeding with retransplantation, clearance of JCPyV is required. His viral load remains detectable, with a current PCR CT value of 29. In this context, the proposed management includes discontinuation of everolimus and continuation with prednisone monotherapy.

DISCUSSION

In this study, we present a case of JCPyVAN in a KTR presenting with a TIN on kidney biopsy, with positive SV40-staining and positive qPCR for JCPyV in both kidney tissue and serum, while BKPyV was consistently negative.

Cases of JCPyVAN in KTRs are rarely reported in the literature. Kazory *et al* described a similar case where, despite reduction of immunosuppression, the patient experienced graft loss, mirroring our findings.[8] However, Wen *et al* observed improvement and stabilisation of kidney function following immunosuppression reduction.[9] Kantarci *et al* reported a case of JCPyVAN successfully treated with intravenous immunoglobulin (IVIG), with subsequent conversion from tacrolimus to sirolimus, leading to stabilisation of kidney function.[10] Although cases of JCPyVAN are rarely reported, Drachenberg *et al* suggested that JCPyVAN may be more common than previously assumed.[11] Their study retrospectively analysed 980 KTRs, selecting patients based on the presence of decoy cells in urine. Among these, six patients with JCPyV viruria and without BKPyV viruria exhibited histological signs suggestive of polyomavirus-associated nephropathy in the kidney biopsy, resulting in a JCPyVAN incidence of 0.9%.

An important consideration is why JCPyV, in certain cases, leads to nephropathy rather than PML. Interestingly, such a shift in viral tropism is not unique to JCPyV, as BKPyV has also been reported to cause PML-like presentations.[12 13] One possible explanation is that differences in host susceptibility, combined with the degree of immunosuppression, could influence viral tropism. Another possible explanation may involve (lack of) mutations in the genome of JCPyV, since point mutations in the VP1 gene and rearrangements in the NCCR of JCPyV are known

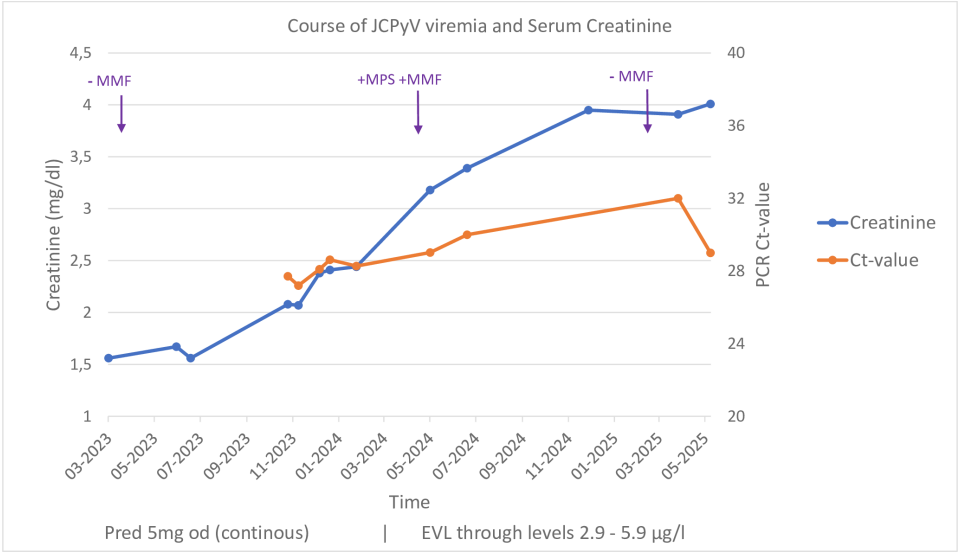

Figure 2 The graph shows the course of serum creatinine (mg/dl) and cycle threshold (Ct) for real-time PCR on the serum for JC polyomavirus (JCPyV). –MMF indicates cessation of enteric-coated mycophenolate sodium (MMF). +MMF indicates the start of MMF. +MPS indicates the start of treatment with methylprednisolone (MPS) 1000 mg/day for 3 days. During this period, oral prednisone was continued at 5 mg once daily (OD), and everolimus (EVL) trough levels remained between 2.9 and 5.9 µg/L.

to play a key role in shifting JCPyV tropism toward glial cells in the brain, thereby facilitating the development of PML.[14]

Importantly, although rare as a single entity, JCPyV has been detected in kidney biopsies from patients with BKPyVAN, raising the question of whether JCPyV is an under-recognised pathogenic (disease-modifying) cofactor in these cases. Zhang *et al* investigated 140 KTRs with biopsy-proven polyomavirus-associated nephropathy, all of whom had BKPyV detected in urine or blood.[15] Among these, 18 patients (~12%) also had detectable JCPyV DNAemia. The study showed that patients with concurrent JCPyV DNAemia had more severe tubulitis on kidney biopsy and experienced a higher rate of graft loss—50% compared with 25.4% in those without JCPyV DNAemia. Notably, this difference occurred despite similar BKPyV viral loads in urine and blood between the two groups. These findings suggest that co-infection with JCPyV may exacerbate disease severity in patients with BKPyVAN. The exact mechanisms underlying the interaction between these viruses and their implications for renal pathology and transplant outcomes remain unclear and warrant further investigation. This is particularly relevant now that therapeutic options—primarily targeting BKPyV rather than both BKPyV and JCPyV—are entering the clinical arena (NCT0429447 and NCT05769582).

In summary, we report a rare case of JCPyVAN in a KTR presenting with a SV40-positive TIN, negative BKPyV and positive JCPyV qPCR in both kidney and serum. The role of JCPyV in kidney transplantation, including its potential impact on allograft function and its interaction with BKPyV, remains an area requiring further research.

Learning points

- JC polyomavirus (JCPyV) can cause nephropathy in kidney transplant recipients, mimicking BK polyomavirus-associated nephropathy, and should be considered in cases of tubulointerstitial nephritis with negative BK polyomavirus (BKPyV) PCR but positive SV40 staining.
- SV40 immunohistochemistry confirms polyomavirus infection but cannot distinguish between BKPyV and JCPyV, as both viruses are closely related and share the large T antigen targeted by SV40 staining.
- The role of JCPyV in kidney transplantation, including its potential impact on allograft function and its interaction with BKPyV, remains an area requiring further research.

Contributors All authors contributed to the diagnosis and clinical management of the patient. WTM drafted the manuscript. All authors critically revised the manuscript for intellectual content and approved the final version for submission. AV is the guarantor. During the preparation of this manuscript, AI was only used to assist with English language corrections.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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