Evaluation of Renal Biopsies for BK Virus Nephropathy in Non-Renal Transplant Immunosuppressed Patients

Böbrek Nakli Hastaları Dışındaki İmmünsüpresif Hastalarda BK Virüs Nefropatisinin Patolojik Değerlendirilmesi

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ABSTRACT

OBJECTIVE: Although BK virus nephropathy (BKVN) has mostly been reported to occur in transplanted kidneys, there has been a gradual increase in cases of BKVN in the native kidney. This study was directed towards investigating the incidence of BKVN in patients undergoing renal biopsy due to acute kidney injury (AKI) who were also immunosuppressed due to a condition other than organ transplantation.

MATERIAL and METHODS: Out of the 1223 patients undergoing renal biopsy for various conditions between January 2001 and January 2013, 52 patients who underwent a biopsy for AKI and were immunosuppressed at the time of the biopsy were included into the study. After renal biopsies of all patients were reevaluated, all biopsy specimens were exposed to immunohistochemical staining for SV40 antibody.

RESULTS: Of the 52 patients, 29 had primary glomerulonephritis, 18 had secondary glomerulonephritis and 5 had a malignancy. All patients except one case of acute lymphoblastic leukemia and one case of non-Hodgkin lymphoma were immunosuppressed due to immunosuppressive therapy. None of the patients had any signs of BKVN on immunohistochemical staining of renal biopsy specimens.

CONCLUSION: Failure to detect BKVN in this study may be because BKV causes gradual impairment of renal functions and the sample did not include patients frequently observed to have BKVN in the native kidney.

KEY WORDS: Acute kidney injury, BK virus nephropathy, Immunosuppression, Renal biopsy, Renal transplantation, SV40 antibody

ÖZ

AMAÇ: BK virüs nefropatisi (BKVN) çoğunluğu böbrek nakli olgularında tanımlansa da, öz böbreklerde de giderek artan oranda BKVN olguları tanımlanmaktadır. Çalışmada, akut böbrek yetmezliği nedeniyle böbrek biyopsisi yapılan organ nakli dışında bir nedene bağlı immünsüpresif hastaların renal biyopsi örneklerinde BKVN sıklığını araştırmayı amaçladık.

GEREÇ ve YÖNTEMLER: Ocak 2001- Ocak 2013 tarihleri arasında çeşitli nedenlerle böbrek biyopsisi yapılmış 1223 hastadan akut böbrek hasarı nedeniyle biyopsi yapılmış ve biyopsi esnasında immünsüpresif olup çalışmaya uygun olan 52 hasta çalışmaya dahil edildi. Çalışmaya alınan hastaların böbrek biyopsileri tekrar değerlendirilerek ışık mikroskopisinde BKV'ye ait olabilecek değişiklikler arandıktan sonra tüm biyopsi materyallerine SV40 immünhistokimyasal antikor boyaması yapıldı.

BULGULAR: Olguların tanısal dağılımı şu şekildeydi; 29 hasta primer glomerülonefrit (GN), 18 hasta sekonder GN ve 5 hasta malignite. Hastaların ikisi (ALL ve NHL olguları) hariç hepsi immünsüpresif tedavi nedeniyle immünsüpresiftiler. Böbrek biyopsilerinde yapılan immün histokimyasal boyamada 52 olgunun hiçbirinde BKVN'ye ait bulguya rastlanmadı ve tüm olgularda SV40 negatif saptandı.

SONUÇ: Sonuç olarak çalışmamızda, akut böbrek hasarı nedeniyle böbrek biyopsisi yapılmış olgularda BKVN'yi saptayamamış olmamız, BKVN'nin böbrek fonksiyonlarında yavaş seyirli bir bozulmaya sebep olmasından veya bu çalışmanın BKV'nin öz böbrek nefropatisinin daha çok izlendiği hastaları içermemesinden kaynaklanmış olabilir.

ANAHTAR SÖZCÜKLER: Akut böbrek yetmezliği, BK virüs nefropatisi, İmmünsüpresyon, Renal biyopsi, Böbrek nakli, SV40 antikor

Received : 01.11.2015
Accepted : 21.11.2015

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INTRODUCTION

BK virus (BKV) was first isolated from a renal transplant recipient with ureteral stenosis in 1971 and shown to cause BK virus nephropathy (BKVN) in renal transplant recipients in 1978 (1, 2). Primary BKV infection usually appears in childhood. The first infection is asymptomatic or characterized with a mild respiratory disease. After the first infection, the virus becomes latent in the uroepithelium (transepithelium, renal tubular epithelium and parietal epithelium of Bowman's capsule), lymphoid tissue and many different tissues (cells of salivary glands, leukocytes in peripheral blood, squamous cells of the cervix and glandular epithelial cells of the prostate); 70-90% of healthy individuals in the general population have antibodies against BKV (3-8).

BKV goes through the stages of viruria and viremia during its latency in the uroepithelial tissue due to the immunosuppression after renal transplantation and then leads to BKVN, a kind of interstitial nephritis. Of all patients undergoing renal transplantation, 30-50% develop viruria, 10-20% develop viremia and 5-7% develop BKVN (9). BKVN appears within one to two years of renal transplantation in 95% of the cases. It causes graft loss in about half of the cases developing nephropathy. Renal dysfunction develops slowly and permanent renal damage has already developed when the creatinine levels are increased. However, Comai et al. have reported a case of BKVN presenting with acute kidney injury after renal transplantation (10).

Although BKVN has mostly been reported to occur in transplanted kidneys, there has been a gradual increase in cases of BKVN in the native kidney. In addition, there have been cases of BKVN in the native kidney after hematological malignancies like acute lymphocytic leukemia and chronic lymphocytic leukemia after transplantation of bone marrow and solid organs other than kidneys. Reactivation of BKV in these immunosuppressed patients is similar to that observed after renal transplantation. Sharma et al. have reported eight cases of BKVN in the native kidney presenting with acute renal failure (11).

Considering that BKV is activated by immunosuppression and that BKVN in the native kidney usually presents with acute kidney injury in all cases except for organ transplant recipients, this study was directed towards investigating the incidence of BKVN in patients undergoing renal biopsy due to acute renal failure and having immunosuppression due to a condition other than organ transplantation.

MATERIAL and METHODS

Biopsies of the native kidneys performed in Nephrology clinics of Dışkapı Yıldırım Beyazıt Education and Research Hospital and Hacettepe University Hospital between 1 January 2001 and 1 January 2013 (1223 patients) were retrospectively evaluated. Patients not receiving immunosuppressive therapy and/or not under immunosuppression and those about whom necessary data were unavailable in the hospital records were excluded. Out of all patients receiving immunosuppressive therapy and/or being immunosuppressed due a systemic disease (any disease impairing functions of the immune system), those undergoing renal biopsy due to acute renal failure (52 patients) were included in the study.

Immunosuppressants received by the patients were prednisolone, azathioprine, methotrexate, cyclosporine, cyclophosphamide, rituximab and leflunomide for primary and secondary glomerulonephritis and navelbine, paclitaxel, imatinib, cisplatin, cyclophosphamide, adriamycin and 5-fluorouracil for malignancy. The patients in the present study did not have a history of mechanical injury triggering BKVN such as renal ischemia and catheterization except for immunosuppression. Data about the demographic features, clinical histories, immunosuppressive therapies administered and causes of immunosuppression were obtained from forms filled in to request pathological examinations and from hospital records.

After renal biopsies of all the patients included in the study were reevaluated, evidence for BKVN was searched under light microscopy and all biopsy specimens were exposed to immunohistochemical staining for SV40 antibody.

After paraffin-embedded blocks of the renal specimens prepared previously were kept in the incubator and deparaffinized, they were treated with monoclonal sv40 antibody (cell marque, California, USA) to polyoma virus large-T antigen and examined under the microscope.

We were able to use this method in old biopsy specimens since paraffin blocks of renal specimens prepared previously were available at the time of the study. Immunohistochemical staining can be performed on preserved paraffin blocks of renal specimens. In the present study, paraffin blocks of renal specimens obtained previously were prepared for treatment with SV40 antibodies.

Statistical Analysis

Statistical analysis was conducted using the SPSS software (version 18, SPSS; Chicago, IL, USA). Normality of distribution was tested by using the Kolmogorov-Smirnov test and histograms for continuous variables. Normally distributed variables were expressed as mean ± standard deviations (SD) and the others were presented as median and interquartile ranges (IQR; the range of values lying between the 25th and 75th centiles).

RESULTS

A total of 1223 biopsies of native kidneys were found to have been performed between 1 January 2001 and 1 January 2013. Sixty patients undergoing biopsy due to acute renal failure and suffering from immunosuppression were included in the study. Eight patients were excluded due to missing data and statistical analyses of data were performed in the remaining 52 patients.

Of the 52 patients, 28 were male and 24 were female. The mean age of the males and females was 44.4±16.4 and 39.8±13.5 years respectively. Demographic features of the patients are presented in Table I. Table II shows the disorders causing immunosuppression in the patients. Primary glomerulonephritis was the most frequent disease (29/52). Only two patients had immunosuppression due to malignancy and the remaining 50 patients had immunosuppression due to immunosuppressive therapy.

Immunosuppressants received by the patients were prednisolone, azathioprine, methotrexate, cyclosporine, cyclophosphamide, rituximab and leflunomide for primary and second-

Table I: Demographic features of the patients.

Underlying diseases	n	Gender (male/female)	Age (years)
Primary glomerulonephritis	**29**		
IgA GN	7	4 / 3	42.5 (±12.6)
MGN	6	3 / 3	49 (±13.1)
FSGS	6	2 / 4	43.6 (±17.7)
MPGN	4	3/ 1	34 (±9.4)
MCD	3	2 / 4	32.6 (±10.5)
RPGN	2	1 / 1	53.5 (±10.6)
Anti-GBM antibody disease	1	1 / -	25
Secondary glomerulonephritis	**18**		
SLE	12	3 / 9	32.5 (±12)
Amyloidosis	6	2 / 4	46.3 (±8.8)
Malignancy	**5**	3 / 2	58.8 (±18.3)

MGN: Membranous glomerulonephritis, **FSGS:** Focal segmental glomerulosclerosis, **MCD:** Minimal change disease, **IgA GN:** Immunoglobulin a glomerulonephritis, **RPGN:** Rapidly progressive glomerulonephritis, **GBM:** Glomerular basement membrane, **SLE:** Systemic lupus erythematosus, **ALL:** Acute lymphoblastic leukaemia, **NHL:** NonHodgkin lymphoma.

Table II: Underlying diseases, immunosuppression and renal functions of the patients.

Underlying diseases	n	Cause of immunosuppression	Duration of immunosuppression (years)	Basal cr (mg/dL)	cr at the time of biopsy (mg/dL)
Primary Glomerulonephritis	**29**				
MGN	6	IS therapy	2.3 (±1.51)	1.6 (±0.73)	2.2 (±0.81)
FSGS	6	IS therapy	1.5 (±1.16)	1.08 (±0.47)	3.0 (±2.47)
MCD	3	IS therapy	2.16 (±1.44)	0.9 (±0.26)	2.1 (±0.73)
IgA GN	7	IS therapy	1.64 (±1.72)	1.45 (±0.39)	2.74 (±0.66)
RPGN	2	IS therapy	0.75 (±0.35)	1.15 (±0.35)	9.25 (±0.35)
MPGN	4	IS therapy	1.25 (±0.5)	1.12 (±0,2)	2.15 (±0.68)
Anti-GBM antibody disease	1	IS therapy	0.5	1.6	2
Secondary Glomerulonephritis	**18**				
SLE	12	IS therapy	4.7 (±5.05)	1.04 (±0,59)	4,05 (±3.4)
Amyloidosis	6	IS therapy	1.25 (±0.61)	1.28 (±0.64)	2.47 (±1.12)
Malignancy	**5**				
ALL	1	IS therapy and malignancy			
NHL	1	IS therapy and malignancy	1 (±0.61)	0.9 (±0.31)	3.51 (±1.91)
Breast cancer	1	IS therapy			
Tongue cancer	1	IS therapy			
Lung cancer	1	IS therapy			

IS: Immunosuppressive, **cr:** Creatinine, **MGN:** Membranous glomerulonephritis, **FSGS:** Focal segmental glomerulosclerosis, **MCD:** Minimal change disease, **IgA GN:** Immunoglobulin a glomerulonephritis, **RPGN:** Rapidly progressive glomerulonephritis, **GBM:** Glomerular basement membrane, **SLE:** Systemic lupus erythematosus, **ALL:** Acute lymphoblastic leukaemia, **NHL:** NonHodgkin lymphoma.

ary glomerulonephritis and navelbine, paclitaxel, imatinib, cisplatin, cyclophosphamide, adriamycin and 5-fluorouracil for malignancy. The most frequently used immunosuppressant was prednisolone (38/52).

Although all the patients had proteinuria (200-13100 mg/day), 21 patients had proteinuria severe enough to cause nephrotoxicity. The mean basal creatinine level one month before biopsy was 1.2±0.5 mg/dL and the mean creatinine level at the time of biopsy was 3.2±2.6 mg/dL. The median duration of immunosuppression was 2.25 years (6 months - 13 years). Thirteen patients had immunosuppression lasting for less than a year. Two patients with malignancy were on chemotherapy at the time of renal biopsy.

None of the 52 patients had any signs of BKVN on immunohistochemical staining of renal biopsy specimens and none had SV40 antibody.

DISCUSSION

In this study, none of the patients with immunosuppression due to conditions other than renal transplantation were found to have signs of BKVN on renal biopsy due to acute renal failure.

Risk factors for BKVN after renal transplantation can be donor-related including BK seropositivity, HLA mismatch and HLAC7; recipient-related including the male gender, advanced age and the presence of diabetes; and transplant-related including ATG use, tacrolimus and/or MMF-based immunosuppressive therapy, prolonged ischemia, delayed graft function, previous rejection episodes and ureteral stents (12). Although most of the patients with BKVN are renal transplant recipients, it has been reported in the literature that BKVN develops in the native kidney. Risk factors for development of BKVN in the native kidney are not clear. However, all cases of BKVN in the native kidney have one thing in common, i.e. immunosuppression. BKVN of the native kidney has been reported to occur after transplantation of solid organs such as the liver, pancreas, heart and lungs and after bone marrow transplantation (11). Ducharme et al. (13) reported that prolonged time after heart transplantation, low glomerulofiltration rates, prior EBV infection and use of sirolimus were risk factors of BK in heart transplant recipients. Risk factors of renal BKVN are not clear yet and further studies are needed to reveal these factors.

A typical course of BKVN after renal transplantation starts as BKV is activated in the tubular cells. As a result of its cytopathic effect on the tubules, BKV, defined as decoy cells, and infected tubular cells are released into the urine. About four weeks later, viremia develops and about eight weeks after persistent viremia, kidney injury starts to appear. Until kidney injury develops, the infection is asymptomatic. It usually causes a slow, gradual impairment of renal functions, which results in an increase in creatinine levels. However, Comai et al. described a case of BKVN presenting with acute renal failure earlier than expected after renal transplantation, which caused confusion in terms of acute rejection (10). In addition, there has been an increase in cases of BKVN in the native kidney presenting with acute renal failure. It has been shown in the literature that most of the patients with BKVN in the native kidney developing acute renal failure were recipients of transplants other than the kidney (11, 14, 15). For this reason, this study was directed towards investigating whether BKV reactivated and caused BKVN in a group of immunosuppressed patients.

A close follow-up of BKV load and renal functions in renal transplant recipients allows nephrologists to perform necessary interventions to prevent viremia from turning into nephropathy. Presence of few cases of BKVN presenting with an acute increase in creatinine levels can be explained by the natural course of BKV infection.

In a report of eight cases of BKVN in the native kidney by Sharma et al. (11), the median duration of immunosuppression was 3.15 years (1-10 years). Six cases had a hematological malignancy, three cases were on chemotherapy due to bone marrow transplantation, three cases were on chemotherapy due to hematological malignancy, one case was on immunosuppressive therapy due to cystic fibrosis and one case was on immunosuppressive therapy due to diabetes and tuberculosis. Most of the patients received two or more immunosuppressive agents (IVIG, MMF, tacrolimus, steroids and chemotherapeutic agents). In the present study, the mean duration of immunosuppression was shorter (2.2 years) and 29 patients received lower doses of immunosuppressive therapy (13 patients received immunotherapy for less than one year and 16 patients used a single immunosuppressive agent). The reason for the failure to detect BKVN in the present study may be that the patients did not receive immunotherapeutic agents in sufficiently high doses to cause BKV reactivation.

Patient series with immunosuppression due to a condition other than organ transplantations in which BKV reactivation has been evaluated have SLE (16-18), ANCA-related vasculitis (19) or multiple sclerosis (20). In a comparative study by Sundsfjord et al. (16) on 44 patients with SLE and 88 healthy controls, the rate of BK viruria was significantly higher in the patients with SLE (16% vs. 0%). In the current study, out of 20 patients with viruria, 16 had persistent or recurrent viruria lasting for one year, but there was no relation between viruria and immunosuppressive therapy. Colla et al (17) compared viruria and viremia between 40 patients with SLE and 20 healthy controls and found that 32% of the patients and 17,2% of the controls had viruria and that 15% of the patients and 1.8% of the controls had viremia. They reported no significant difference in BKV reactivation between the groups and noted that the patients with BKV viruria and viremia had higher levels of urine protein and creatinine and that duration of SLE history was shorter. Geetha et al. (19) compared BKV viremia between 37 cases of vasculitis not undergoing renal transplantation and 16 patients undergoing renal transplantation due to vasculitis. The patients

undergoing renal transplantation (Group A) were evaluated after the transplantation and the patients not undergoing renal transplantation (Group B) were evaluated during the first 36 months of their disease. In most of the patients in Group A, evaluations were made during administration of maintenance therapy including two immunosuppressive agents. None of the patients in Group A were found to have BKV viremia, but five patients in Group B were found to have BKV viremia. Geetha et al. evaluated BKV viremia in a single serum specimen in each patient and did not evaluate it regularly, which was considered as a limitation in terms of evaluation of BKV reactivation. Absence of BKV reactivation in the patient groups receiving high doses of immunosuppressive therapy suggests that BKV reactivation in renal transplant recipients occurs through different mechanisms.

Although similar protocols of maintenance immunosuppressive therapy are used, absence of BKV replication after transplantation of other solid organs suggests that factors causing renal injury such as ischemia and reperfusion injury during renal transplantation play an important role in BKV replication. Although most of the patients in the present study were on immunosuppressive therapy, considered as a risk factor for BKV replication, they did not have many factors effective in BKV replication in renal transplant recipients. Immunosuppressive therapy alone is not sufficient to lead to BKV replication.

This retrospective study was directed towards describing pathology due to BK virus through the immunohistochemical method. Preservation of paraffin blocks of renal specimens obtained from the patients made it possible to use this method. Immunohistochemical staining with SV40 in paraffin blocks prepared before have been shown to be efficient in several studies reported so far (21, 22).

The present study has two limitations. First, it is a retrospective study. The second limitation of the study is the inability to reveal the degree of BKV reactivation and to what extent it was different from healthy individuals depending on the inability to evaluate viruria and viremia in the patients not developing BKVN.

In conclusion, the reason for the failure to detect BKVN in the patients undergoing renal biopsy due to acute kidney injury may be that BKVN causes a slow impairment of renal functions and that the sample did not include patients who were mostly observed to have BKVN in the native kidney, i.e. those having transplantations of solid organs other than the kidneys, transplantations of the bone marrow and hematological malignancies.

Prospective studies in which viruria and viremia likely to be due to BKV are followed regularly are needed to reveal BKV reactivation in immunosuppressed patients and a difference in the presence of BKV between immunosuppressed patients and healthy individuals.

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