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Case Series

JC Polyomavirus Nephropathy: A Rare Complication Late after Kidney Transplantation

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Kidney transplantation · Infection · JC virus · Polyoma nephropathy · BK virus

Abstract
Introduction: JC-polyomavirus-associated nephropathy (JC-PVAN) is a rare cause of allograft dysfunction with only a few cases described in the literature. ***Case Presentation:*** We present 2 cases of JC-PVAN, both of which occurred >5 years after kidney transplantation. In both cases, transplant biopsies were performed because of worsening of kidney function. We found tubulitis and interstitial inflammation; immunohistochemistry was positive for SV40, but BK virus was not detected. The presence of JC virus confirmed the diagnosis of JC-PVAN. Immunosuppressive therapy was adopted, but in both cases graft function progressively deteriorated. ***Conclusions:*** Our cases show that JC-PVAN, although much rarer than BK-PVAN, should be considered a possible cause of graft dysfunction even years after transplantation. Complete diagnostic workup, including kidney biopsy, is crucial for correct diagnosis and treatment.

Introduction

BK and JC viruses are the most common polyomaviruses (PVs) that may affect humans. Infections generally occur at a young age and are asymptomatic, but might become relevant in immunocompromised patients [1]. In kidney transplant recipients, BK virus causes

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nephropathy and urologic complications, such as hemorrhagic cystitis or ureteral stenosis. JC virus is known to cause progressive multifocal leukoencephalopathy (PML) in HIV patients, but its involvement in polyomavirus allograft nephropathy (PVAN) is rare [2]. Here we describe two cases of JC-related nephropathy occurring late after kidney transplantation and provide a review of the literature. The CARE Checklist used for this report is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000540294).

Case Report

Patient 1

A 46-year-old male patient with end-stage renal disease secondary to autosomal-dominant polycystic kidney disease underwent deceased-donor kidney transplantation after 2 years on hemodialysis. The immunological risk was low, with 6/8 mismatches and no preformed donor-specific antibodies. The initial immunosuppressive regimen consisted of basiliximab, tacrolimus, mycophenolate mofetil, and steroids. During the first 2 years after transplantation, he experienced an episode of acute T-cell-mediated rejection Banff grade IB. The biopsy was with 13 glomeruli, 4 arteries, and medulla adequate according to Banff criteria, and there were no signs of PVAN. He was treated with corticosteroids (prednisone 75 mg/d) and an episode of acute T-cell-mediated rejection Banff grade IIA, for which he received intravenous pulse methylprednisolone 500 mg every 24 h for 3 days followed by increased dosages of prednisone. Five years after transplantation, mycophenolic acid was switched to azathioprine because of diarrhea, with improvement in symptoms. Two months later, renal function worsened with serum creatinine levels rising from 140 to 200 μmol/L and proteinuria between 500 mg and 1 g per day. Allograft renal biopsy showed interstitial fibrosis and tubular atrophy, inflammatory lympho-histiocytic infiltrates with a prominent component of plasma cells, and tubulitis in 30% of the cortex. No definite inclusion bodies were found in the tubular epithelium, but immunohistochemistry for simian virus 40 (SV40) was positive in many tubules, leading to the diagnosis of PVAN. Surprisingly, there was no BK viruria or viremia, but an isolated JC viremia was detected with 42,368 GEq/mL. Concomitant PML was excluded by magnetic resonance imaging of the brain.

Tacrolimus dose was reduced with a target plasma trough level of 6 μg/L; leflunomide was added due to its postulated antiviral activity, while prednisone was reduced from 10 to 7.5 mg per day. Transplant function stabilized with creatinine values around 180 μmol/L.

Allograft biopsy was repeated 14 months later because of further increase in creatinine values up to 210 μmol/L and showed worsening of PV nephropathy with presence of viral inclusion bodies in addition to positivity for SV40 in many tubules (Fig. 1). Azathioprine was stopped to reduce burden of immunosuppressive therapy.

JC viremia was detectable at low levels (1,200 GEq/mL) for 9 years. After this period, leflunomide was stopped, while maintenance immunosuppression consisting of tacrolimus and prednisone was continued. Transplant function progressively deteriorated over the following years, and 12 years later, the patient went back on hemodialysis. Time course of creatinine level and medication of the patient are shown in Figure 2.

Patient 2

A 43-year-old man received a cadaveric renal transplantation after 4 years on hemodialysis because of kidney failure due to IgA nephropathy. He had 4/8 HLA mismatches and no donor-specific antibodies. The initial immunosuppressive therapy consisted of basiliximab, cyclosporine A, mycophenolate mofetil, and corticosteroids. After 5 years with stable

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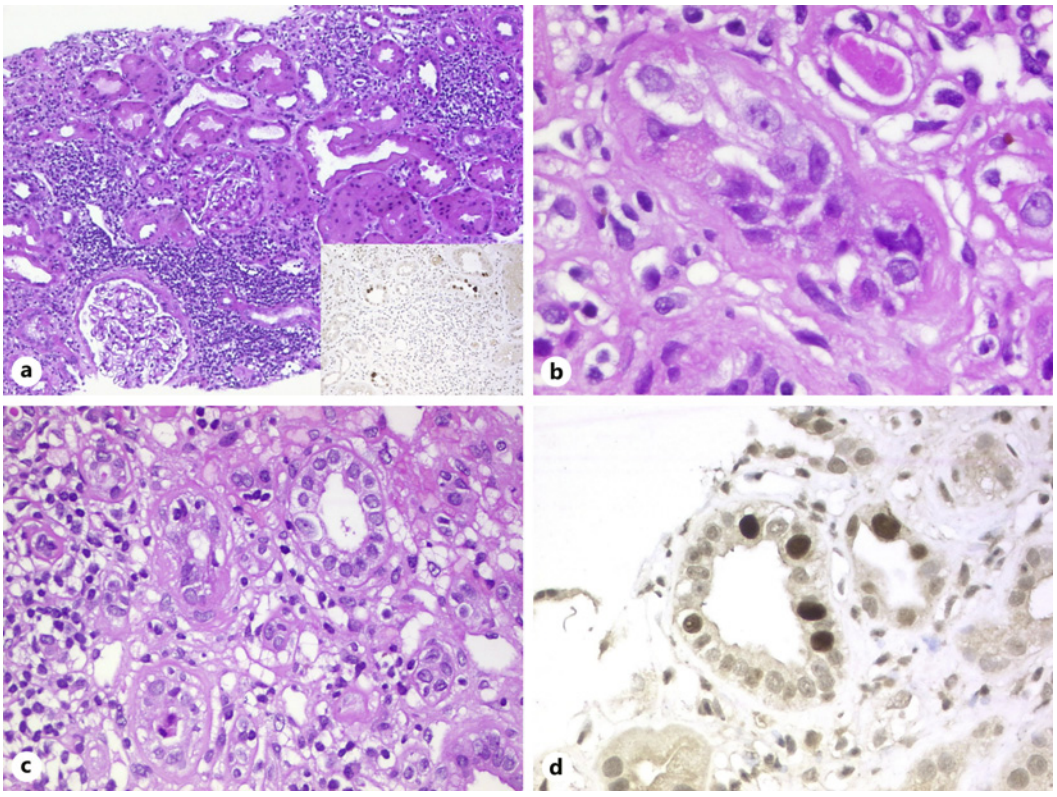

Fig. 1. a PV nephropathy with focal interstitial mononuclear infiltrates (HE, original magnification ×50). Inset: positive staining for PV in multiple tubular epithelial cells (SV40 immunohistochemistry, original magnification ×120). **b**, **c** Tubules with intranuclear inclusions typical for PV (HE, original magnification ×400 in B and ×200 in C). **d** Positive staining for PV in multiple tubular epithelial cells (SV40 immunohistochemistry, original magnification ×250).

transplant function, there was a rapid rise in creatinine levels from 180 to 270 μmol/L over 5 months. Allograft biopsy showed 40% of interstitial fibrosis, tubular atrophy, viral inclusions in tubular epithelium, and positivity of SV40 in the tubules, diagnostic for PVAN (Fig. 3). No BK viremia and viruria were detected. However, presence of JC viremia combined with typical histological findings led to the diagnosis of JC virus nephropathy. Dosage of mycophenolate mofetil was reduced from 1,000 mg b.i.d. to 2 × 750 mg b.i.d. Two months later, the patient developed a stricture of the ureter which required urologic intervention. A biopsy of the ureter did not reveal any signs of PV infection. Kidney biopsy was repeated and confirmed the persistence of PV nephropathy. Mycophenolate was switched to azathioprine.

After 2 years with stable allograft function, there was an increase in proteinuria from 500 to 1,500 mg/d. Allograft biopsy showed vascular signs for toxicity due to calcineurin inhibitors and PVAN with diffuse positivity in the tubules. Renal function gradually deteriorated in the following 5 years, until the patient required dialysis again, 12 years after transplantation. The patient was considered eligible for a second kidney transplant, and the first kidney allograft was explanted to reduce the risk of infection of the future transplanted organ. Histologic evaluation of the explanted organ showed few cells with positivity for SV40 in the medulla. Due to the patient's high level of immunization, he is still on the transplant list and has not yet undergone retransplantation. Time course of creatinine level and medication of the patient are shown in Figure 2.

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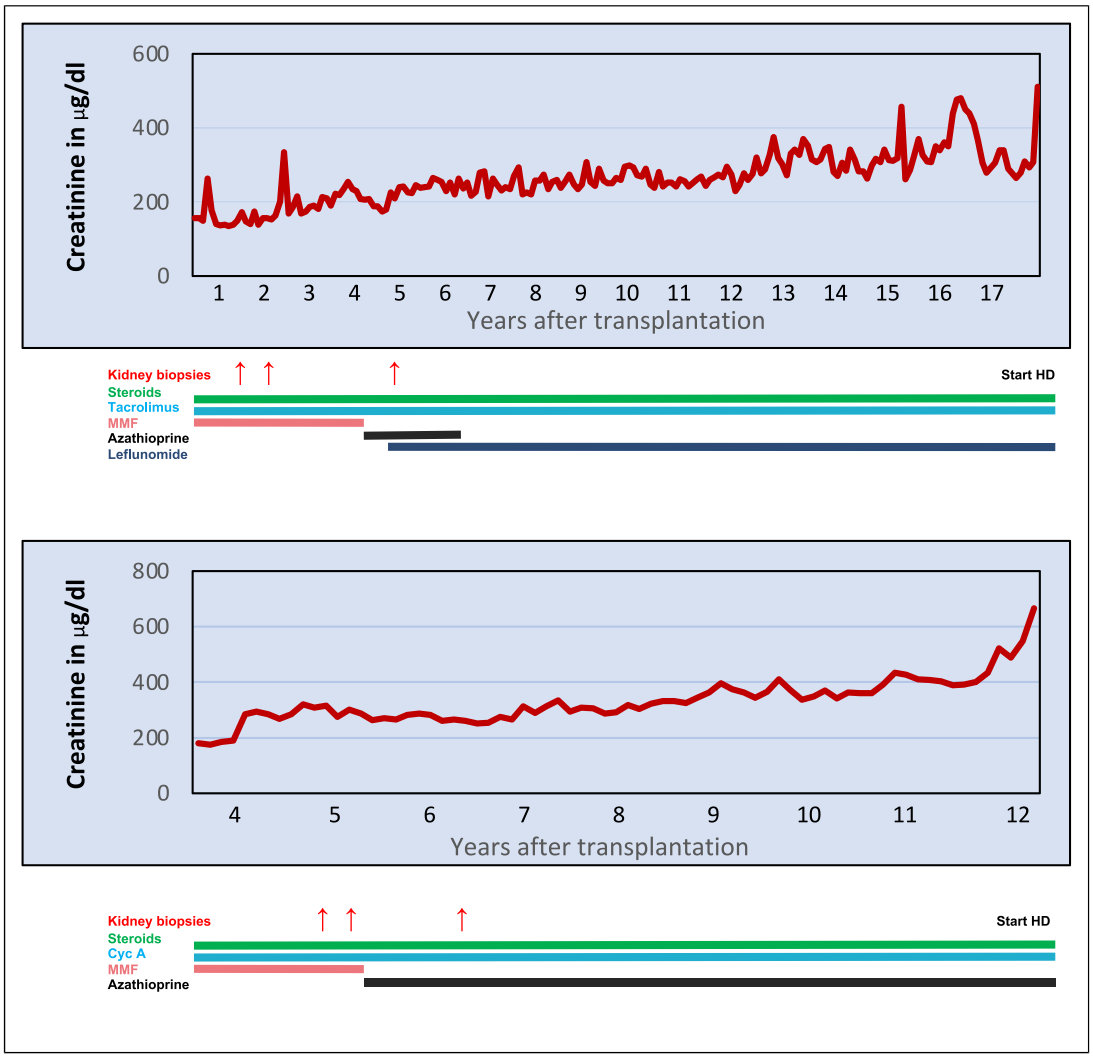

Fig. 2. Time course of creatinine level and medication of patients 1 and 2.

Discussion

JCV and BK virus are widely spread in the human population, with a seropositivity of 60–80% in healthy individuals [3]. Transmission occurs probably through mucosal contact with contaminated body fluids, food, or water [1]. After primary infection, which is usually asymptomatic, the virus persists in different organs, such as the kidney, the ureters, the brain, and the spleen [3]. In immunodeficient patients, the virus can proliferate and cause symptomatic disease. While BK virus typically has a tropism for the urogenital system, thereby causing PVAN as well as ureteral stenosis in kidney transplanted patients, JC virus has an affinity for the central nervous system, causing PML usually in patients with HIV infection/AIDS. Rarely, PML can also occur in patients with organ transplantation, hematologic malignancy, solid cancer, and autoimmune disease treated with immunomodulators [4–6].

Despite the tropism for CNS, JCV has also been shown to cause PVAN in a small number of patients after kidney transplantation (<3% of the reported cases), with the first case described in 2003 by Kazory et al. [3]. In the following years, other cases of JC-polyomavirus-associated

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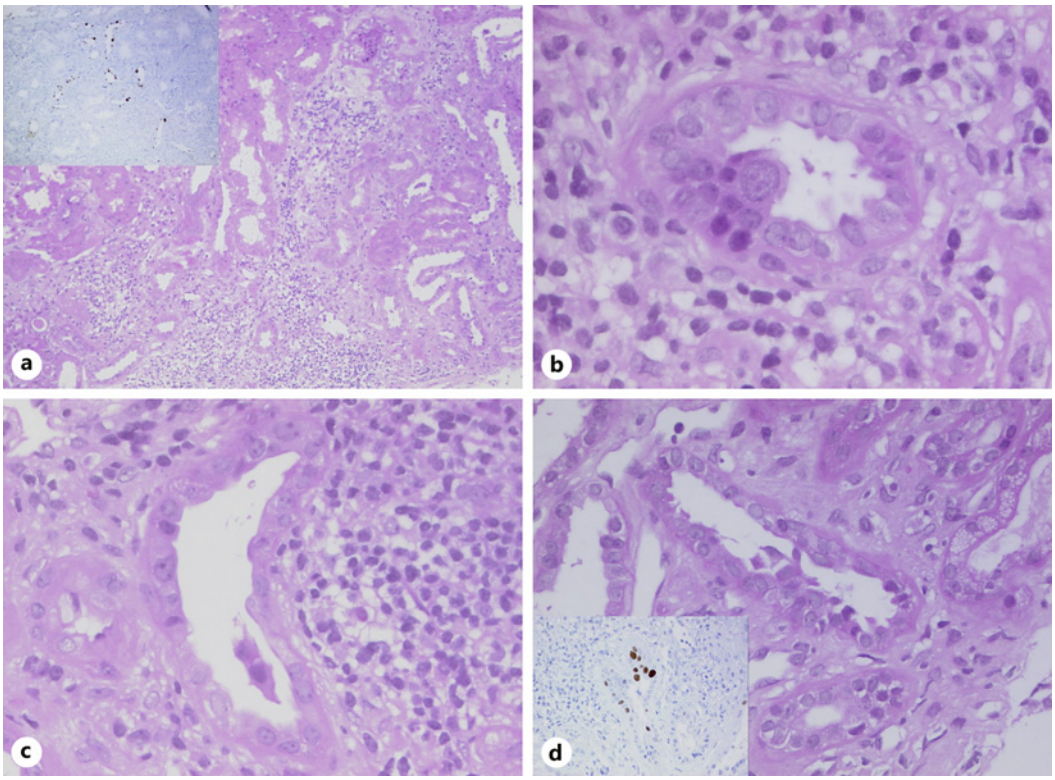

Fig. 3. a PV nephropathy with focal interstitial mononuclear infiltrates (HE, original magnification ×60). Inset: positive staining for PV in multiple tubular epithelial cells (SV40 immunohistochemistry, original magnification ×50). **b–d** Tubules with intranuclear inclusions typical for PV (HE, original magnification ×280 in **b** and **c**, ×250 in **d**). Inset in (**d**): positive staining for PV in multiple tubular epithelial cells (SV40 immunohistochemistry, original magnification ×180).

nephropathy (JCV-PVAN) have been described, and they are summarized with their clinical features and outcomes in Table 1 [2, 6–14].

Risk factors for developing BK-PVAN include steroid pulse therapy to treat rejection, induction therapy with rabbit anti-thymocyte globulin, a higher number of HLA mismatches, renal cell injury due to previous rejection, longer cold ischemia time, male recipient, older donor age, and ureteral stent implantation [3, 15, 16]. It is not known whether the same risk factors also apply for JC-PVAN. Keykhosravi and colleagues recently described higher rate of JC viremia in patients with diabetes and history of kidney stones [17].

While the majority of BK-PVAN occurs during the first year after transplantation [16], JC-PVAN seems to appear later, between 4 and 6 years after transplantation – as shown by the 2 patients reported here. JCV-PVAN leads to a deterioration in allograft function; however, disease severity is probably less severe compared to BK-PVAN [8]. In our observations, graft failure occurred, respectively, 12 and 7 years after the diagnosis of JC-PVAN. Similarly, Wiegley et al. [2] documented 7 cases of JC-PVAN, tracking patients for periods ranging from 2.5 to 12 years. Among their cohort, graft failure was identified in 2 out of 7 individuals, late in the posttransplantation timeline, at 9 and 12 years posttransplant, respectively. Moreover, JC virus is not known to cause urological complications such as ureteral strictures. Coinfection with JCV in kidney transplant patients with BK-PVAN was reported in 17/75 (16.5%) of the cases reported from Drachenberg et al. [8]. The authors suggested that the presence of BK-PVAN could facilitate proliferation of JC virus. The main characteristics and differences between JC-PVAN and BK-PVAN are listed in Table 2.

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Table 1. Cases of JC-PVAN reported in the literature

Article	Year	Patients, *n*	Time after TPL	Prior rejection	MMF	AZA	TAC	SIR	Cyc	Steroids	BKV screening	BKV viremia	BKV viruria	JCV viremia	JCV viruria	Interstitial nephritis	Intranuclear inclusion	SV40 ST staining	Strategy	Outcome
Kazory [3]	2003	1	6 years	No	–	x	–	–	x	x	No	No	Nt	Yes	No	Yes	Yes	Nt	↓IS	Graft loss
Wen [7]	2004	1	12 months	Yes	x	–	x	–	–	x	No	Nt	Nt	Nt	Yes	Yes	Yes	Nt	↓IS	Stabilization of graft function
Drachenberg [8]	2007	6	29 months	Yes, 1 patient	x	–	x	x	x	x	Yes	No	No	Yes (4/6), low	Yes	Yes	Yes	Yes	↓IS	Stabilization of graft function
Lautenschlager [9]	2014	1	12 months	No	–	x	x	–	–	–	Yes	No	No	No/low	Yes	Yes	Yes	Yes	↓IS	Graft loss (ABMR)
Kantarci [10]	2011	1	6 months	Yes	x	–	x	–	–	x	No	No	No	No	Yes	Yes	Yes	Yes	↓IS	Stabilization of graft function
Aubert [11]	2013	1	29 months	No	x	–	x	–	–	x	No	No	No	Yes	Yes	Yes	Yes	Yes	↓IS	Graft loss
Chan [12]	2015	1	18 months	Yes	x	–	x	–	–	x	Nt	No	No	No	Yes	Yes	Yes	Nt	Fusidate sodium	Stabilization of graft function
Yang [6]	2017	1	4 years	No	x	–	x	x	–	–	Nt	No	No	Yes	Yes	Yes	Yes	Yes	↓IS	Stabilization of graft function
Aguilar [13]	2020	1	7 years	No	x	–	x	–	–	–	Nt	No	No	Yes	Yes	Yes	Yes	Yes	↓IS, IVIG	Stabilization of graft function
Wiegley [2]	2021	7	4.7 years (mean)	Yes, 2 patients	x	–	x	–	–	x (4/7)	Nt	No	No	Yes (6/7)	Yes	Yes	Yes (5/7)	Yes	↓IS (7/7), cidofovir (2/7)	Stabilization of graft function 5/7, graft loss 2/7 after 33, 34 months
Jawdeh [14]	2023	1	5.5 years	No	–	–	x	x	–	x	Yes	No	No	Yes	Nt	Yes	No	Yes	↓IS, IVIG	Stabilization of graft function
This report	2024	2	5.5 years	Yes, 1 patient	x	–	x (1)	–	x (1)	x	Yes	No	Nt	Yes	Nt	Yes	No	Yes	↓IS	Stabilization of graft function

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Diagnosis of JCV-PVAN can be challenging. Allograft biopsy is the gold standard, but sampling error can preclude the diagnosis due to the focal pattern of the disease [15]. Typically, the involved tubular cells show enlarged nuclei with basophilic and ground glass inclusions due to viral accumulation. PV infection is confirmed by detecting SV40 large T antigen by immunohistochemical analysis, since there is a cross-reactivity of SV40 staining for both BK and JC virus. Different types of PV can be distinguished using species-specific antibodies, in situ hybridization, or polymerase chain reaction [18]. In advanced disease, tubular inclusions can be absent, and interstitial fibrosis and tubular atrophy as well as inflammation dominate, resembling cellular rejection [8]. Differentiating these two entities has important therapeutic consequences, since JCV-PVAN is treated with reduction of immunosuppressive therapy agents during rejection with intensification.

JCV viremia, even at low levels, seems to correlate with parenchymal involvement similar to BKV-PVAN [8, 19], which makes it a useful parameter during follow-up. JC viremia is normally lower than BK viremia in patients with PVAN [8]. JCV viruria has a low predictive positive value for diagnosis of JCV-PVAN, since it is common in immunocompetent individuals (40%) [8]. This holds also true for detection of decoy cells (detached tubular epithelial or urothelial cells containing intranuclear viral inclusion bodies) in urinary cytology [8].

There is no specific treatment for JC-PVAN. As for BK-PVAN, the general approach consists of reducing immunosuppression. Due to the lack of randomized clinical trials and the complexity and variety of patients with PVAN, there is no standardized strategy for reducing immunosuppressive therapy. Different approaches consist in reducing the dose of calcineurin inhibitors, sirolimus, or antimetabolites [16]. In a prospective randomized study, which compared tacrolimus to cyclosporine, no single calcineurin inhibitor seemed to be more related to BKV viruria or PVAN than the other [20]. Our approach in reduction immunosuppression would be to follow the recommendation for the treatment of BK-PVAN, which considers reducing CNI by 25–50% as the first step, followed by a reduction of the antimetabolite, or alternatively, reducing the antimetabolite first and then the CNI as a second step, under the control of viremia levels [19]. In our patients, adherence to immunosuppressive therapy, a factor that could influence outcomes, was consistently evaluated through monthly monitoring of tacrolimus and ciclosporin levels.

In our patients, adherence to immunosuppression, which could have an impact on outcomes, was assessed regularly with tacrolimus or cyclosporine levels which were performed approximately once a month. In addition to reducing immunosuppression, adjuvant drugs such as leflunomide, cidofovir, and intravenous immunoglobulins have been used to treat PVAN [16] with moderate effect on virus clearance and stabilization of graft function. The lack of prospective randomized studies comparing these medications to the standard approach of reducing immunosuppressive therapy limits considerations about their antiviral efficacy.

Mirtazapine seems to have inhibitory effects on JC virus replication in vitro by blocking entry of JC virus into serotonin 5HT2AR receptor-transfected cell lines. It has been successfully used in single cases for therapy of PML [21] and may be used for treatment of JC-PVAN in the future. New therapies with small-molecule inhibitors of JCV that target the initial interaction between the virus and host cell and therefore block viral entry are under development [22], such as retrograde transport inhibitors Retro 2 and Retro 2.1, endosome acidification inhibitors preventing the infection process, and signaling pathway inhibitors involved in viral replication support. These drugs have shown efficacy in reducing JC virus infection in vitro, though further studies are needed to evaluate their effectiveness in vivo. In addition, it is worth noting that virus-specific T cells targeted against the BK virus have been employed in single cases to treat JC viral infection and PML following stem cell transplantation

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Table 2. Main characteristics and differences between JC-PVAN and BK-PVAN

	BKV-PVAN	JCV-PVAN
Occurrence	Frequent	Rare
Prevalence viremia	12%	6–7%
Prevalence nephropathy	3–5%	<1%
Timing	Early	Late
Urological complications	Yes	No
Outcome	29–67% graft loss at 6 months (KAZORY TID 2003, Geehta 2010)	13% graft loss
Correlation between viremia and PVAN	Yes	Yes

[23]. This approach has been used in small case studies for refractory BKV-PVAN, showing potential efficacy. However, its safety and efficacy in treating JCV-PVAN remain to be explored, and further research is warranted in this area.

Strategies to prevent recurrences in retransplanted patients after graft loss due to PVAN are controversial. While nephrectomy prior to retransplantation appears to be a logical approach, given the prolonged survival of both BK virus and JC virus in renal tubular cells and epithelium, unanswered questions persist about its efficacy. Previous studies investigating patients who underwent allograft nephrectomy following graft loss for BK-PVAN have reported instances of recurrent BKV nephropathy [24].

Conclusion

JC nephropathy, a rare complication following kidney transplantation, warrants attention due to its unique diagnostic considerations, incidence patterns, risk factors, and therapeutic approach. Diagnosis of JC nephropathy should be considered in transplant recipients presenting with histological evidence of SV40 positivity and concurrent absence of BK viremia. JC nephropathy can manifest years after transplantation, with cases reported even 6–7 years postsurgery. This emphasizes the necessity of ongoing surveillance for renal complications throughout the recipient's lifetime, regardless of the duration since transplantation, and to perform late allograft biopsies. Shared risk factors with BK PV nephropathy, including intensity of immunosuppression, older age, male gender, and prior rejection episodes, highlight the importance of tailored immunosuppression regimens and vigilant monitoring for high-risk individuals.

Therapeutically, management of JC nephropathy mirrors that of BK PVAN, focusing on reducing immunosuppression while balancing the risk of graft rejection. Although antiviral medications have shown limited efficacy, ongoing research explores novel agents targeting JC virus replication.

JC nephropathy poses several unanswered questions in its management, warranting further research to optimize patient outcomes. One such question pertains to the potential protective role of allograft nephrectomy followed by retransplantation in cases of advanced JC nephropathy which remains controversial, with limited evidence guiding clinical practice. Future research should focus on elucidating the benefits and risks associated with this practice, including its impact on viral clearance, risk of disease recurrence, and graft survival following retransplantation.

Statement of Ethics

The patients have given their written informed consent to publish their case (including publication of images). Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jennifer Scotti Gerber and Sara De Marchi collaborated on writing the manuscript and conducting the literature review. Ariana Gaspert was responsible for capturing and providing the histological pictures included in the manuscript. Thomas Fehr and Pietro E Cippà contributed to the revision process, assisting in the incorporation of feedback and making revisions to improve the manuscript's clarity and coherence.

Data Availability Statement

All data underlying the results are available as part of the article, and no additional source data are required. Further inquiries can be directed to the corresponding author.

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