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Kidney histological changes in BK virus associated nephropathy after kidney transplantation

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Abstract
Background: End-stage renal disease (ESRD) patients can survive kidney transplantation, however complications such BK virus-associated nephropathy make graft survival difficult. BKVAN causes kidney transplant allograft dysfunction and failure. This study will examine BKVAN histological alterations, including tubular and interstitial involvement, vascular changes, and immunohistochemistry.
Method: This research examined 35 BKVAN-diagnosed kidney transplant patients' biopsy findings. Histological findings included tubular epithelial cell infection, interstitial inflammation, fibrosis, vascular involvement, and SV40 T-antigen immunohistochemistry staining. The Banff and Polyomavirus Nephropathy (PVN) classifications were used to assess nephropathy severity. All patients showed significant tubular epithelial BK virus infection with swollen nuclei and viral inclusions.
Results: The worst cases included up to 65% of the cortical region and showed tubulointerstitial inflammation, interstitial fibrosis, and tubular atrophy (IFTA). Thirty individuals had intimal thickening and a few had arterial hyalinosis. A positive SV40 T-antigen staining indicated BK virus replication in all patients. The majority of patients had PVN stage 2 or 3, suggesting moderate to severe nephropathy.
Conclusion: Serious histological alterations are linked with progressive BK virus-related nephropathy, which causes post-transplant graft dysfunction. Tubular epithelial infection, interstitial fibrosis, and vascular damage in advanced instances were hallmarks. Early identification and treatment improve transplant survival and patient outcomes.

Keywords: Kidney transplantation, BKVAN, histopathological, tubulointerstitial inflammation, immunohistochemical

Introduction
Kidney transplantation is the preferred treatment for end-stage renal disease (ESRD), offering improved survival and quality of life compared to dialysis [1]. Transplantation alleviates the burdens of chronic dialysis and reduces mortality by improving cardiovascular health, nutrition, and physical well-being [2]. Advances in surgical techniques and immunosuppression have resulted in over 90% one-year graft survival globally [4]. However, long-term graft survival is challenged by complications such as acute rejection, chronic allograft nephropathy, infections, and conditions like BK virus-associated nephropathy (BKVAN) [4]. BKVAN, caused by reactivation of latent BK virus under immunosuppression, is a significant post-transplant complication [5]. BK virus reactivation affects 10–15% of kidney transplant recipients, with 1–10% developing BKVAN, a condition characterized by renal tubular inflammation and injury due to viral replication [6]. Clinical manifestations, including elevated serum creatinine and graft dysfunction, often appear late, necessitating early detection to prevent irreversible damage [7]. Histological examination of kidney biopsies is the diagnostic gold standard, revealing tubulointerstitial nephritis, viral inclusions, and fibrosis correlating with disease severity [8]. While polymerase chain reaction (PCR) aids in detecting viral DNA, definitive diagnosis requires histopathological evaluation [9]. Despite aggressive management, up to 50% of BKVAN patients lose their graft within five years of diagnosis [10]. The pathophysiology of BKVAN involves direct cytopathic effects of viral replication and immune-mediated inflammation, leading to tubular atrophy, interstitial fibrosis, and graft dysfunction [11]. Immunosuppressive therapy, essential for preventing acute rejection, paradoxically predisposes recipients to viral reactivation, with enhanced risks

associated with intense immunosuppression during early transplantation periods [12]. Management involves balancing immunosuppression to minimize viral replication while preventing rejection. BKVAN-associated graft loss often necessitates a return to dialysis, which increases mortality risks due to associated comorbidities. Additionally, immunosuppression heightens susceptibility to infections and malignancies, including post-transplant lymphoproliferative disorder (PTLD) [13]. This study aims to evaluate the histopathological changes in BKVAN, particularly focusing on tubular and interstitial involvement, vascular changes, and immunohistochemical findings.

Methods

This retrospective cohort analysis was conducted at Erbil Teaching Hospital and focused on kidney transplant recipients diagnosed with BKVAN. The study aimed to assess histopathological changes, clinical characteristics, treatment strategies, and patient outcomes. The study included 35 kidney transplant recipients diagnosed with BKVAN based on clinical presentation, laboratory findings, and histopathological confirmation via kidney biopsy. Patients were selected based on the inclusion criteria of confirmed BKVAN diagnosis and complete medical records. All patients received induction immunosuppressive therapy with Antithymocyte Globulin (ATG) [14]. Maintenance immunosuppressive therapy consisted of a combination of cyclosporine, mycophenolate mofetil, and prednisone, in line with standard practice at our center. Upon BKVAN diagnosis, patients were treated primarily with intravenous immunoglobulin (IVIG) [15]. Adjustments to maintenance immunosuppressive therapy were made on an individualized basis to reduce viral replication while maintaining graft function. Patient data were collected using a structured questionnaire and hospital electronic medical records. Key data points included demographic information, medical history, transplantation details, clinical presentation, laboratory findings, biopsy results, and treatment history for BKVAN. Data were collected using a structured questionnaire. The questionnaire was designed to capture the following information:

1. **Demographic Information:** Data included the patient's age, gender, ethnicity, and body mass index (BMI).
2. **Medical History:** Information about the duration of end-stage renal disease (ESRD) was collected, along with the underlying cause of ESRD (e.g., diabetic nephropathy, hypertensive nephrosclerosis). The questionnaire also inquired about any history of previous kidney transplants and rejection episodes, as well as the presence of other comorbidities such as diabetes and cardiovascular disease.
3. **Transplantation Details:** Participants provided details about the date of kidney transplantation, the type of donor (Deceased or living), the number of HLA mismatches, and the induction immunosuppressive therapy used (e.g., ATG, basiliximab). Information on the maintenance immunosuppressive regimen (e.g., cyclosporine, mycophenolate mofetil, prednisone) was also collected.
4. **Clinical Presentation and Laboratory Findings:** The questionnaire gathered data on the patient's most recent serum creatinine levels, eGFR (Estimated glomerular filtration rate), and BK virus viral load. Participants were asked about the presence of symptoms of graft dysfunction (e.g., fatigue, fluid retention), as well as any history of opportunistic infections such as cytomegalovirus (CMV) or Epstein-Barr virus (EBV).
5. **Biopsy Information:** Participants indicated the reason for undergoing kidney biopsy (e.g., routine surveillance, suspicion of graft dysfunction). Histological changes noted on previous biopsies, such as tubulointerstitial nephritis, viral inclusions in tubular epithelial cells, tubular atrophy, and fibrosis, were recorded.
6. **Treatment History for BKVAN:** The questionnaire inquired about any reduction in immunosuppressive therapy following the diagnosis of BKVAN and the specific antiviral therapies administered (e.g., IVIG). Details on the current treatment plan for managing BKVAN were also captured.
7. **Outcomes:** The questionnaire included information on the current status of the transplanted graft (e.g., functioning, dysfunction, graft loss) and the current status of the BK virus infection (e.g., resolved, persistent, recurrent). Mortality risk factors, such as recurrent infections or cardiovascular complications, were also documented

Kidney biopsies were analyzed by pathologists using the Banff classification system [16]. Histopathological features such as tubulointerstitial nephritis, viral inclusions, fibrosis, and tubular atrophy were documented. Immunohistochemical staining for SV40 T-antigen confirmed BK virus infection, and BKVAN was staged using the Polyomavirus Nephropathy (PVN) classification. Patients were regularly monitored for graft function, BK viral load, and opportunistic infections. Biopsies were conducted when clinical signs of graft dysfunction were detected, and treatment responses were evaluated based on changes in viral load and graft function. Statistical analysis was performed using IBM® SPSS® Statistics software. Descriptive statistics summarized patient characteristics, histological findings, and treatment outcomes. Comparative analyses were conducted to evaluate the relationships between BKVAN severity, treatment protocols, and patient outcomes. A p-value of <0.05 was considered statistically significant. The study adhered to ethical guidelines established by Erbil Teaching Hospital Ethics Review Board. Informed consent was obtained from all participants, and confidentiality was maintained by anonymizing all patient data.

Results

This study analyzed biopsy results from 35 kidney transplant recipients diagnosed with BKVAN. The age of the patients ranged from 12 to 70 years, with a male predominance. All patients had received kidney transplants from either living or unrelated donors. The onset of BKVAN occurred between a few months to two years post-transplantation, with most patients presenting with graft dysfunction, as indicated by elevated serum creatinine levels ranging from 1.5 mg/dL to 4.5 mg/dL. A subset of patients also had concomitant conditions such as IgA nephropathy, diabetic nephropathy, or chronic active T-cell-mediated rejection (Figure 1A-D).

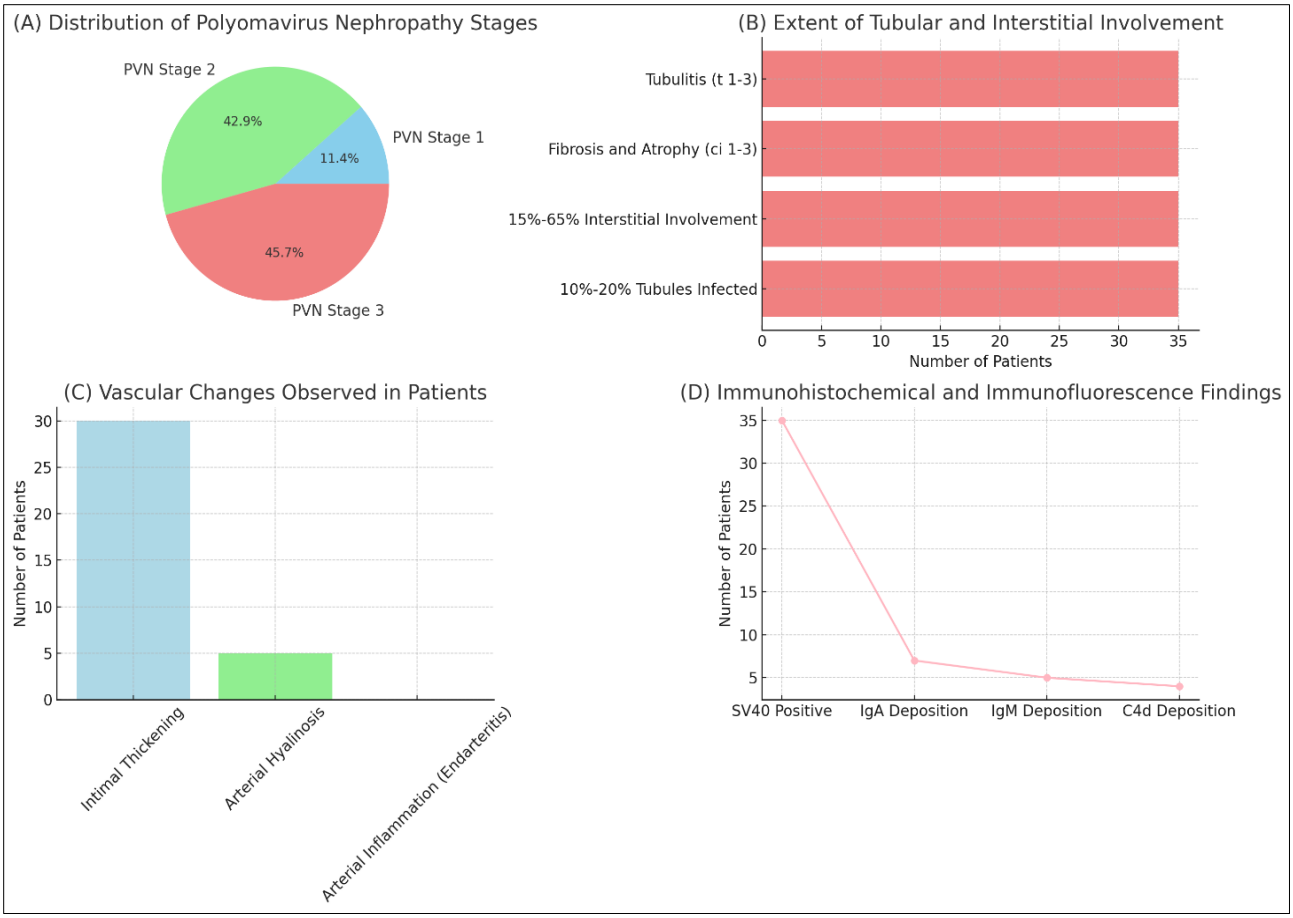

Fig 1: (A) Distribution of polyomavirus nephropathy stages (B) Extent of tubular and interstitial involvement (C) Vascular changes observed in patients (D) Immunohistochemical and immunofluorescence findings

Histopathological examination of allograft biopsies revealed widespread tubular involvement by the BK virus. The BKPyV-infected tubular epithelial cells exhibited characteristic enlarged nuclei with a ground-glass appearance and intra-nuclear viral inclusions. These infected cells were predominantly located in the renal cortex, though more severe cases extended into the medulla. Tubular epithelial cell necrosis was observed across varying degrees, with the proportion of infected tubules ranging from 10% to 20% of the total tubular population (Table 1). In most patients, the degree of interstitial mononuclear cell infiltration was heavy, with infiltrates composed primarily of lymphocytes, plasma cells, and eosinophils. This inflammation extended into both scarred and non-scarred areas of the cortex, contributing to significant tubulitis and tubular injury. The extent of interstitial fibrosis and tubular atrophy (IFTA) varied across the cohort, ranging from 15% to 65% of the cortical area, correlating with the stage of polyomavirus nephropathy.

Table 1: Extent of Tubular and Interstitial Involvement in BK Virus-Associated Nephropathy

Feature	Range Across Patients
BKPyV-Infected Tubular Cells	10%-20% of total tubules
Interstitial Inflammation	15%-65% of cortical tissue
Tubulitis (Banff t score)	1-3
Tubular Necrosis	Moderate to severe
Interstitial Fibrosis (Banff ci score)	1-3
Tubular Atrophy (Banff ct score)	1-3

The severity of tubular and interstitial involvement was closely associated with more advanced stages of polyomavirus nephropathy (PVN), with higher PVN stages showing increased interstitial fibrosis and tubular atrophy.

The glomeruli in most patients were unaffected by direct BK virus infection. The majority of patients exhibited normal glomerular cellularity with patent capillary lumens (Table 2). However, a subset of patients presented with global glomerulosclerosis, which was likely secondary to chronic ischemic injury rather than a direct result of BK virus infection. Ischemic glomeruli were also noted in a few cases, accompanied by peri-glomerular fibrosis. Mesangial matrix expansion was observed in a small number of patients, though without the presence of active glomerular lesions.

Table 2: Glomerular Changes in BK Virus Nephropathy Patients

Glomerular Feature	Number of Patients Affected
Global Glomerulosclerosis	11/35
Ischemic Glomeruli	9/35
Mesangial Hyper cellularity	5/35
Normocellular Glomeruli	Majority

Vascular changes were evident in many of the biopsies, consistent with chronic damage. Intimal thickening was a common feature, particularly in more advanced PVN stages (Table 3). Both small arteries and arterioles exhibited intimal thickening, though arterial inflammation (Endarteritis) was rare, with only a few cases showing mild involvement.

Table 3: Vascular Changes Observed in Biopsies

Vascular Feature	Number of Patients Affected
Intimal Thickening (Banff cv score)	2-3
Arterial Hyalinosis (Banff ah score)	Rare
Arterial Inflammation (Endarteritis)	0

Immunohistochemical staining for the SV40 T-antigen, a marker of BK virus replication, was performed on all biopsies and confirmed the presence of BKPyV in the tubular epithelial cells of all patients (Table 4). Immunofluorescence microscopy was utilized to assess additional underlying nephropathies, including IgA and IgM nephropathies, as well as potential antibody-mediated rejection (AMR). All cases showed positive nuclear staining for SV40 T-antigen in the infected tubular epithelial cells, confirming the diagnosis of BKVAN. A subset of patients showed incidental granular mesangial IgA and IgM deposition in the glomeruli, which were not directly related to the progression of BK nephropathy. Positive C4d staining was noted in the peritubular capillaries (PTC) of a small number of patients, suggesting the possibility of AMR. However, no clear histological features of rejection were observed.

Table 4: Immunohistochemical and Immunofluorescence Findings

Staining Feature	Number of Patients Affected
SV40 T-Antigen Positive	35/35
IgA Deposition (Mesangial)	7/35
IgM Deposition (Mesangial)	5/35
C4d Deposition in PTC	4/35

The Polyomavirus Nephropathy (PVN) staging system was used to categorize the severity of nephropathy in the patients. The majority of patients were classified as having stage 2 or 3 PVN, indicating moderate to severe polyomavirus nephropathy (Table 5). The severity of nephropathy correlated with the extent of interstitial fibrosis and tubular atrophy, as well as the degree of inflammation.

Table 5: Staging of Polyomavirus Nephropathy (PVN) in Study Cohort

PVN Stage	Number of Patients
PVN Stage 1 (Mild)	4/35
PVN Stage 2 (Moderate)	15/35
PVN Stage 3 (Severe)	16/35

The progression of BK virus-associated nephropathy was evident in most patients, with 89% of the cohort exhibiting moderate to severe nephropathy (PVN stages 2 and 3). Patients with more advanced stages of PVN demonstrated greater degrees of interstitial fibrosis and tubular atrophy, leading to more significant graft damage and increased risk of graft failure. To sum up this cohort of 35 kidney transplant recipients, BK virus-associated nephropathy was characterized by extensive tubular and interstitial involvement, confirmed by positive SV40 T-antigen staining in all cases. The majority of patients exhibited moderate to severe nephropathy, with high PVN stages correlating with greater degrees of fibrosis and atrophy. Glomerular involvement was limited, with most glomeruli remaining normocellular. However, vascular changes such as intimal thickening were common, and a minority of patients showed positive C4d staining without clear evidence of antibody-mediated rejection. Overall, the findings indicated a progressive course of disease with significant tubular injury and graft dysfunction.

Discussion

BK virus-associated nephropathy (BKVAN) is a significant cause of morbidity and mortality in kidney transplant recipients, leading to impaired graft function and allograft loss [17]. Despite advances in short-term graft survival due to immunosuppressive therapies, BKVAN remains a critical barrier to long-term outcomes [18]. BK virus, a ubiquitous pathogen, typically causes asymptomatic infection in immuno competent individuals but can progress to chronic renal disease in immunocompromised patients [19, 20]. Diagnosing, managing, and treating BKVAN effectively remains challenging, emphasizing the need for improved therapeutic strategies [6, 21]. This cross-sectional study analyzed histopathological alterations, clinical features, and outcomes in patients with BKVAN. Tubulointerstitial infiltration was a hallmark feature, consistent with the virus's tropism for renal tubular epithelial cells. Morphological changes, including endothelial alterations such as AV shunts with enlarged nuclei containing viral inclusions, were observed. These changes, staining positively for SV40 T-antigen, align with previous studies and underscore the destructive effects of BK virus reactivation in immunosuppressed individuals. The study found that cortical area losses reached up to 65% in advanced stages, correlating with interstitial fibrosis, tubular atrophy, and poor graft prognosis [22]. The high incidence of vascular changes, including intimal thickening in over 30% of patients, highlights a potentially underappreciated factor in BKVAN progression. These findings suggest that vascular involvement may contribute significantly to graft deterioration alongside tubular damage [23-25]. Most patients had moderate to severe nephropathy (PVN stages 2 and 3), consistent with prior studies linking advanced PVN stages to graft dysfunction and loss [26]. The findings emphasize the importance of vigilant post-transplant surveillance, including viral load monitoring and routine biopsies, particularly during the first year post-transplantation when immunosuppression is most intensive. Management in this cohort primarily involved intravenous immunoglobulin (IVIG) and immunosuppressive adjustments. However, the progression of nephropathy in many patients indicates current strategies may be insufficient. The median graft survival among BKVAN patients was 60 months, with 50% experiencing graft loss within five years, underscoring the need for improved antiviral therapies and selective immunosuppression regimens. Limitations of the study include its retrospective design, small sample size, and reliance on biopsy data, which may not fully capture the clinical spectrum of BKVAN. The study underscores the necessity of early diagnosis and tailored immunosuppressive approaches to manage BKVAN. Future research should focus on developing specific antiviral therapies and optimizing immunosuppressive protocols to enhance graft survival and patient outcomes.

Conclusion

In kidney transplant patients with BKVAN, the study found histological characteristics linked to disease development and graft damage. Infection of tubular epithelial cells, interstitial inflammation, and variations in fibrosis and tubular atrophy were indicated. BK virus replication was confirmed histopathologically by SV40 T-antigen staining.

The authors noted that intimal thickening was present in almost one third of patients and in advanced nephropathy patients. Since 62.5% of patients experienced moderate to severe PVN, prompt diagnosis is critical to prevent implant degradation. This study emphasises the need of BKVAN monitoring after transplantation, especially in the first year, to prevent irreparable kidney injury. The risk of reactivating viruses while preventing rejection with immunosuppressive medication emphasises the need for patient-specific therapies. Improved graft diagnosis and therapy would assist address BKVAN's long-term influence on transplant survival. Further research should focus on developing specialised antiviral medicines that do not harm the immune system to avoid allograft rejection and enhance kidney transplantation outcomes.

Conflict of Interest: Not available

Financial Support: Not available

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