JOHN CUNNINGHAM VIRUS-ASSOCIATED NEPHROPATHY IN A KIDNEY TRANSPLANT RECIPIENT

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John Cunningham (JC) virus is a well-known cause of progressive multifocal encephalopathy. Only a few cases of polyomavirus-associated nephropathy due to JC virus have been reported so far. We report one such case in a kidney transplant recipient who presented with proteinuria and increased serum creatinine. Allograft biopsy revealed polyoma virus-associated nephropathy. Real-time polymerase chain reaction revealed negative result for BK and JC virus in the blood, negative for BK virus and positive for JC virus in the urine, and finally, when performed on the biopsy sample it detected more than 10^6 copies of JC virus DNA, which allowed us to establish JC virus-associated nephropathy as a definitive diagnosis. The patient was treated with intravenous immunoglobulins and reduction of immunosuppression. Serum creatinine returned to initial levels with decrease of proteinuria. This case documents that JC virus may cause significant changes in renal allograft and should be included in the differential diagnosis of allograft dysfunction.

Key words: immunosuppression, kidney transplantation, JC virus, JC virus nephropathy

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INTRODUCTION

While BK virus presents a well-known cause of renal allograft dysfunction, far fewer cases describing John Cunningham (JC) virus as a culprit have been reported. Both of the viruses, along with several others described, belong to the same group of species-specific polyomaviruses (1). These viruses are ubiquitous with seroprevalence in humans ranging from 65% to 90% for BK virus and 44%-92% for JC virus (2). JC virus primary infection usually occurs during the first years of life and is most commonly asymptomatic. After primary viremia, JC virus latently infects kidney epithelial cells and may be found in the urine (3,4). Some authors suggest that JC virus may develop persistent infection in kidneys and lymphoid organs (5). The virus is also neurotropic and may cause progressive multifocal leukoencephalopathy (5,6). While BK virus-associated nephropathy (BKVAN) is relatively common, manifested in up to 10% of renal transplant recipients (1), JC virus-associated nephropathy (JCVAN) is seen far less often; a review from 2016 (7) has reported only 20 cases described in the English-language literature with the first one in 2003 (8).

CASE REPORT

A 68-year-old male with a history of alcoholism and essential hypertension was diagnosed with focal segmental glomerulosclerosis and IgG kappa monoclonal gammopathy of unknown significance in 2008. He was started on hemodialysis in 2015 and received a kidney transplant from a deceased donor in July 2017. He received basiliximab for induction and tacrolimus, mycophenolate mofetil and steroids for maintenance. The post-transplantation period was complicated with urinary tract infections and spontaneous vertebral fractures, which were treated with denosumab. Addition-

ally, he had leukopenia, which demanded decreased doses of mycophenolate. In August 2018, serum creatinine increased from the baseline value of 150 μmol/L with proteinuria of 0.6 g/day to creatinine 209 μmol/L and proteinuria of 4 g/day, so renal biopsy was performed. Donor specific antibodies were negative. The patient's blood and urine samples were analyzed employing the real-time polymerase chain reaction (RT-PCR) by the LightMix Kit for detection of Polyomaviruses. The blood samples were negative for both BK virus and JC virus DNA, but in urine >10^6copies of JC virus DNA were detected with negative BK virus DNA.

The biopsy specimen showed pathological findings that were described as a Banff score class III polyomavirus-associated nephropathy (pvl1, ci3) along with findings described as chronic parenchymal changes, which may have been the consequences of previous bacterial infections. Also, epithelial polymorphy with nuclear hyperchromasia and intranuclear viral inclusions was visible in some tubules, which also displayed positive immunohistochemical reaction to SV40 antigen (Figures 1 and 2), common to both JC and BK viruses. In order to prove JC virus as a pathogen, RT-PCR analysis of the biopsy sample was performed. It detected >10^6 copies of JC virus *per* mL with negative BK virus DNA. The diagnosis of JCVAN was established.

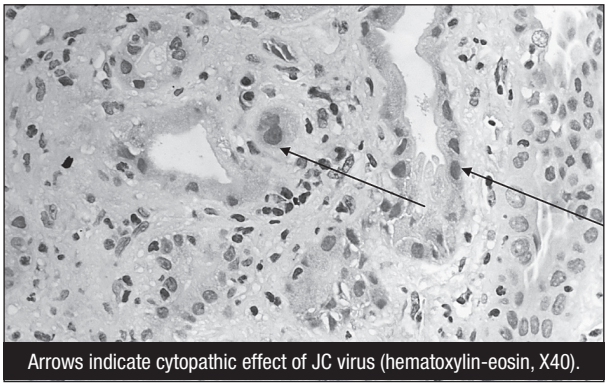

Fig. 1. *Micrograph of the biopsy sample showing papyloma virus-associated nephropathy pathology.*

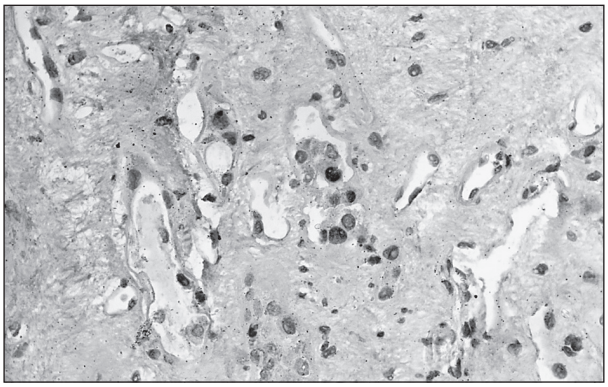

Fig. 2. *Positive SV40+ staining.*

At the time, his immunosuppressive therapy included tacrolimus monohydrate at a dose of 1.75 mg (through level 4.8 ng/mL), mycophenolate mofetil 2x500 mg and 10 mg of prednisone. After the diagnosis, immunosuppressive therapy remained the same but was lowered to 1 mg/2x500 mg/5 mg, respectively. Intravenous immunoglobulins (IvIg) (2 g/kg) were also applied, divided over four days. After IvIg therapy, his renal parameters began to fall towards the earlier values. He was released home on day 22 of his hospital stay.

Not a month after discharge from the hospital, he suffered yet another urosepsis but recovered quickly. His current kidney function is steady with serum creatinine levels of 145 μmol/L, proteinuria 1.5 g/day and immunosuppressive therapy consisting of tacrolimus (target through level around 3-4 ng/mL) and prednisone 5 mg.

DISCUSSION

John Cunningham virus is a well-known cause of progressive multifocal leukoencephalopathy in immunocompromised patients, such as HIV-infected with low CD4+ count (5). It is far less common for JC virus to cause polyomavirus-associated nephropathy. In a prospective cohort study by Drachenberg *et al.*, 0.9% of kidney transplant patients were diagnosed with JCVAN, while studies on BK virus report on 1%-10% incidence of BKVAN in kidney transplant population (1,8-12).

The most prominent problems with JCVAN are diagnosis and screening. Although Drachenberg *et al.* displayed a strong association between JC viremia and JCVAN, it was not present in all of the patients as 2 out of 6 patients were not proven to have JC viremia at the time of the study (10). Other cases of JCVAN without PCR-proven JC-viremia have also been noted (13). John Cunningham viremia may yet prove to be useful in diagnosing JCVAN, as a vast number of patients with JC viremia do develop JCVAN (4,10). Some authors suggest that JC viruria is not a helpful screening tool for detection of JCVAN, as its incidence is not significantly increased in kidney-transplant patients; the more so, it does not appear to be increasing at all in immunosuppressed patients, unlike the BKV viruria (14). Regarding the viral quantitative load, it is still unclear whether it does increase in the immunosuppressed patients (4).

The most common immunosuppression used in our institution for kidney transplant patients is a combination of tacrolimus, mycophenolate mofetil and prednisone. Querido *et al.* proposed some risk factors for

development of JCVAN in kidney transplant patients including the use of mycophenolate mofetil and tacrolimus as immunosuppressive agents (15). Besides immunosuppression, additional risk factors found in our patient were male gender and deceased donor transplantation. He neither received anti-thymocyte globulin induction therapy nor had acute rejection episodes.

We reversed the course of JCVAN successfully with high doses of intravenous immunoglobulins and reduction of immunosuppressive therapy. Some cases of JCVAN have been reported to improve after conversion from tacrolimus to everolimus (15), which was not possible in our patient due to proteinuria. Attempts to improve glomerular filtration rate with tacrolimus to cyclosporine have also been made, as well as some antiviral agents and adding leflunomide to therapy (11,13).

CONCLUSION

Available data on the diagnosis and treatment of JCVAN are scarce. Our case demonstrated that due to biology similarities of JC virus and BK virus, experiences and methods used in the treatment of BKVAN may be employed in the treatment of JCVAN.

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SAŽETAK

NEFROPATIJA POVEZANA S VIRUSOM JOHN CUNNINGHAM U PRIMATELJA TRANSPLANTATA BUBREGA

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Dok je John Cunningham (JC) virus dobro poznati uzročnik progresivne multifokalne encefalopatije, dosad je opisan kao uzročnik nefropatije u tek nekoliko slučajeva. Prikazujemo bolesnika s transplantiranim bubregom koji se prezentirao proteinurijom i porastom serumskog kreatinina. Biopsijom presatka je dokazana poliomavirusna nefropatija. Uporabom lančane reakcije polimeraze BK virus i JC virus su bili negativni u krvi, u mokraći je BK virus bio negativan, a JC virus pozitivan, dok je iz bioptata dokazano više od 106 kopija DNA JC virusa, čime smo potvrdili dijagnozu nefropatije presatka uzrokovane JV virusom. Bolesnik je liječen intravenskim imunoglobulinima uz smanjivanje intenziteta imunosupresije. Ovaj bolesnik potvrđuje da JC virus može uzrokovati značajne promjene u bubrežnom presatku i da ga treba uključiti u diferencijalnu dijagnozu pogoršanja funkcije presatka.

Ključne riječi: **imunosupresija, transplantacija bubrega, JC virus, JC virusna nefropatija**