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Immunosuppression and the occurrence of HPV in kidney transplant patients verified by urinary cytology

Imunossupressão e ocorrência de HPV em pacientes transplantados renais a partir de exame citológico urinário

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ABSTRACT

Introduction: Human papillomavirus (HPV) is the main cause of cervical cancer, and immunosuppression is recognized as a risk factor for HPV infection and its persistence. After renal transplantation, immunosuppressive agents are used to prevent rejection, but predispose recipients to chronic infections and malignancies. **Objective:** This study aimed to verify, based on urinary cytology (UC), the prevalence of HPV in immunosuppressed kidney transplant patients. **Material and method:** In this cross-sectional study, the population was composed of kidney transplant patients that had undergone routine UC from August 2012 to August 2014. **Results:** There were 2,305 urine cytopathological tests. Thirteen patients with presence of koilocytes in such examination were observed. Therefore, the relative frequency of patients with HPV detected in urine was 0.56%. In the interval until the first post-transplant year, 10 (76.92%) patients presented koilocytes ($p < 0.0001$) in the UC. The dosages of immunosuppressive agents until the first post-transplant consultation, which showed correlation with the period between transplantation and the first UC test with the presence of koilocytes ($p < 0.0001$), were prednisone 10.5-20 mg/day, mycophenolate sodium 901-1,440 mg/day, and tacrolimus 4.5-12 mg/day. **Conclusion:** This study showed immunosuppression as an important risk factor for infection by HPV or its reactivation. Screening UC tests after transplantation may evidence HPV infection.

Key words: immunosuppression; risk factors; kidney transplantation; papillomavirus infections.

INTRODUCTION

Human papillomavirus (HPV) is the main cause of cervical cancer among women, and immunosuppression is recognized as one of the risk factors for HPV infection and its persistence[1]. According to Meeuwis *et al*. (2011), HPV prevalence is higher in immunosuppressed women in comparison to their immunocompetent homologues. Immunosuppression probably causes greater susceptibility to HPV infection and/or higher risk of HIV infection persistence[2].

Kidney transplant recipients have high risk of developing pre-malignant neoplasms associated with the virus, such as HPV-related anogenital lesions. Most kidney transplant women are known to be infected by HPV, with a 14-fold higher risk of developing cervical cancer, 50-fold higher risk for vulvar cancer, and up to 100-fold higher risk for anal cancer[3].

Recognizing HPV infection, by the cell alteration (koilocytosis) observed when this virus is present, became important due to its identification as carcinogenic in the development of squamous cell carcinoma of the genital tract[4]. During the viral course of HPV, viral particles invade the cell nucleus and cause characteristic degenerative alterations[4]. Koilocytosis is considered a pathognomonic sign of HPV infection. The typical koilocytosis presents nuclear enlargement, with reactive changes, and characteristic sharply demarcated halo separated from cytoplasm by a clearly condensed rim[4].

As reported by Reis *et al*. (2010), HPV infection is frequently common among young adults of both sexes, with estimated prevalence of 20%-46%. HPV dissemination is generally universal among sexually active individuals, with men playing an important role in spreading this virus among women[5].

Infection by specific HPV types is the main risk factor for cervical cancer. Other risk factors are: early age of first sexual intercourse,

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lifetime number of sex partners, promiscuous partners, poor nutrition, parity or multiparity, tobacco smoking, oral contraceptive use, and low socioeconomic status[5-8]. The host's immune status is another risk factor, as the evolution of cervical lesions may be associated with immune responsiveness. HPV-infected cells lack efficient response to antigens, making their multiplication easy due to delayed recognition by the immune system[8].

After kidney transplantation, patients must be treated with immunosuppressants to prevent rejection. These drugs have different mechanisms of action, disrupting interaction and/or stimulation of antigen-presenting cells or T-lymphocytes of the human immune system[9]. Immunosuppressive therapy protects the transplanted organ, but predisposes the recipient to chronic infections and malignant diseases. Transplant patients are in risk of cervical intraepithelial neoplasia (CIN) and cervical cancer, due to a decreased immune response, in the case of primary infection, or reactivation of a latent infection, such as HPV of high oncogenic potential[10].

Urine cytology (UC) is an excellent screening method for monitoring kidney transplant patients: it is very convenient, useful and sensitive[11, 12]. In accordance with Almeida *et al*. (2006), serial analysis of UC is an adequate screening method[13].

The present work was aimed at, based on UC, verifying the prevalence of HPV in immunosuppressed kidney transplant patients at a reference hospital.

MATERIAL AND METHOD

A cross-sectional study was carried out, in which the analyzed population was composed of kidney transplant patients from a hospital in Porto Alegre who underwent routine UC from August 2012 to August 2014. Patients older than 18 years, of both sexes, who signed the informed consent, participated in the study.

All the morning spontaneous urine specimens were collected in sterile containers. Each sample was processed in duplicate as follows: a portion of 10 ml urine was centrifuged at 1,300 revolutions per minute (rpm) for 10 min, and the pellet was cytocentrifuged (Cytospin) at 800 rpm for 6 min. Slides were stained with Papanicolaou method and visualized under an optical microscope at 200× and 400× magnification. The entire slide area (5 mm diameter) was analyzed.

Slides were assessed in a double-blind fashion by two experienced cytologists from the reference service. The adopted criterion for HPV detection was identification of superficial and intermediate cells with nuclear atypia, clear cytoplasmic halo, and thickening of the peripheral membrane. The diagnosis of HPV infection was made by the presence of koilocytes in microscopic analysis.

Patient selection

Subjects were selected by convenience sampling. Kidney transplant patients were identified by the presence of HPV (koilocytes) in the mentioned exam. An interview was carried out and the study was explained for patients to sign the informed consent. At the end of this step, participants received printed material about prevention of cervical cancer supplied by the Ministry of Health (MS).

Data collection

Data from patients' records were used as collection instrument. The study followed the guidelines of Resolution nº 466/2012 of the National Council of Health/MS, and was approved by the ethics committee of Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA). The researchers declare that there are no conflicts of interest. All the participants signed the informed consent.

Data analysis

All the UC results from kidney transplant patients in the mentioned period were analyzed. All patients under suspicion of HPV in the report had their slides revised by at least one of the researchers. The slides considered positive for HPV met the same cytopathologic screening criteria for diagnosis of cervical HPV, that is, cells had perinuclear halo. As quality control, after analysis by researchers, two experienced pathologists checked the diagnoses in a double-blind manner, and in case there were no discrepancies in the results, they were taken into consideration. Images of patients' UC slides were captured by means of an optical microscope connected with a camera and specific software.

Report data were collected, stored in an electronic spreadsheet and analyzed by statistical software. Correlation between variables was evaluated by means of t test with 5% ($p < 0.05$) statistical significance.

RESULTS

In the analyzed period, 2,305 UCs were performed to assess the presence of viral cytopathic effects (decoy cells – polyomavirus) in kidney transplant patients. Among this total, 13 cases detected

the presence of koilocytes in the UC test (**Figure**). The relative frequency of patients with the presence of HPV in urine was 0.56%.

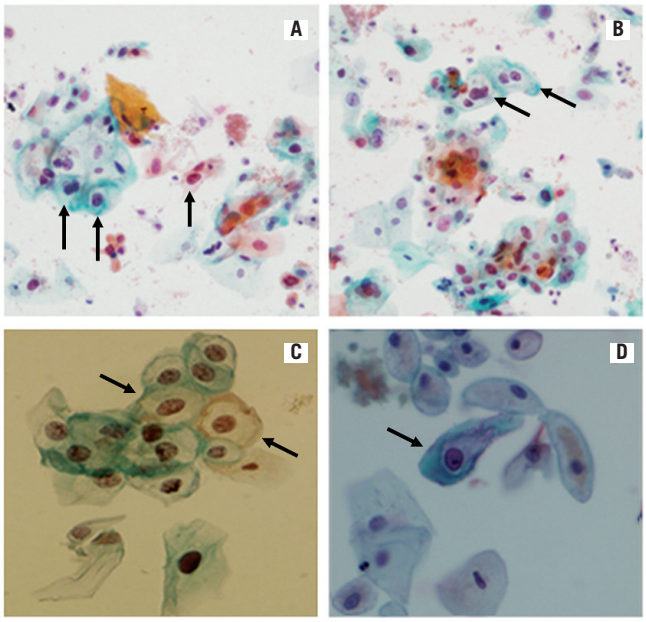

FIGURE – *Presence of koilocytes in UC. A and B: 20×; C and D: 40×, optical microscopy, Papanicolaou staining. Images by Leon, RM*
UC: urine cytology test.

Among the patients with HPV detected in urine (n = 13), 10 (76.9%) were females. The age group with the highest frequency was that of 51-70 years (53.8%), followed by those of 18-30 years (23.1%) and 31-50 years (23.1%).

Regarding the profile of patients as to pre-transplant sexually transmitted diseases (STDs) (**Table 1**), all presented human immunodeficiency virus (HIV)-negative serology and negative syphilis (Venereal Diseases Research Laboratory [VDRL]) test. Among the 13 patients, two (15.4%) were positive for hepatitis B virus (HBV), and four were positive for hepatitis C virus (HCV). HBV-HCV co-infection was observed in two (15.4%) patients.

The immunosuppressive regimen used in patients during the first month after transplantation consisted of tacrolimus (Tac), mycophenolate sodium (MPS), and prednisone (Pred). Dosage (Table 1) presented higher frequencies in the ranges of Tac 4.5-8 mg/day, corresponding to 54.5% of patients; MPS 1,081-1,440 mg/day in 63.6%; and Pred 18-20 mg/day in 72.7%.

Time between transplantation and the first UC with the presence of koilocytes (**Table 2**) was observed. One can note the highest frequencies occurred in up to six months after transplantation in six (46.15%) patients, and between six months and one year in four (30.77%) patients, summing up 76.92%.

TABLE 1 – Patients' profiles as to pre-transplant STDs and immune status at the first post-transplant visit

Variable	*n* (%)
Negative HIV and VDRL	13 (100)
Negative HBV	11 (84.6)
Positive HBV	2 (15.4)
Total	13 (100)
Negative HCV	9 (69.2)
Positive HCV	4 (30.8)
Total	13 (100)
Tac dose (mg/day)	
4.5-8	6 (54.5)
8.5-12	3 (27.3)
12.5-16	2 (18.2)
Total	11 (100)
MPS dose (mg/day)	
180-720	2 (18.2)
721-900	1 (9.1)
901-1,080	1 (9.1)
1,081-1,440	7 (63.6)
Total	11 (100)
Pred dose (mg/day)	
0	1 (9.1)
5-10	2 (18.2)
10.5-17.5	0 (0)
18-20	8 (72.7)
Total	11 (100)

STDs: sexually transmitted diseases; HIV: human immunodeficiency virus; VDRL: Venereal Diseases Research Laboratory; HBV: hepatitis B virus; HCV: hepatitis C virus; Tac: tacrolimus; MPS: mycophenolate sodium; Pred: prednisone.

TABLE 2 – Time between transplantation and the first UC with the presence of koilocytes

Time (months)	*n* (%)	(%) Accumulated
≤ 6	6 (46.15)	46.15
> 6 and < 12	4 (30.77)	76.92
> 12	3 (23.08)	100
Total	13 (100)	

UC: urine cytology test.

The percentage of women who underwent pre-transplant cervical cytology or anatomical pathology testing in the reference hospital was 30%: two with normal results and one (10%) with the presence of koilocytosis. After transplantation, cervical cytology was performed in three (30%) patients that presented alteration (low grade CIN [CIN I]). However, among the 10 women of the study, five (50%) did not undergo any pre- or post-transplant gynecological exam in the reference hospital. The use of oral contraceptives was observed in three (30%) patients of the study.

In the analysis of time between transplantation and the first UC with HPV cytopathic effect, 10 (76.92%) patients presented koilocytes ($p < 0.0001$) in the interval up to the first year after transplantation.

Dosages of immunosuppressant drugs, until the first post-transplant visit, which demonstrated correlation with the period between transplantation and the first UC with the presence of koilocytes ($p < 0.0001$) were Pred 10.5-20 mg/day, MPS 901-1,440 mg/day and Tac 4.5-12 mg/day.

DISCUSSION

Urine cytology test

UC is performed in all kidney transplant patients as a routine practice, and it can evidence the presence of the viral cytopathic effect. Considering that the presence of koilocytes is a pathognomonic sign of HPV infection[4], UC has an adjuvant potential to screen for this infection. Although it is not specific for HPV detection, the relative frequency of kidney recipients' urine found positive for HPV (0.56%) demonstrates the possibility of detecting this virus by means of a low-cost non-invasive test. An interesting finding of the study was the presence of HPV in the urine of three male patients. The male population is known to not undergo routine HPV testing, thus they may infect their partners. Male partners can in fact contribute to the risk of developing cervical cancer in women, acting as ''carriers'' and ''vectors'' of HPV oncogenic types[14, 15]. In the study by Antunes *et al*. (2004), the prevalence of koilocytosis in penile biopsies was 51.2% of 80 patients[14].

As stated by Sousa *et al*. (2012), koilocytosis was found in 63% of cervical smears from women diagnosed as CIN I. This cytopathic effect was observed in 26.2% and 25.7% of smears from women diagnosed as CIN II and CIN III, respectively[16]. In a study with HIV-positive female patients, koilocytosis was found in 27.2% of women against 9.2% of HIV-negative women[17]. Among 33 patients with bladder carcinoma, koilocytosis was seen in tissue sections from 13 patients, and was observed in the UC of three. All the three were positive for high-risk HPV deoxyribonucleic acid (DNA); in conclusion, koilocytosis is a good morphological marker for HPV in the urothelium[18].

Time after transplantation and presence of viral cytopathic effect in urine cytology

Time between transplantation and the first UC detecting koilocytosis, until six months and between six months and one year, presented increased frequency with statistical significance ($p < 0.0001$). This finding for HPV is similar to that of other studied viruses according to the literature. In the study by Agrawal *et al*. (2010) with 327 kidney transplant patients during a period of four years, 13 patients were identified with kidney disease by polyomavirus; and four, by cytomegalovirus. All the patients were on a triple immunosuppressive regimen, with cyclosporine, Tac, and Pred or mycophenolate mofetil (MMF). The average time to diagnose viral infection after transplantation was 12.4 months for nephropathy by polyomavirus, and 4.8 months for nephritis by cytomegalovirus[19].

Immunosuppressive doses and time between transplantation and urine cytology showing koilocytes

Infection in a kidney transplant recipient is an important cause of morbidity and mortality. It is many times detected late or remains undetected due to the impaired immune response caused by immunosuppressive therapy[19].

In the present study, the doses of immunosuppressants up to the first visit after transplantation, which demonstrated correlation with the period between transplantation and the first UC showing koilocytes ($p < 0.0001$), were Pred 10.5-20 mg/day, MPS 901-1,440 mg/day, and Tac 4.5-12 mg/day. In this study, the higher the dose of immunosuppressants, the shorter the time between transplantation and the presence of koilocytes in the UC. Certain immunosuppressive agents, such as calcineurin inhibitors (Tac), and mycophenolate (antiproliferative), are associated with the increased risk of viral infections; the first year after transplantation corresponds to a period of intense immunosuppression in kidney transplant patients[20].

According to Cukuranovic *et al*. (2012), viruses are among the most common causes of post-transplant opportunistic infections, and many viral infections after transplantation result from the reactivation of a ''latent'' viral infection in the host. Several factors contribute to post-transplant viral activation, including immune suppression (especially reduction of cytotoxic immunity), graft rejection therapy, inflammation (cytokines) and tissue lesion. The intensity of immune suppression used to prevent graft rejection and other factors related to the host regulate susceptibility to viral infection[21].

The importance of HPV screening in kidney transplant patients

The age group that presented the highest frequency of HPV presence in UC (51-70 years) comprises the period of higher risk to develop cervical cancer, between 40 and 60 years[22, 23].

Among the three patients that underwent pre-transplant cervical cytology test, two presented normal results; and one, alteration (koilocytosis). Among the three patients who underwent post-transplant cervical cytology test, all presented alteration. In the study by Paternoster *et al*. (2008), transplant patients underwent Papanicolaou test and HPV exams six months before and after transplantation. All of them had negative Pap smears before their grafts. After the procedure, 16 patients (10.59%) had negative Pap smears, but positive viral typing. Eleven (7.28%) presented positive Pap smears. The final incidence of HPV infection (15.23%) was consistent with the literature. The incidence of minor intraepithelial lesions of the female genital tract (7.28%) was higher than in the normal population and analogous studies (4.5%-8.5%). The study suggests beginning screening for HPV infection approximately six months before the graft to avoid an irreversible situation of difficult treatment[24].

Pre-transplant screening of recipients offers opportunity to determine prophylaxis and the prevention strategies adopted after transplantation, as well as to educate patients and their families on preventive measures[21].

According to Oliveira *et al*. (2014), knowing the relationship between immunosuppression, viral infection and neoplasia, it is necessary to close follow transplant patients, conducting periodical exams to early detect a possible cancer. In cases of persistent infections, this monitoring must be performed more frequently. Besides, depending on the type of immunosuppressant administered, whether potent or not, monitoring must be even more rigorous[25].

Quadrivalent HPV vaccine is recommended for post-transplant patients, as it is safe and well-tolerated[26]. In the future, the inclusion of HPV vaccine in the immunization schedule for young adult patients in the kidney pre-transplant period is a strategy that may decrease the risk of developing cervical cancer in these patients.

CONCLUSION

Based on the results of our study, immunosuppression proved to be a major risk factor for HPV infection or HPV reactivation. Thus, gynecological follow-up must be part of pre- and post-transplant routine. Post-transplant UC screening, which is very important, can detect HPV infection. As immunosuppression is a risk factor for HPV infection, perhaps UC may be extended to other types of organ transplantation.

RESUMO

Introdução: *O papilomavírus humano (HPV) é a principal causa de câncer de colo do útero, e a imunossupressão é reconhecida como fator de risco para infecção pelo HPV e sua persistência. Após o transplante renal, agentes imunossupressores são usados para evitar rejeição, mas predispõem o receptor a infecções crônicas e doenças malignas.* ***Objetivo:*** *Este trabalho teve como objetivo verificar, a partir do exame citológico urinário, a prevalência do HPV em pacientes transplantados renais imunossuprimidos.* ***Material e método:*** *Neste estudo transversal, a população foi composta por pacientes transplantados renais que fizeram o exame de rotina citológico urinário no período de agosto de 2012 a agosto de 2014.* ***Resultados:*** *Realizaram-se 2.305 exames citopatológicos de urina. Foram observados 13 pacientes com presença de coilócitos no referido exame. A frequência relativa de pacientes com HPV detectado na urina foi de 0,56%. No intervalo até o primeiro ano pós-transplante, 10 (76,92%) pacientes apresentaram coilócitos (*$p < 0,0001$*) no exame citológico urinário (ECU). As dosagens de imunossupressores até a primeira consulta pós-transplante, que demonstraram correlação com o período entre o transplante e o primeiro ECU com presença de coilócito (*$p < 0,0001$*), foram prednisona 10,5-20 mg/dia, micofenolato de sódio 901-1.440 mg/dia e tacrolimo 4,5-12 mg/dia.* ***Conclusão:*** *Este estudo mostrou a imunossupressão como um fator de risco importante para infecção pelo HPV ou sua reativação. O acompanhamento por meio do ECU pós-transplante pode evidenciar a infecção por HPV.*

Unitermos: *imunossupressão; transplante de rim; fatores de risco; infecções por papilomavírus.*

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