

Vaginal Smear Findings In our Kidney Transplant Recipients

AYSE OZBAN

The Private Health Hospital

OMER GULER

Pamukkale University

MURAT OZBAN (✉ muratozban@yahoo.com)

Pamukkale University

BELDA DURSUN

Pamukkale University

CAGATAY AYDIN

Istanbul Medipol University

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Abstract

BACKGROUND

The aim of this study was to evaluate the results of the smear tests in renal transplant recipients, determine the prevalence of abnormal outcomes and compare these patients with the general population in our center.

METHODS

A total of 79 female patients who underwent renal transplantation at Pamukkale University were retrospectively evaluated. All patients were followed up during and after the surgical procedures by a gynecologist and the smear results were recorded periodically.

RESULTS

The mean time of Pap smear results after transplantation in kidney transplant recipients was 36.7 ± 4.5 months. There was a significant difference between the two groups in terms of atrophic cervicitis. In transplantation group, 7 patients (8.86%) had LG-SIL, 3 (3.79%) had ASC-US and 1 (1.26%) had HG-SIL. In control group, the numbers are 3 (3.79%), 2 (2.53%) and 0, respectively. The difference between the patient and control groups in terms of LG-SIL results (7 (8.86%) vs 3 (3.79%)) was statistically significant ($p < 0.05$).

CONCLUSIONS

We predict that kidney transplant recipients are at higher risk for precancerous cervical lesions and cervical cancer development due to immunosuppressive therapy. Smear screening and HPV testing should be repeated periodically to detect or prevent precancerous lesions and cervical cancer.

Introduction

Female organ transplant recipients are at risk for many cancers including cervical cancer of viral origin, autoimmune diseases and infections, due to long-term immunosuppressive therapy when compared to the women in general population [1]. Papanicolaou (Pap) smear test remains as the primary method for screening cervical pathology, including preinvasive and invasive lesions. The results of this screening method have been associated with decreased incidence and mortality of cervical cancer. It is well known that persistent high-risk HPV infections increase the risk of cervical cancer development [2]. In female renal transplant recipients, high-risk HPV prevalence has been reported to be between 5–63%. The number of studies showing the distribution and prevalence of HPV genotypes in renal transplant recipients are limited in the literature. While the risk of developing cervical intraepithelial neoplasia (CIN) due to immunosuppressive therapy is higher in female transplant population [3], a close follow-up with smear tests is quite important in early detection of these lesions. The immunosuppressive therapy can increase the risk of malignancy through various mechanisms increased rates of infection with oncogenic

viruses such as HPV. The abnormal outcomes include atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LGSIL or LSIL), high-grade squamous intraepithelial lesion (HGSIL or HSIL), and atypical squamous cells. The progression of cellular abnormalities and preinvasive diseases can lead to development of cervical cancer [4]. The aim of this study was to evaluate the results of the smear tests in renal transplant recipients, determine the prevalence of abnormal outcomes and compare these patients with the general population in our center.

Methods

A total of 79 female patients who underwent renal transplantation at Pamukkale University between January 2006 and December 2018 were retrospectively evaluated. The patient group was compared with a control group consisting of same number of healthy adults of similar age group. The transplant group ABD the control group patients where selected patients between the ages of 20–49, who where married, had at least one child, and had no family of genitourinary cancer. The surgical procedures before and after the surgery were performed following the standard protocols. All patients were followed up during and after the surgical procedures by a gynecologist and the smear results were recorded periodically. We don't plan a kidney transplant operation for any patient with precancerous lesions in routine cancer screening prior to transplant preparation. We routinely perform smear scans to our patients during operation preparation. In our clinic, we perform an immunosuppressive therapy protocol including basiliximab, tacrolimus, mycophenolate mofetil and corticosteroid. All smear examinations were evaluated following the Bethesda 2001 criteria. In this study, we compared both the smear results obtained before the operation and the scans performed after an average of 36 months. We aimed to diagnose possible invasive cancer early by following up patients with precancerous lesions regularly. A written informed consent was obtained from the patients and from healthy participants. The study protocol was approved by the Pamukkale University Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

All data analysis was performed using a statistical software (SPSS, version 15.0, IBM Corporation, SPSS Inc., Armonk, NY, USA). Chi-square test was used to compare the variables. $P < 0.05$ was accepted as statistical significance.

Results

The mean age of renal transplant patients was 38.1 years. The mean time of Pap smear results after transplantation in kidney transplant recipients was 36.7 ± 4.5 months. Candida infection was detected in 14 (17.72%) kidney transplant recipients and 5 (6.32%) control subjects. One (1.26%) patient and two (2.53%) control subjects had *Trichomonas vaginalis* infection. Even though there was a statistically significant difference in renal transplant recipients in terms of candida infection, there was no significant difference with regard to other infections. Chlamydia infection, reactive changes caused by intrauterine devices and radiation-related changes were not detected in either group. There was a significant

difference between the two groups in terms of atrophic cervicitis. Based on Bethesda 2001 classification, chronic cervicitis and atrophic cervicitis was observed in 10 (12.65%) and 9 (11.39%) patients, respectively. However, there was no significant difference compared to the control group. In transplantation group, 7 patients (8.86%) had LG-SIL, 3 (3.79%) had ASC-US and 1 (1.26%) had HG-SIL. In control group, the numbers are 3 (3.79%), 2 (2.53%) and 0, respectively. The difference between the patient and control groups in terms of LG-SIL results (7 (8.86%) vs 3 (3.79%)) was statistically significant ($p < 0.05$) (Table 1). No additional risk factors were recorded for gynecological cancers in patients in the control group. HPV vaccine was not administered to our patients in the routine before transplantation. There is no practice of this vaccine established in the routine health system in our country.

Discussion

Immunosuppressed renal transplant recipients are at risk in terms of HPV and associated malignancies (especially uterine cervical intraepithelial neoplasia) and some types of infections. These lesions can be investigated by screening methods such as Pap smear, HPV tests and colposcopy before and after the transplantation surgery. Pap smear screening potentially may help recognize cervical preinvasive and invasive lesions. The rate of incidence in these patients is 11% [5]. They have a 3-times higher risk of in-situ cancer incidence compared to the general population [6]. In our study, we did not detect any patients with cervical cancer. Routine cervical screening with Pap smear has shown that there is no increase in invasive cervical cancer incidence. This screening method is easy, low-cost, highly sensitive and specific. This cytological screening test is recommended for all females.

Calcineurin inhibitors (cyclosporine and tacrolimus) potentially induce carcinogenesis through the production of cytokines that regulate TGF- β , metastasis and angiogenesis. All immunosuppressive agents affect the immunological system, reduce the immunological tolerance of neoplastic cells and increase the incidence of infections related to oncogenic viruses (HPV, etc.) that cause DNA damage [7]. Oncogenic HPV types such as HPV-16 are less common in LG-SIL (CIN 1) lesions compared to HG-SIL (CIN 3) lesions. Non-oncogenic HPV types are more common in CIN 1 lesions. The average time necessary for the lesion to progress from ASC-US to LG-SIL or worse and from LG-SIL to HG-SIL or worse is shorter in patients with oncogenic HPV types than those without HPV infection [8]. Randomized trials have shown that detection of high-risk HPV is more sensitive than conventional cytology in screening of cervical intraepithelial neoplasia [9]. A limitation of our study was that the HPV status could not be determined in patient group. We believe that HPV vaccination before the transplantation and an HPV test are mandatory in renal transplant patients to avoid HPV-associated malignancies. In our study, a statistically significant association between the increase in LG-SIL risk and renal transplantation was detected. In another study by Paternoster et al., HG-SIL has been detected in 5 patients and LG-SIL has been detected in another 5 patients in renal transplant recipients [10].

Another important effect of immunosuppression on cervical cytology is on fungal infections. In our study, 14 of 19 patients with candida infection were kidney transplant recipients. There was a significant difference between the two groups in terms of candida infection. However, there was no statistically

significant difference between the two groups with regard to *Trichomonas vaginalis* and bacterial vaginosis infections. It is possible to see the association between renal transplantation and immunosuppression in terms of cervical atrophy. Thinning of squamous epithelium and decrease in mucus production and the use of long-term immunosuppressive drugs lead to atrophy. There was a significant difference between the two groups in terms of atrophy. The presence of this condition and the presence of a shift suggesting bacterial vaginosis in the flora may be due to disturbances in the estrogen cycle.

In conclusion, we predict that kidney transplant recipients are at higher risk for precancerous cervical lesions and cervical cancer development due to immunosuppressive therapy. Our study has also shown significantly increased LG-SIL incidence compared to normal population. Therefore, smear test screening and HPV vaccination should be performed before renal transplantation. The incidence of low-grade squamous intraepithelial lesion was significantly greater in transplant recipients than the general population. Intensive follow-up with Pap smear in transplant recipients is important in the early detection of these lesions. Smear screening and HPV testing should be repeated periodically to detect or prevent precancerous lesions and cervical cancer.

Table 1
Pap Smear Results of Study and Control Patients

VARIABLES	Transplant Group (n:79) %	Control Group (n:79) %	P≤*
Mean Age(y)	38.1	38.3	
Infections			
<i>Trichomonas Vaginalis</i>	1(1.26)	2(2.53)	NS
<i>Candida</i>	14(17.72)	5(6.32)	.0001
<i>Bacterial Vaginosis</i>	11(13.92)	7(8.86)	NS
Bethesda(2001) Findings			
<i>Chronic Cervicitis</i>	10(12.65)	14(17.72)	NS
<i>Atrophic Cervicitis</i>	9(11.39)	5(6.3)	.0001
<i>LG-SIL</i>	7(8.86)	3(3.79)	.05
<i>ASC-US</i>	3(3.79)	2(2.53)	NS
<i>HG-SIL</i>	1(1.26)	0(0)	NS
Abbreviations: ASC-US, atypical squamous cells of undetermined significance; LGSIL, low-grade squamous intraepithelial lesion; HG-SIL, high-grade squamous intraepithelial lesion. *NS, not significant (P > .05).			

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