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# Incidence of Polyoma Virus Allograft Nephropathy among Iraqi Kidney Transplant Patients

**Jawad Ibrahim Rasheed[1], Ali Abdulmajid Dyab Allawi[2], Safa Auldeen Jameel Alzuhairi[3]**

[1] Department of Internal Medicine, Baghdad Teaching Hospital, Iraq

[2] Department of Internal Medicine, Baghdad College of Medicine, University of Baghdad, Baghdad, Iraq

[3] Alkarama Transplantation Centre, Alkarama Teaching Hospital, Baghdad, Iraq

**Abstract:** ***Background: polyoma virus is a ubiquitous human virus with a peak incidence of primary infection in children 2 to 5 years of age and a seroprevalence rate of more than 60% to 90% among the adult population worldwide. Material and methods: All recruited patients were considered from nephrology and transplant outpatients' clinic medical city (162cases, 97 males& 65 females). The patients with graft dysfunction were recorded on an already prepared data sheet for the type of induction therapy antithymocyte globulin (ATG or baxiliximab ), type of immunosuppressant regimens , renal function test by estimation of Glomerular filtration rate(GFR by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, renal Doppler ultrasound , urine for decoy cell and renal graft biopsy for light microscopy and immunohistochmestry stain. Results: This cohort study enrolled Male patients were 97 while female patients were 65, the age ranges from 20 to 60 years 1 .There was high incidence of PVAN among patients receiving antithymocyte globulin (ATG) (28.6%) as compare to baxiliximab group (3%). There were increasing incidence of BK virus nephropathy among patients taking (Calcineurin inhibitors (CNIs), + Steroid + Mycophenolate mofetil (MMF)), group (1) patients, the difference was statistically significant (p=0.012). There was increasing incidence of decoy cells in the urine of patients with PVAN (100%). Conclusions: There was increasing incidence of PVAN among transplant recipient's patients. Histological feature of PVAN is reliable diagnostic tool and should be consider in every renal transplant patients.***

**Keywords:** Graft Rejection, Kidney Transplantation, Polyomavirus

## 1. Introduction

Polyoma virus is a DNA virus that is a member of the polyomavirus family. It shares >70% homology to the other polyomaviruses such as JC virus [1].

BKVN is currently a major cause of allograft failure in RT recipients [2].After primary infection, polyoma virus preferentially establishes latency within the genitourinary tract and frequently is reactivated in the setting of immunosuppression [3].

In renal transplant recipients, polyoma virus is associated with a range of clinical syndromes including asymptomatic viruria with or without viremia, ureteral stenosis and obstruction, interstitial nephritis, and polyoma virus allograft nephropathy[4]. During the last decade, BK nephropathy has emerged as an important cause of allograft dysfunction after renal transplantation[5].

The highest prevalence of polyoma viruria and viremia occurs at 2 to 3 months and 3 to 6 months, respectively[6]. The risk for development of polyoma viremia increases when urine viral load is greater than 104 copies/ml, whereas polyoma virus allograft nephropathy is unusual in the absence of polyoma viremia [7].

PVAN commonly presents within asymptomatic rise in serum creatinine during the first post transplantation year. However, BK nephropathy may occur as early as the first week (where it is resemble delayed graft function DGF in first week) [8] to as late as 6 years after transplantation[7[.

Diagnosis is made by allograft biopsy, which demonstrates BK viral inclusions in renal tubular cell nuclei and occasionally in glomerular parietal epithelium[9] .There are variable degrees of interstitial mononuclear inflammation, often with plasma cells, degenerative changes in tubules, and focal tubulitis, which may mimic acute rejection[10].

PVAN often is associated with very focal and sharply demarcated areas of tubulointerstitial inflammation, corresponding to foci of viral infection. Immunohistochemistry [11, 12, 13].

In late PVAN, few characteristic intranuclear inclusions are seen, and the histologic changes may be indistinguishable from chronic rejection[14].

A histological classification system for PVAN based on the degree of active inflammation, acute tubular injury, and tubulointerstitial scarring may have prognostic significance[15].

Urine cytology for decoy cells and quantitative determinations of surrogate markers for the diagnosis of PVAN[16,17,18].

The detected virus could originate anywhere along the urinary tract[19].Therefore, transplant kidney biopsy remains the gold standard for diagnosing PVAN[20] , However, in renal biopsy specimens it is often difficult to differentiate between the tissue effects of viral pathology and changes caused by acute cellular rejection[21].

The lack of specific targeted therapies has prompted a pre-emptive active surveillance strategy with routine screening intervals post transplantation for viral replication using polymerase chain reaction assays [22].

Saturation of the IL-2R α subunit persists for up to 120 days after daclizumab induction and 25 to 35 days after treatment with basiliximab. No major side effects have been associated with anti-CD25 therapy [23].

ATG is a potent immunosuppressive,The lack of specificity coupled with marked immunosuppression increases [24].

## 2. Material and Methods

The study was conducted in the nephrology and renal transplant center, medical city. The period of data collection started from May 2013 till the end of August 2014.

This cohort study enrolled 162 transplant recipient patients within the first year post renal transplantation presented to the center with renal dysfunction. All recruited patients had their ages, gender and case histories recorded on an already prepared data sheet.

The patients were recorded on an already prepared data sheet for the type of induction therapy (ATG or baxiliximab ), type of immunosuppressant regimens, renal function test by estimation of GFR by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, renal doppler ultrasound, urine for decoy cell and renal graft biopsy for light microscopy and immunohistochemistry stain.after follow up the patients during one year we categorize the patients in to two groups

Group one; all patients with graft dysfunction with evidence of PVAN by histopathological examination.

Group two; all patients with graft dysfunction without evidence PVAN by histopathological examination.

1) Inclusion criteria for patients; all patients with graft dysfunction and candidate for graft biopsy.
2) The CKD-EPI equation is more accurate than the Modification of Diet in Renal Disease (MDRD) study equation across a wide range of characteristics, including age, sex, race, body mass index, and presence or absence of diabetes or history of organ transplantation. With theCKD-EPI equation, it is now possible to report estimated GFRacross the entire range of values without substantial bias [6].
3) Drugs of patients: were recorded and defined as following:

Induction therapy: Basiliximab versus antithymocyte globulin (ATG)
Regimens that use in patients and control cases in the transplant center:

Group 1
Tacrolimus 0,1mg/kg / mycophenolate mofetil 1-2gm/day / prednisone 1-.0.25mg /kg .

Cyclosporine 4mg/kg/ mycophenolate mofetil 1-2gm/day/ prednisone1-0,25mg/kg.

Group 2
mTOR inhibitors 0.1mg/kg / prednisone 1-0,25mg/kg/ mycophenolate mofetil 1-2gm/day.

Group 3
Calcineurin inhibitors/ prednisone/azathioprine 1-2mg/kg .

4) All patients were sent for decoy cells.It can be identified by urine cytology by using specific stain which is papanicolaou stain [25, 26].

The papanicolaou stain includes three steps;1 haemtoxyline for nuclear staining;2 orange stain for keratin and ;3 eosin for cytoplasm[26].

Graft Biopsy:
The aim is to identify acute rejection, and therefore the diagnosis can be made on a formalin-fixed sample alone for light microscopy. If vascular rejection is suspected, a snap-frozen sample for C4d immunostaining should also be obtained [6]. The characteristic intranuclearpolyomavirus inclusions tubulointerstitial nephritis is suggestive of BK nephropathy [27].

Protocol for pathological examination:

Histological samples obtained through kidney biopsy Were analyzed by optical microscopy (OM), immunofluorescence. The samples (only one biopsy fragment per patient)have been harvested with GBL 16 G guillotine needles, rapidly placed in saline, and divided as follows: 2 mmof tissue ends were separatas with a sharp razor blade(IF) and placed in 4% buffered glutaraldehyde, while the Middle part was placed in a cryostat for frozen sections .

The histologcal stages of polyomavirus nephropathy

Stage A (Early)
Viral activation in cortex and /or medulla with intranuclear inclusion and/or positive immunohistochemistry or in situ hybridization.

Minimal tubular epithelial cell lysis.

No denudation of tubular basement membrane(TBM).

Stage B (Florid)
Marked viral activation in cortex and/or medulla .
Marked virus induced tubular epithelial cell necrosis/lysis and associated denudation of TBM.
Interstitial inflammation (mild to marked)
Interstitial fibrosis and tubular atrophy (minimal to moderate≤50%

Stage C (late)
Viral activation in cortex and /or medulla
Interstitial fibrosis and tubular atrophy>50%
Tubular epithelial cell necrosis/lysis and TBM denudation
Interstitial inflammation (mild to marked)

Statistics:
Analysis of data was carried out using the available statistical package of SPSS-20 (Statistical Packages for Social Sciences- version 20 Statistics) for determination of statistical significance among different variables. A descriptive statistics like mean together with analytic statistics, have been done when appropriate. A p-value of less than 0.05 was considered as significant and calculated by a method of Pearson Chi-square equation.

## 3. Results

This cohort study enrolled 162 kidney transplant recipients with renal dysfunction within the first year post transplantation. Male patients were 97 while female patients were 65, the age ranges from 20 to 60 years, with male to female ratio of 1.4:1. The incidence of BK virus nephropathy was 7% of total transplant patients in this study.

**Table 1:** Age and gender distribution among patients with BK virus nephropathy groups and patients without BK virus nephropathy groups

| variables | Patients with BK virus nephropathy | | Patients without BK virus nephropathy | | P-value |
|---|---|---|---|---|---|
| | No. | Percentage | No. | Percentage | |
| Male | 7 | 7.2% | 90 | 92.8% | 0.9 |
| Female | 5 | 7.7% | 60 | 92.3% | |
| Age < 55 years | 4 | 7.4% | 50 | 92.6% | 1 |
| Age > 55 years | 8 | 7.4% | 100 | 92.6% | |

As can be seen in table 1, there were no statistically significant difference between a males and females patients with BK virus nephropathy as compared to patients without BK virus nephropathy. At the same time there was no statistically significant difference between transplanted patients older than 55 years as compared with those younger than 55 years, (p=0.9).

**Table 2:** Induction therapy for renal transplant patients with BK virus nephropathy group and patients without BK virus nephropathy group

| Induction therapy | Patients with BK virus nephropathy | | Patients without BK virus nephropathy | | total | | P-value |
|---|---|---|---|---|---|---|---|
| | No. | Percentage | No. | Percentage | No. | Percentage | |
| Baxiliximab | 4 | 3% | 130 | 97% | 134 | 100% | 0.0001 |
| ATG | 8 | 28.60% | 20 | 71.40% | 28 | 100% | |
| total | 12 | 7.40% | 150 | 92.60% | 162 | 100% | |

Table 2 shows that there were a high incidence of BK virus nephropathy among patients receiving ATG as compared to baxiliximab group, the difference was statistically significant (p=0.0001).

Table 3: shows that there were increasing incidence of BK virus nephropathy among patients t aking (CNI+Steroid + MMF) group (1) patients, the difference was statistically significant (p=0.012).

**Table 3:** Distribution of immunosuppressant drugs in studied patients with BK virus nephropathy groups and Patients without BK virus nephropathy groups

| immunosuppressant drugs | Patients with BK virus nephropathy | | Patients without BK virus nephropathy | | Total | | P-value |
|---|---|---|---|---|---|---|---|
| | No. | Percentage | No. | Percentage | No. | Percentage | |
| Group 1 (CNI+Steroid + MMF) | 8 | 5.80% | 131 | 94.20% | 139 | 100% | 0.012 |
| Group 2 (mTOR+Steroid+ MMF) | 2 | 33.30% | 4 | 66.70% | 6 | 100% | |
| Group 3 (CNI+Steroid + AZA) | 2 | 11.80% | 15 | 88.20% | 17 | 100% | |
| total | 12 | 7.40% | 150 | 92.60% | 162 | 100% | |

**Table 4:** Urinary Decoy cells distribution among Patients with BK virus nephropathygroupand Patients without BK virus nephropathy group

| Decoy cells | Patients with BK virus nephropathy | | Patients without BK virus nephropathy | | total | | P-value |
|---|---|---|---|---|---|---|---|
| | No. | Percentage | No. | Percentage | No. | Percentage | |
| NO | 8 | 5.10% | 149 | 94.90% | 157 | 100% | 0.0001 |
| YES | 5 | 100% | 0 | 0% | 5 | 100% | |
| total | 12 | 7.40% | 150 | 92.60% | 162 | 100% | |

Table 4: shows that there were increasing incidence of decoy cells in the urine of patients with BK virus nephropathy and the difference was statistically significant.

**Table 5:** Histological features distribution between patients with BK virus nephropathy group and patients without BK virus nephropathy group

| Variables | Patients with BK virus nephropathy | | P-value |
|---|---|---|---|
| | No. | Percentage | |
| Viral inclusion | 12 | 100% | 0.001 |
| Tubulitis | 10 | 10.4% | 0.2 |
| IFTA | 7 | 10% | 0.3 |

Table 5: shows that the histological features of BK virus nephropathy as viral inclusions was increasing incidence of among Patients with BK virus nephropathy as compared with cases with tubulitis and IFTA the difference was statistically significant (p=0.001) .

There were no statistically significant difference among transplanted patients with tubulitis and IFTA cases, (p=0.2 0.3 respectively).

## 4. Discussion

The incidence is coincide with Li RM, Mannon RB, Kleiner D et al [28]. And coincide with Al-Obaidi et al , who found in his study that the incidence of biopsy proven PVAN polyomavirus Allograft nephropathywas5,1% [29].

There was no statistically significant difference among transplanted patients between males and females.Also there was no statistically significant difference among transplanted patients with older than 55 years as compared with younger than 55 years, (p=0.9).These results coincide with Fernando et al [30], Which show no statistically significant differences between the experi¬mental and control groups for the sex ratio (p = 0.523), mean age (p = 0.648), age distribution.

There were high incidence of polyomavirus virus nephropathy among patients receiving ATG as compare to baxiliximab group[30] , the difference was statistically significant (p=0.0001).These results coincide with Sonia C.et al [31]and Brennan D. et al and Binet I et al [32].ATG is a potent immunosuppressive, act on T- and B-lymphocyte which lead to induces a rapid lymphocytopeniaby several mechanisms including: complement dependent cytolysis,cell-dependent phagocytosis, and apoptosis.This marked immunosuppression increases the risk of polyoma virus infection[33,34,35,36,37].

That there was increasing incidence of polyoma virus nephropathy among patients taking (CNI + Steroid + MMF) group(1) patients , the difference was statistically significant (p=0.012).These results coincide with HardingerKetal[38] .It is hypothesized that tacrolimus-MMF create a permissive immunosuppressive environment for polyoma virus replication. Also, coincide with Mengel et al who found that use of tacrolimus in combination with MMF increased the risk of PVAN[39].

There were increasing incidence of decoy cells in the urine of patients with PVANand the difference was statistically significant. This result coincide with Zeljko V et al [40].This could be explained by the polyoma virus can proliferate within the nuclei of renal tubular and urothelial cells producing viral cytopathic effect manifested with nuclear enlargement and basophilic intranuclearinclusions that lead to formation of Decoy cells in urine[41,42].

The histological features of polyoma virus nephropathy in form of viral inclusions were relatively high in patients with polyoma virus nephropathy as compared with tubulitis and IFTA, the difference was statistically significant ( p=0.001 ,0.01) respectively .Biopsies showing lesser degrees of renal scarring at the time of diagnosis were associated with, more likely, resolution of the infection, in response to decrease of immunosuppression .Initial immunosuppression reduction consisted of a decrease in the target level of tacrolimus from11-15 mg/ml. to 5-7mg/ml.and cyclosporine A from 150 -200mg/ml to 75-100mg/ml. dose of MMFwas reduced to1gm/day, plus low dose prednisolone , in addition ciprofloxacin given to some patients More advanced tubulointerstitial atrophy, active inflammation and higher creatinine level at diagnosis correlated with worse graft outcome Due to the focal nature of PVAN, correlation of biopsy results with viruria and viremia are required for diagnosis. the type of inflammation in PVAN was almost mononuclear, consisting of plasma cell and lymphocytes.

There was no statistically significant difference among transplanted patients with tubulitis as compared with IFTAcases, (p=0.2).This result coincides withDaniel L. Bohl and Daniel C[43], also coincides with Drachenberg CB, et al[44]the latter identified three patterns of histological injury: Pattern A with viral cytopathic changes and almost normal parenchyma, Pattern B with viral cytopathic changes and significant inflammation and tubulitis with varying degrees of interstitial fibrosis and tubular atrophy, and Pattern C with diffuse fibrosis and tubular atrophy associated with some inflammation and very little viral cytopathic changes.Pattern B was divided into B1, B2 & B3 based on the degree of interstitial fibrosis and tubular atrophy.In their evaluation, they noted that Pattern A was associated with 15% risk of graft loss, PatternB was associated with 25-75% risk of graft loss and Pattern C was associated with >80% risk of graft loss [45].

## 5. Conclusions

The incidence of BK virus nephropathy is insignificant. The Histological feature of BK virus nephropathy is a reliable diagnostic tool and should be considered in every renal transplant patients.We should avoid routine use ATG drugs in low-risk patients.Decoy cells are a marker of BK virus nephropathy.Patients using drugs regimen including Calcineurin inhibitors prednisone, mycophenolate mofetil is high risk for developing BK virus nephropathy. The pathological changes can be patchy in nature and a renal allograft biopsy can miss the diagnosis of PVAN.Equalize the length of your columns on the last page. If you are using *Word*, proceed as follows: Insert/Break/Continuous.

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## 8. Conflict of Interest

None declared

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