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HIGH-RISK HUMAN PAPILLOMAVIRUS INFECTION IN LATVIAN MALE KIDNEY TRANSPLANT RECIPIENTS

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Kidney transplant recipients have higher incidence of human papillomavirus (HPV)-related malignancies, but studies on the natural history of HPV infection are insufficient, especially regarding in male recipients. The aim of this study was to evaluate the course of high-risk HPV (HR-HPV) infection after kidney allograft transplantation in male recipients: to estimate frequency and activity of HR-HPV infection under immune system suppression. Twenty male renal recipients (age 20 – 68) were enrolled in this investigation and examined in dynamics. Peripheral EDTA-blood samples and urine samples were collected from each patient 2 weeks, 6 months and 12 months after transplantation. Polymerase chain reaction (PCR) with consensus primers was used for initial detection of high range HPV types, a commercial qPCR kit for detection of HR-HPV load in urine samples and ELISA for detection of serum IgG class antibodies to HR-HPV L1-capsid protein. Overall, combining molecular (HR-HPV genomic sequences detected by real-time PCR) and serological studies (IgG class antibodies to HR-HPV L1-capsids' protein), high frequency of HR-HPV infection among male kidney transplant recipients (9/20; 45%) was showed. However, the majority of HR-HPV positive recipients (7/9; 78%) showed signs of infection clearance. It means that, despite the applied immune suppressive therapy, the host's immune system is capable of dealing with HR-HPV infection up to the 12th month after transplantation. However, the sample size should be increased to enable through statistical analysis before final conclusions are made.

Key words: *HR-HPV, kidney transplant recipients.*

INTRODUCTION

Human papillomavirus (HPV) is a wide family of DNA viruses that can infect basal epithelial cells of the skin or inner-lining tissues (Burd, 2003). The majority of sexually active men and women will acquire genital HPV infection at some point during their lifetime. In 2008, it was estimated that 610 000 cancers in men and women were attributed to HPV infection worldwide (Albero *et al*., 2014).

Based on association with cervical cancer and precursor lesions, HPV can also be classified as high-risk (HR-HPV) and low-risk (LR-HPV) oncogenic types (Burd, 2003; Muñoz *et al*., 2003). LR-HPV types, such as HPV 6 and 11, can cause common genital warts or benign hyper-proliferative lesions with very limited tendency to malignant progression, while infection with HR-HPV types, highlighting HPV 16 and 18, is associated with the occurrence of pre-malignant and malignant cervical lesions (Coscia *et al*., 2015). HPV-16 and HPV-18 types are also associated with many penile, cervical, vulvar, anal, and head and neck carcinomas, and contribute to over 40% of oral cancers (Shukla *et al*., 2009; Coscia *et al*., 2015).

Most HPV infections are "cleared" by the immune system and do not result in clinical diseases in healthy individuals; however, in cases of immune system suppression infections can lead to development of malignancies (Brendle *et al*., 2014).

Innate immune response, which includes dendritic, Langerhans, natural killer cells and keratinocytes, becomes the first line of defence against the infection. These cells are important in promoting adaptive immune response against HPV infection (Scott *et al*., 2001; Stanley and Sterling, 2014). Also, helper T-lymphocytes (CD 4+) play a sufficient role in response against HPV infection. CD4+ T cell responses to capsid protein are necessary for optimal antibody and cytotoxic T cell production (Frazer, 2009).

Immunosuppressive treatment of organ transplant recipients is associated with an increase in the occurrence of HPV-related anogenital (pre)malignancies (Meeuwis *et al*., 2015).

Kidney transplant recipients have a higher incidence of HPV-related malignancies. However, studies on the natural history of HPV infection are insufficient, especially regarding male recipients. While immunosuppressive regimens improve the overall survival of renal transplant recipients, they also contribute to the long-term complications of post-transplant malignancies (Genzer *et al*., 2012). In males, oncogenic HPV types are associated with penile, anal, oropharyngeal, and non-melanoma skin cancers (Grulich *et al*., 2007). Of significance for male recipients is that these HPV-associated cancers are also known to be significantly higher in the post kidney transplantation period (Halpert *et al*., 1986; Buell *et al*., 2005).

The aim of this study was to evaluate the course of high-risk HPV (HR-HPV) infection after kidney allograft transplantation in male recipients: to estimate frequency and activity of HR-HPV infection under immune system suppression.

MATERIALS AND METHODS

Twenty male renal recipients (age 20–68) who received kidney allograft during 2013–2014 were enrolled in this investigation and examined in dynamics. The recipients had the following diagnosis: autosomal dominant polycystic kidney (n = 6), chronic glomerulonephritis (n = 3), haemolytic uremic syndrome (n = 1), diabetic nephropathy (n = 2), focal segmental glomerulosclerosis (n = 1), hypertensive nephropathy (n = 3), reflux nephropathy (n = 1), urate nephropathy (n = 1), ANCA associated vasculitis with lung and kidney damage — rapidly progressive glomerulonephritis (n = 1), and chronic kidney disease with unspecified aetiology (n = 1).

All patients had received induction immunosuppression therapy with monoclonal or polyclonal antibodies and triple supportive immunosuppression therapy consisting of glucocorticoids, anti-proliferative drugs and calcineurin inhibitors.

The main inclusion criteria were availability of peripheral EDTA blood and urine samples, and possibility to examine the recipient at three times — 2 weeks, 6 months and 12 months after transplantation.

Aliquots of 200 µl blood plasma were collected from EDTA peripheral blood samples for further serological testing. Cells from urine were collected by centrifugation and washed with PBS three times. Blood plasma samples and cells from urine were stored at –70 °C

DNA from urine samples was extracted using the phenol-chloroform method.

Beta (β)-globin PCR with appropriate primers were used to determine the quality of the isolated DNA (Vandamme *et al*., 1995).

Polymerase chain reaction (PCR) with consensus primers GP5+/GP6+ was used for initial detection of high range HPV types (HR-HPV and LR-HPV types) (Jacobs *et al.,* 1995) and the HPV High Risk Screen Real-TM Quant commercial qPCR kit (Sacace, Italy) for quantitative detection of 12 types of HR-HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) in recipient urine DNA samples. Type-specific PCR was used to detect HPV-16 and HPV-18 genomic sequences in recipient urine DNA samples according to Leiros *et al.*, 2005. Sample contamination in PCR was excluded by using negative controls (negative for HPV DNA and water control).

The ELISA commercial kit (MyBioSource, USA) was used to detect IgG class antibodies to HR-HPV L1-capsids' protein in recipient plasma (presence of these antibodies is associated with HR-HPV clearance) (Stanley, 2008; Skiba *et al*., 2006). Parameters characterising cellular immunity were taken from patient medical histories in order to analyse their immune system status and its influence on HR-HPV infection activity.

The study was approved by the Ethics Committee of Rīga Stradiņš University, and written consent was obtained from all patients.

RESULTS

48 (80%) of 60 urine DNA samples taken from 20 male kidney renal recipients in dynamics (2 weeks, 6 months and 12 months after transplantation) were positive on β-globin, showing good DNA quality, and were used in PCR. Initial PCR results with consensus primers (allowing to detect 23 HPV types) showed that 8/20 (40%) of the recipients were positive on HPV genomic sequences in urine DNA samples. In 3/8 of recipients' urine samples viral DNA was detected two weeks after transplantation, two of them continued showing and two additional recipients showed presence of HPV genomic sequences in urine DNA samples (4/8) six months after transplantation. Twelve months after transplantation five recipients were positive on HPV genomic sequences in urine DNA samples (2/4 that were positive after 6 months and another 3 that were negative at earlier sampling times). Interestingly, only one recipient had HPV genomic sequences in urine DNA samples during the entire study period (2 weeks, 6 and 12 months after transplantation).

qPCR results showed that two of eight recipients were positive on HR-HPV genomic sequences. One recipient showed clinically significant (according to manufacturer's protocol, $3\log_{10}$ viral copies/10^5 cells or more) HR-HPV load – $6.87\log_{10}$ viral copies/10^5 cells two weeks after transplantation. However, HR-HPV genomic sequences were not detectable in this recipient at 6 and 12 months. However, urine DNA samples of this recipient were positive on consensus HPV genomic sequence during the entire observation period. A second recipient showed clinically significant HR-HPV load ($3.85\log_{10}$ viral copies/10^5) six months after

transplantation, which was no longer detectable 12 months after transplantation, but results of PCR with consensus primers showed presence of HPV genomic sequences at that time.

Type-specific PCR results showed that none of the male kidney transplant recipients was positive on HPV-16 or HPV-18 genomic sequences.

Serological study showed that 7 of 20 recipients had IgG class antibodies to HR-HPV L1-capsid protein, while urine DNA samples of five of them were negative in PCR with consensus HPV as well as in HR-HPV qPCR. All 7 recipients were HR-HPV seropositive 12 months after transplantation. At the same time, two recipients with high HR-HPV load lacked IgG class antibodies to HR-HPV L1-capsid protein during the whole period of observation.

Overall, combining qPCR (2/20) and serological results (7/20), signs of HR-HPV infection was shown in 9/20 (45%) recipients.

To compare parameters of recipients, cellular immunity examination of their medical histories was made and data on immunocompetent cell absolute counts in 1 mm^3 were retrieved (12 months after transplantation). Mean absolute counts for immunocompetent cells were evaluated for recipients with and without IgG class antibodies to HR-HPV L1-capsid protein. At 12 months after transplantation, mean counts of CD4+ (T helpers) and $CD19^+$ cells (B lymphocytes) tended to be higher in the recipient group with IgG class antibodies to HR-HPV L1-capsid protein than in the recipient group without antibodies (not significant, $p = 0.66$ and $p = 0.62$, respectively) (Table 1). Also, the CD4+/CD8+ index tended to be higher in recipients with IgG class antibodies to HR-HPV L1-capsid protein than in recipients without them (1.56 ± 1.28 vs. 1.15 ± 0.66, $p = 0.44$), showing better immune system function (Table 1).

Evaluation of recipient medical histories did not show presence of any specific HR-HPV-associated complications.

Table 1

MEAN ABSOLUTE COUNTS OF IMMUNOCOMPETENT CELLS' POPULATIONS (1 MM^3) IN KIDNEY TRANSPLANT RECIPIENTS WITH AND WITHOUT IGG CLASS ANTIBODIES TO HR-HPV L1-CAPSID PROTEIN

Parameters	IgG negative n = 13	IgG positive n = 7	p*
Leu	6680 ± 2010	6240 ± 2120	0.66
Ly	1880 ± 700	1660 ± 660	0.49
CD3+	1515 ± 525	1438 ± 578	0.76
CD4+	611 ± 327	692 ± 418	0.66
CD8+	595 ± 268	521 ± 241	0.53
CD16+	271 ± 232	170 ± 117	0.21
CD19+	75 ± 47	92 ± 81	0.62
CD95+	891 ± 371	861 ± 354	0.86
CD4+/CD8+	1.15 ± 0.66	1.56 ± 1.28	0.44

* p value of immunocompetent cells parameters changes between two groups, IgG negative and IgG positive.

The most common complications in HR-HPV positive recipients were secondary anaemia (6/9; 66%) and arterial hypertension (9/9; 100%), which are not associated with HR-HPV infection. In one HR-HPV positive recipient, oral candidiasis and II type diabetes were observed and in another, HR-HPV positive recipient — decreased kidney cysts were present.

DISCUSSION

The aim of investigation was to determine frequency and activity of HR-HPV infection in Latvian male kidney transplant recipients under immune system suppression; this has been investigated worldwide, but not in Latvia.

During this investigation we encountered with several problems: 1) there is no standardisation in detection of HR-HPV (a variety of methods and systems for HR-HPV detection exist); 2) today over 15 types of HR-HPV are known, and therefore, it is difficult to type all HR-HPV and to evaluate the oncogenic potential of each of them.

Another problem was in collection of the samples — two weeks after renal transplantation was the earliest time period when collection of material from patients for the first HR-HPV testing was possible, because a large proportion of the recipients had anuria before the operations.

This study presents the first data on HPV infection frequency among Latvian male kidney transplant recipients. HPV genomic sequences were found in 40% (8/20) of recipient urine samples (using consensus primers), of which two showed additionally clinically significant HR-HPV load, estimated using a commercial qPCR kit. Three of 20 recipients (15%) had HPV genomic sequences in urine sample two weeks after transplantation, but it could not be excluded that this infection was present already before transplantation, as a short time had passed since surgery and we were not able to carry out HPV infection screening before transplantation due to anuria in the majority of patients. Five other recipients (25%) were positive 6 and 12 months after transplantation, showing that the majority of recipients have HPV reactivation or are infected in the later period after transplantation. Considering that one of two recipients also showed clinically significant HR-HPV load ($3.85\log_{10}$ viral copies/10^5) on the 6^{th} month after transplantation, we suggest that this period of time is the most important for recipients; however, activation of HR-HPV in the early period of immunosuppressive treatment after transplantation also is possible.

Two recipients positive on HR-HPV genomic sequences were negative on IgG class antibodies to HR-HPV L1-capsid protein and of seven seropositive recipients only two were positive in PCR with a consensus HPV genomic sequence. In this case, the mentioned antibodies might have appeared during viral clearance and show past infection (Skiba *et al.*, 2006; Stanley, 2008). Another explanation is that anti HR-HPV IgG class antibody presence and absence of HR-HPV genomic sequences in urine DNA samples indi-

cates another site of persistence or a low and HR-HPV load that is undetectable using the qPCR kit.

Also, information on immunocompetent cell parameters from clinical histories showed that seropositve recipients develop antibodies against HR-HPV L1 capsid protein on the 12th month after transplantation; at that time, mean absolute cell counts of CD4+ and CD19+ cells (cell subpopulations involved in antibody production) were higher than in recipients without IgG antibodies (not significant: $p = 0.66$ and $p = 0.62$, respectively).

At present there is still no convincing and consensual HPV screening methodology for kidney transplant patients. Nowadays, many researchers suggest using first-void urine samples for HPV testing as an alternative and non-invasive method for screening (Golijow *et al*., 2005; Pathak *et al*., 2014). However, our study results show that 20% of urine DNA samples have poor quality and need to be excluded from further examination. Therefore, a urine sample is not a fully reliable template for HPV screening and should be supported additionally with other methods and results.

Overall, combining molecular and serological studies this study showed a high frequency of HR-HPV infection among male kidney transplant recipients (9/20; 45%); the majority of HR-HPV positive recipients (7/9; 78%) did not show signs of infection clearance. This means that, despite the applied immunosuppressive therapy, the hosts immune system is capable of dealing with HR-HPV infection up to the 12th month after transplantation, and occurrence of IgG class antibodies to HR-HPV L1-capsid protein in recipients could be used as a positive prognostic marker suggesting that the host immune system is capable of dealing with HR-HPV infection.

Epidemiological data provided by Forman et al (2012) show that Eastern Europe has a higher HPV prevalence rate (21.4%) than in Northern, Western and Southern Europe (10.0%, 9.0%, and 8.8%, respectively). Lower prevalence occurs in Western Asia and Northern America (1.7% and 4.7%, respectively), and the highest in the Caribbean (35.4%) (Forman *et al*., 2012).

According to literature data, a high range of genital HR-HPV prevalence (3–20%) has been observed in immunocompetent men (Nyitray *et al*., 2011; Alfonso *et al*., 2016; Cai *et al*., 2016); however, in immunocompromised men the prevalence of genital HR-HPV infection is much higher and can reach 51% (Li *et al*., 2016). This is in concordance with results of this study, which however included a small group of recipients (n = 20).

The majority of male recipients who were positive on HR-HPV infection (7/9; 77.7%) were at age between 50 and 66.

To evaluate the full influence of immunosuppressive therapy on HR-HPV infection, more detailed examination of each case should be made. However, the immunosuppressive therapy applied from beginning in the majority of cases was the same for all recipients, but which was changed individually based on developed complications. Differences in immunosuppressive therapy can have different effect on the host's immune system, including anti-viral response.

It is important to evaluate the oncogenic potential of all HR-HPV types in immunosuppressed hosts, but it is very difficult to carry out such investigations due to the high diversity of virus types (over 15 types). We conducted type-specific PCR for HPV 16 and HPV 18 in male recipients, of which none were positive.

To draw final conclusions on HR-HPV infection activity and its oncogenic potential, further investigation should be carried out with an increased sample size for thorough statistical testing.

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AUGSTA RISKA CILVĒKA PAPILOMAS VĪRUSA INFEKCIJA VĪRIEŠU DZIMUMA NIERU TRANSPLANTĀTA SAŅĒMĒJIEM LATVIJĀ

Nieru transplantācijas recipientiem ir lielāka saslimstība ar cilvēka papilomas vīrusa (HPV) izraisītiem ļaundabīgiem audzējiem. Īpaši trūkst pētījumu par HPV infekciju vīriešiem. Šī pētījuma mērķis bija novērtēt augsta riska HPV (HR-HPV) infekciju kursu pēc nieru transplantācijas vīriešu recipientiem: novērtēt HR-HPV infekciju biežumu un aktivitāti imūnsistēmas nomākuma gadījumā. Šajā pētījumā tika iesaistīti 20 vīrieši (vecumā 20–68 gadi) pēc nieru transplantācijas, un viņu turpmākā novērošana notika dinamikā. Perifēro asiņu un urīna paraugi tika savākti 2 nedēļas, 6 mēnešus un 12 mēnešus pēc nieru transplantācijas. Polimerāzes ķēdes reakcija (*polymerase chain reaction,* PCR) ar konsensus praimeriem tika izmantota, lai sākotnēji noteiktu plašu HPV tipu spektru, bet qPCR komplekts, lai noteiktu HR-HPV klātbūtni DNS paraugos, kuri izdalīti no recipientu urīna. Iegūtās molekulārās atradnes tika papildinātas ar imunoloģisko rādītāju datiem. Kopumā, apvienojot molekulāros un seroloģiskos rezultātus, pētījums ir parādījis biežu HR-HPV infekcijas sastopamību vīriešu dzimuma nieru transplantācijas recipientu vidū (9/20; 45%), tomēr vairumā HR-HPV infekcijas gadījumu (7/9; 78%) parādījās vīrusa eliminmāciju pazīmes. Tas nozīmē, ka, neraugoties uz lietoto imūnsupresīvo terapiju, pacientu imūnsistēma tomēr spēj tikt galā ar HR-HPV infekciju 12 mēnešu laikā pēc transplantācijas, tomēr, lai veiktu statistisko apstrādi un varētu izdarīt galējus secinājumus, ir jāpalielina pētījumā iekļauto pacientu un izmeklēto paraugu skaits.