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Anal dysplasia among solid organ transplant recipients; a cross sectional study



Aimal Khan^{a,*}, Thaer Obaid^a, Lawrence Cetrulo^b, Luanne Force^c,
Roshmi Bhattacharya^a, Richard H. Greenberg^a

^a Einstein Healthcare Network, Department of Surgery, Philadelphia, PA, United States

^b University of Washington, Department of Surgery, Seattle, WA, United States

^c University of Miami, Miami, Department of Surgery, FL, United States

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ABSTRACT

Introduction: The incidence of anal cancer in United States has increased over of the last few decades impacting immunosuppressed populations like solid organ transplant recipients, in particular. The aim of this study was to evaluate the prevalence of anal dysplasia among solid organ transplant patients. We also attempted to identify factors that predispose solid organ transplant recipients to developing anal dysplasia.

Methods and materials: Patients presenting to transplant office for routine care were recruited to participate in the study. All anal cytology specimens were collected using standard anal pap technique. The results were assessed using Bethesda classification. Information on perceived risk factors for development of anal dysplasia among our subjects was obtained. **Results:** Among 80 patients approached, 47 agreed to participate in the study. Of all the samples 19.1% had an inadequate amount of specimen to perform any analysis. Dysplastic cells were found in 10.5% of the specimens available for analysis. We were not able to identify any risk factors including age, gender distribution, smoking, and duration of immunosuppression that were statistically significant different between patients with anal dysplasia versus those without anal dysplasia.

Conclusions: The rate of anal dysplasia detectable on cytology is high enough to warrant anal dysplasia screening in transplant recipients, which can then be followed up with high-resolution anoscopy with biopsy. Defining a cohort of patients among solid organ transplant recipients who are at an increased risk for the development of anal dysplasia mandating screening continues to be a challenge.

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* Corresponding author.

E-mail: aimalkhan42@gmail.com (A. Khan).

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Displasia anal entre receptores de transplantes de órgãos sólidos – um estudo transversal

R E S U M O

Palavras-chave:

Câncer anal
Triagem de displasia anal
Imunossuprimido
Receptores de transplantes

Introdução: A incidência de câncer anal nos Estados Unidos aumentou nas últimas décadas, afetando populações imunossuprimidas, especialmente receptores de órgãos sólidos. O objetivo deste estudo foi avaliar a prevalência de displasia anal entre pacientes que receberam transplante de órgãos sólidos. Os autores buscaram identificar fatores que predisponem os receptores de transplante de órgãos sólidos a desenvolverem displasia anal.

Métodos e materiais: Pacientes que se apresentaram ao consultório de transplante para acompanhamento de rotina foram recrutados para participar do estudo. Todos os espécimes de citologia foram coletados usando a técnica padrão de Papanicolau anal. Os resultados foram avaliados usando a classificação de Bethesda. Foram coletados dados sobre os fatores de risco percebidos para o desenvolvimento de displasia anal entre os participantes.

Resultados: Dos 80 pacientes abordados, 47 concordaram em participar do estudo. Do total de amostras, 19,1% tinham uma quantidade inadequada para realizar qualquer análise. Células displásicas foram encontradas em 10,5% dos espécimes disponíveis para análise. Não foi possível identificar quaisquer fatores de risco, incluindo idade, distribuição de gênero, tabagismo e duração da imunossupressão, que foram estatisticamente diferentes entre pacientes com displasia anal e aqueles sem displasia anal.

Conclusões: A taxa de displasia anal detectável na citologia é alta o suficiente para justificar a triagem em receptores de transplante, que pode então ser acompanhada com anoscopia de alta resolução com biópsia. A definição de triagem para uma coorte de pacientes entre os receptores de transplantes de órgãos sólidos que apresentam risco aumentado para o desenvolvimento displasia anal continua a ser um desafio.

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Introduction

Over the past two decades, the incidence of Human Papillomavirus (HPV) related Squamous Cell Cancer of the Anus (SCCA) in the United States has increased by 96% in men and 39% in women¹ with a cumulative incidence estimated to be 35 cases per 100,000.² Immunosuppressed solid organ transplant recipients are at a higher risk of HPV-related cancers compared to the general population.^{3–5} Anal cancer is the second most frequent HPV-related tumor developing in these patients after genital cancers.⁶ As solid-organ transplant recipients' survival increases, anal carcinoma will pose a significant health risk to this growing cohort.

The progression of anal dysplasia into SCCA is well established in literature. In addition to the high incidence of anal dysplasia, Immunocompromised patients are also much more likely to undergo malignant transformation of their anal dysplasia.⁷ Despite the increasing burden of this cancer, there is a lack of structured screening program to detect anal dysplasia amongst transplant recipients. The American Society of Transplantation currently recommends regular pelvic examinations and cytologic studies only in women with kidney transplants who present with external anogenital lesions.⁸ No official screening guidelines exist for anal dysplasia in solid organ transplant recipients due to lack of data supporting such screening program.

In this pilot study, we investigated the prevalence of anal dysplasia amongst solid-organ transplant recipients and an attempt to identify factors that may place transplant recipients at increased risk of developing anal dysplasia.

Methods and materials

Study setting

Einstein Medical Center is a tertiary healthcare center in Philadelphia where solid organ transplants have been performed since 1960. IRB approval was obtained to prospectively recruit 50 solid organ transplant patients for obtaining anal cytology specimens. The study was funded with a grant from the Albert Einstein Society.

Inclusion and exclusion criteria

Solid organ transplant recipients (liver, kidney and pancreas) that were at least one year out from their surgery and were on their immunosuppressive medications were approached for enrollment into the study during their routine visits the transplant office. The enrollment period lasted from March 2016 through December 2016, and no financial incentives were employed. Patients with a history of prior failed transplant, surgical excision of an anal mass, immunocompromised conditions (besides transplant-related immunosuppression), and

prior anal pap smear for any reason, were excluded from the study.

Sample and data collection

A single nurse collected all pap smears during the study visits. Informed consents were obtained from the patients to undergo screening for anal dysplasia using Pap smear. The collection method consisted of placing participants in the left lateral decubitus position for a complete perianal examination. Polyester tipped swab moistened in tap water was then inserted into the anal canal, and the sample collected from the (transition zone) junction of the anus and rectum. Each swab was placed into liquid-based cytology media for storage and sent out to Quest Diagnostics (Secaucus, NJ) for cytopathologic evaluation and grading. All samples were graded according to the modified 2001 Bethesda guidelines for cervical cytology diagnosis to evaluate each specimen as follows: normal; ASCUS (atypical squamous cells of unknown significance); ASC-H (Atypical Squamous Cells-cannot exclude High-grade SIL); Low-Grade SIL (LGSIL); HGSIL; or squamous cell carcinoma. During the visit, patients were also given a questionnaire to fill out. Questions about their demographic, social history, medical history, and sexual history were included. To supplement this data, we collected information from their medical records regarding: date of transplantation(s), rejection episodes, immunosuppressive regimen, and any previous cancer diagnoses and treatments.

Data analysis

All data analysis was performed on STATA 13 software. All data was reported as (mean \pm standard deviation). Pearson's Chi-Square was used for comparing percentages. Fischer's exact test and Student's t-test was used to compare means. *p*-value of less than 0.05 was considered significant. A flow chart of study is given below (Fig. 1).

Results

Patient demographics and transplant characteristics

Among 80 solid organ transplant recipients approached for participation, 47 were recruited into the study. The mean age of our study participants was 59.3 ± 10.7 years (mean \pm SD).

Table 1 – Comparison of our study population characteristics with institutional transplant database.

Characteristics	Study participants (n = 47)	Institutional transplant database (n = 2810)
Mean age (in years)	59.8	53
Gender		
Male	24 (51.1%)	1781 (63.4%)
Female	23 (48.9%)	1029 (36.6%)
Race		
AA	23 (48.9%)	898 (32%)
Other	19 (51%)	1912 (68%)
Type of transplant		
Kidney	38 (80.9%)	1725 (61.4%)
Kidney/pancreas	2 (4.3%)	59 (2.1%)
Kidney/liver	7 (14.9%)	53 (1.9%)
Liver	0	962 (34.2%)
Pancreas	0	11 (0.4%)

AA, African-American; other: Latino, Caucasian, Haitian, Indian and West Indian.

Our study population was almost equally distributed between two sexes with 48.9% (*n* = 23) women and 51.1% (*n* = 24) men. African-Americans comprised the largest ethnic group at 48.9% (*n* = 23), followed by Latinos at 14.9% (*n* = 7), Caucasian at 12.8% (*n* = 6), Haitian at 6.4% (*n* = 3), Indian at 4.3% (*n* = 2), and West Indian at 2.1% (*n* = 1). Ethnicity data was not available for 10.6% (*n* = 5) of the study participants.

Of all the study participants, 80.9% (*n* = 38) patients had undergone only kidney transplant, 14.9% (*n* = 7) had both kidney and liver transplants performed whereas only 4.3% (*n* = 2) patients underwent kidney and pancreas transplant. Almost all of our patients were on a combination of prednisone, Cellcept, and Tacrolimus for their immunosuppression. Cyclosporine was used for immunosuppression in two of our patients; Leflunomide was employed in two patients, Everolimus in one patient and azathioprine in one patient.

Of the 47 study participants, 31.9% (*n* = 15) had some history of smoking with 10.6% (*n* = 5) of them being current smokers. Chart review revealed a history of prostate, renal cell carcinoma and non-small cell lung in 6.4% (*n* = 3) of our patients. Table 1 detailing general characteristics of our study population compared to the institutional transplant database is listed below.

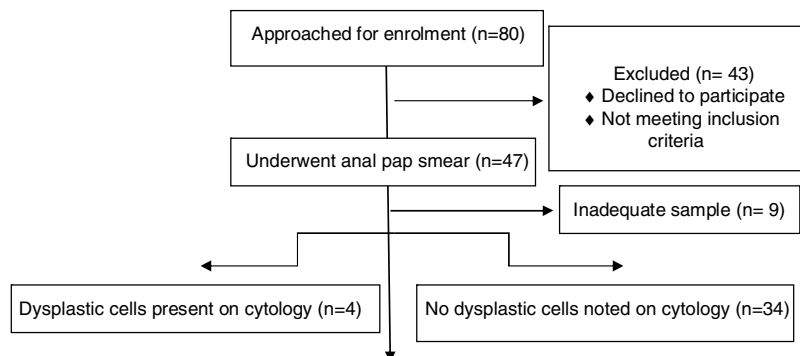


Fig. 1 – Flow chart of the study.

Anal cytology results

Of the 47 anal cytology results available for analysis, 19.1% ($n=9$) had an inadequate amount of specimen to perform any analysis and were excluded from the study. Of the remaining 38 samples, 10.5% ($n=4$) demonstrated evidence of dysplastic cells. The majority of the samples, 89.5% ($n=34$) were negative for any evidence of dysplasia. Of the samples positive for dysplasia, 7.9% ($n=3$) had ASCUS (Atypical Squamous Cells of Unknown Significance) and 2.6% ($n=1$) had HSIL (High Grade Squamous Intraepithelial Neoplasia). Dysplasia was found in two kidney transplant patients, one kidney/pancreas transplant and one kidney/liver transplant.

Risk factors associated with dysplasia

The patients with dysplastic cells were slightly older than the overall sample population (mean age 62.4 ± 9.6 years vs. 59.5 ± 10.9 years). Gender distribution in the dysplasia group consisted of 50% female and 50% male patients. Average duration from the day of transplant to Pap smear testing was 1357 ± 473.6 days (mean \pm SD) in patients with positive results and 2522.4 ± 2150.2 days (mean \pm SD) in patients with negative results. Excluding hepatitis B and C, only one patient with atypical cells had a history of a Sexually Transmitted Disease (STD). None of these differences between the two groups reached statistical significance. A detailed comparison of the two groups of patients with and without atypical cells is listed below (Table 2).

Discussion

In our study we found in dysplastic cells in 10.5% of anal cytology specimens collected from solid organ transplant recipients during office visits. We were not able to identify any characteristics including age, gender distribution, smoking, and duration of immunosuppression that had statistically significant differences between patients with anal dysplasia and those without.

Previous studies have reported anal dysplasia rates of 18%–20% amongst solid organ transplant recipient, which is higher than our reported rate of 10.5%.^{9,10} In our study, we found high-grade dysplasia in only one patient (2.6%), compared to previously reported numbers of 5%.^{9,10} These differences may be attributed to the use of anal cytology alone for detecting anal dysplasia in our population compared to anal cytology in conjunction with High-Resolution Anoscopy (HRA) and biopsy in previous studies. Ogilvie et al. reported an overall rate of anal dysplasia in 18% of their kidney transplant recipient population. However, employing only anal cytology, they only had 5.88% (2 out of 34) positive samples of all collected specimens. Despite the differences of anal dysplasia rates between our patients and previous studies, a rate of 10.5% still confers a significant risk, as anal dysplasia is more likely to undergo malignant transformation in this population compared to general public.⁹

The limited sensitivity of cytology in detecting anal dysplasia may also have been a factor the reported low rate of anal dysplasia in our population. Although there is a lack of data assessing the sensitivity of anal cytology in solid organ transplant recipients, numerous studies exist looking at this among HIV patient population. Multiple authors have debated whether cytology itself is sensitive by itself to detect majority of dysplastic cells. In the HIV population the use of anal cytology does have a high reported sensitivity for predicting dysplasia on biopsy (69%–98%).^{11–13} However there are some reports that suggest that the pap smear is inadequate to detect dysplasia in high risk HIV populations as its only sensitivity is 58%.¹⁴ Most authors therefore recommend that HRA and biopsy should follow any abnormal cytological findings.^{15,16} A recent report demonstrated a 95% positive predictive value when any abnormal cytology specimen is used to predict any degree of dysplasia on biopsy.¹⁷

We were unable to identify any specific risk factors associated with the presence of dysplastic cells in our solid organ transplant recipient population. Among the risk factors assessed were age, gender distribution, smoking, prior history of Hepatitis B or C, and duration of immunosuppression. These

Table 2 – Risk factors for presence of atypical cell on anal Pap smear.

Risk factor	Dysplastic cells on pap smear ($n=4$)	No dysplastic cell on pap smear ($n=34$)	p-value <0.05
Mean age (years)	62.4	59.5	No ^a
Male gender	2	17	No ^b
African American race	2	15	No ^b
Average duration of immunosuppression days	1357	2522.4	No ^b
Hx of rejection episode(s)	0	7	No ^b
History of prior cancers	1	1	No ^b
History of prior STD (including Hepatitis B and C)	1	6	No ^b
History of prior STD (excluding Hepatitis B and C)	1	0	No ^b
Tobacco use (current or prior)	2	10	No ^a

$p < 0.05$ considered significant.

^a Fischer's exact test.

^b t-test.

risk factors did not differ between patients with and without anal dysplasia. Data on potentially significant factors such as multiple sexual partners or men having sex with men were not collected, as most patients did not provide this information on the questionnaire. We believe that sexual history is an essential factor and should be addressed in any future study by interview style questions rather than a questionnaire.

Much can be learned about anal dysplasia screening in transplant patients from similar screening programs instituted in HIV positive individuals. Despite the lack of national guideline for anal dysplasia screening in HIV positive individuals, centers with appropriate expertise are currently screening high-risk populations with anal pap smears and/or High-Resolution Anoscopy (HRA) with good results.^{18,19} Institutions like the US Department of Veterans Affairs (VA) and The City of San Francisco have started screening programs for anal dysplasia among HIV patients with excellent results.^{20,21} These screening programs are supported by studies have shown that early detection of AIN may be beneficial in identification and treatment of small, localized lesions which may lead to lower morbidity and mortality.²¹ Moreover, the cost-effectiveness of these anal screenings has been found to be comparable to standard cervical cancer screening in cost per life-year saved.^{5,22,23}

There are several limitations to our study. First the relatively small sample size may not represent the general solid organ transplant recipient population. Second, it is debatable whether anal cytology has the sensitivity required for detecting anal dysplasia. This brings up the possibility that our designated nurse collected a large number of inadequate samples. The rate of adequately collected samples in our study was 19.1% which represents one of the challenges of anal cytology being used as a screening tool. Other authors circumvented this by repeating the sampling in their patients. We, however, had not budgeted for this in our study. Furthermore, pertinent data regarding sexual history were not collected during the patient encounter. Anal intercourse is identified as a significant risk factor in the development of dysplasia and will be addressed in our future study. Despite its limitations, we believe that anal cytology provides a valuable and cost effective tool to identify patients with dysplasia among solid organ transplant recipients. To implement a screening program, it has to be cost-effective, reliable and convenient for the patient. HRA with biopsy is a preferable option; however, it is an invasive procedure that is not convenient as a screening tool; Pap smear, on the other hand, is a quick, noninvasive procedure that can be performed in the office.

We believe that training nurses and staff working in the transplant offices to perform anal pap smears, with the option of referral to a colorectal surgeon, is a viable option for a long-term screening program.

Conclusion

The rate of anal dysplasia detectable with cytology is high enough to warrant anal dysplasia screening in transplant recipients. Screening of high-risk patients using Pap smear is a convenient yet cost-effective way for early detection and treatment of anal dysplasia. However, defining the right cohort

among the transplant recipients and the sensitivity of anal dysplasia continues to be a challenge that needs further investigation.

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Disclosure information

None.

Conflicts of interest

The authors declare no conflicts of interest.

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