Screening-Related Factors in Anal Canal Lesions in HIV-Positive Patients

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Abstract

The incidence of anal dysplasia in HIV-positive men who have sex with men (MSM) is increasing. This dysplasia is described as either high-grade anal intraepithelial (HAIN) or low-grade anal intraepithelial (LAIN). Anal squamous cell carcinoma (ASCC) is more frequent in HIV-positive patients and is related to human papillomavirus (HPV) infections, conditions of low systemic immunity and long use of highly active antiretroviral therapy. The anal Pap smear protocol and high-resolution anoscopy seem to be effective for screening for anal dysplasia and early anal cancer. The aim of this study was to identify some factors that could raise the risk of HAIN and LAIN among HIV-positive patients. We evaluated 134 HIV-positive and HIV-negative patients who had previously had anal intercourse, at CRT/AIDS São Paulo from October 2011 to March 2012. HIV-negative patients and HIV-positive patients without recent CD4 lymphocyte counts were excluded. All of the patients underwent the anal Pap smear protocol and high-resolution anoscopy. The anal lesions were treated with 90% trichloroacetic acid (TCA) and 5% imiquimod for 12 weeks. The patients with residual lesions were operated. The statistical analysis was performed using Student’s t test and the significance level was set at less than 5%. 101 HIV-positive patients were evaluated (81 males and 10 females), among whom 31 had warts and 3 had LAIN and warts. One patient was operated after the treatment with 90% TCA and 5% imiquimod. In conclusion, HIV-positive patients with anal warts presented low CD4 lymphocyte counts and anal dysplasia.

Keywords: Acquired immunodeficiency syndrome; Anal canal; Carcinoma; Squamous cell; HIV; Human papilloma virus; Trichloroacetic acid; Imiquimod

Introduction

The incidence of anal squamous cell carcinoma (ASCC) and anal dysplasia is currently increasing significantly. This dysplasia is described as either high-grade anal intraepithelial (HAIN) or low-grade anal intraepithelial (LAIN). Factors that are important in such cases include epidemic infection caused by the human immunodeficiency virus (HIV), conditions of low systemic immunity, long use of highly active antiretroviral therapy (HAART), coexistence with preceding anal intercourse (i.e. among men who have with men, MSM) and infection caused by the human papillomavirus (HPV) [1].

Infection caused by HPV is more common in HIV-positive patients than in HIV-negative patients [2]. HIV infection has changed the epidemiological profile of ASCC [3]. Previously, ASCC was evident in elderly female patients, whereas nowadays young male patients with this cancer are seen [3]. ASCC is now considered to be directly related to sexual transmitted disease, since it has been shown to have a close relationship with HPV infection [4].

Thus HIV-positive patients have less tolerance and lower response to chemotherapy and radiotherapy prescribed for ASCC [5] than do HIV-negative patients. However the data is controversial, Abramowitz et al. found similar rates of toxicity during chemotherapy for HIV-positive and negative patients with ASCC [6]. The HAART administration during chemotherapy may enable the development of antitumor responses and does not appear to reduce cancer risk overall [7].

The screening procedures for LAIN and HAIN include anal Pap smears and high-resolution anoscopy [8]. These seem to be effective in screening for anal dysplasia and early anal cancer. Recent studies have suggested that screening programs are cost-effective among the population that previously has had anal intercourse [9,10]. The aim of the present study was to identify some factors that could raise the risk of HAIN and LAIN among HIV-positive patients [1].

Material and Method

The study is a cross-sectional descriptive case detection, conducted at two study groups: HIV-positive and HIV-negative patients. We evaluated 134 HIV-positive and HIV-negative patients who had previously had anal intercourse, at CRT/AIDS São Paulo-Brazil from October 2011 to March 2012. The study was approved by the Board of Ethics in Research of CRT/AIDS São Paulo. All of these patients had been referred to undergo the anal lesion screening protocol by oncologists. These patients had previously had anal intercourse and either were or were not infected with HIV. The HIV-positive patients were under treatment with HAART.

The screening consisted firstly of a general clinical evaluation and this was followed by an anal Pap smear and high-resolution anoscopy. The anal Pap smear was collected from the anal canal using a cytobrush, the swab was rotated in a cone-shaped arc against the anal canal for 30 seconds smeared onto a glass slide and immediately fixed in ethanol for cytological evaluation [2,11]. The specimens were analyzed by a pathologist and reviewed by a senior pathologist. They were classified as normal, atypical squamous cells of undetermined significance (ASCUS), LAIN and HAIN [12].

The high-resolution anoscopy was performed after topical

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The patients with anal warts that were identified during the anoscopy were treated with 90% trichloroacetic acid (TCA) and 5% imiquimod for 12 weeks [14,15]. One patient had a residual lesion after the clinical treatment and was operated. His biopsy showed low-grade dysplasia and his evolution was good, without any recurrence.

Results

11 women and 123 men were evaluated. The mean age among the HIV-negative patients was 34.48 years and the mean age among the HIV-positive patients was 44.51 years. One woman was HIV-negative and ten were HIV-positive. We had 32 HIV-negative men and 91 HIV-positive men. One HIV-negative man showed LAIN and warts during high-resolution anoscopy. Nine HIV-negative men had normal Pap smears but showed warts during high-resolution anoscopy.

31 HIV-positive patients had warts during high-resolution anoscopy. Three of them were women and 28 were men. Three HIV-positive male patients had LAIN and warts during high-resolution anoscopy; one of them had a residual lesion after the clinical treatment and was operated. The pathologist confirmed that the latter case consisted of LAIN, after the surgery. Two HIV-positive patients had LAIN, but the high-resolution anoscopy was normal. These patients were subsequently reevaluated every six months.

We did not identify any cases of ASCUS, HAIN or ASCC. All of the results were analyzed by means of the Student’s parametric test, using the SPSS software in its version 9.0, and were found to be statistically significant at the 5% level.

Analysis on the HIV-positive individuals showed that low serum CD4 T lymphocyte counts were a determining factor for the appearance of anal warts. The mean CD4 T lymphocyte count for the patients without warts was 701 and the mean CD4 T lymphocyte count for the patients with anal warts was 454.67 (p=0.002). There was no statistical difference among the patients with anal warts with regard to the HIV viral load (p=0.196). There was no statistical difference among the mean CD4 T lymphocyte counts with regard to the Pap smear results (p=0.408). The evaluation of LAIN among HIV-positive patients with anal warts was statistically significant (p=0.004).

We estimated the statistical relationships between the variables in order to analyze the impact of CD4 T lymphocyte count on the presence of anal warts. The presence of anal warts was a binary variable, i.e. the values were taken to be 0 or 1, such that 0 was defined as absence of anal warts and 1 as presence of anal warts. Because of the nature of this variable, it was decided to model the relationship between the variables using a set of models of discrete dependent variables, which in a special case applies to binary values. Probit and logit are models of this nature.

One big problem when estimating a simple linear relationship for binary dependent variables is that the forecasted value may lie outside of the interval from 0 to 1. The abovementioned models solve this problem by using the independent variable within a cumulative distribution function for the independent variable. Probit assumes a cumulative distribution function for the standard normal distribution, and its functional form is defined as:

\[ \Pr(y_i|x_i, \beta) = 1 - \Phi(-x_i\beta) = O(x_i\beta) \]  

(1)

On the other hand, logit assumes a cumulative distribution function for the logistic distribution [16], and its functional form is given by:

\[ \Pr(y_i|x_i, \beta) = \frac{e^{x_i\beta}}{1 + e^{x_i\beta}} \]

(2)

These two models were estimated (i.e. the values for \( \beta \) that best fitted the data were determined) with and without a constant term, using the STATA software in its version 12. When present, the constant term represented the minimum level for the dependent variable. The latter was dubbed logit 1 and probit 1 and the former, logit 2 and probit 2. The results from the estimations are presented in Table 1.

The most important result in Table 1 is that there was a negative and statistically significant relationship between CD4 T lymphocyte count and the presence of anal warts. Hence, higher CD4 T lymphocyte counts should diminish the chances of observing warts in the patient. The presence of a constant was statistically significant at the level of 5% in the logit model and at the level of 6% in the probit model (shown in the column labeled “P-value”). Since in both cases the constant seems to add explanatory power, we deem the models to be valid. Another important point to take into consideration is that their values do not translate directly into the values of the dependent variable, but rather, should be plugged into equations (1) and (2) to produce the probability that the patient will present anal warts.

In this regard, since the functions appear on the right-handside of equations (1) and (2), the impact of the independent variable (anal warts) on the dependent variable (CD4 T lymphocyte count) does not follow directly from the estimated coefficients. In these cases, the traditional approach for determining the impact is to calculate the marginal effects, which is done by deriving each function in relation to the independent variable.

It is important to remember that the numerical result from this depends on the point estimate of the independent variable. Here, we took two values: 454.67, which was the mean serum CD4 T lymphocyte count value found in HIV-positive patients with anal warts; and 625.17, which was the mean serum CD4 T lymphocyte count value found in the HIV-positive patient group. These outcomes are presented in Table 2.

| Model | Coefficient | Estimate | Standard error | P-value | McFaddenR-squared |
|-------|-------------|----------|----------------|---------|------------------|
| Logit1 | CD4 | -0.0017 | 0.00 | 0.00 | - |
| Logit2 | CD4 | -0.0038 | 0.00 | 0.00 | - |
| Probit1 | CD4 | -0.0010 | 0.00 | 0.00 | - |
| Probit2 | CD4 | -0.0021 | 0.00 | 0.00 | - |

Table 1: Estimation of probit and logit models for CD4 T lymphocyte counts in HIV-positive patients

| Model | Marginal effect | Standard error | P-value | Point estimate |
|-------|----------------|----------------|---------|----------------|
| Logit1 | -0.0003682 | 0.00 | 0.00 | 454.67 |
| Logit2 | -0.00006904 | 0.00 | 0.00 | 454.67 |
| Probit1 | -0.00006838 | 0.00 | 0.00 | 625.17 |
| Probit2 | -0.00003729 | 0.00 | 0.00 | 625.17 |

Table 2: Marginal effects of probit and logit models on CD4 T lymphocyte values in HIV-positive patients
Discussion

We identified low CD4 T lymphocyte count as an important factor relating to appearance of anal warts. Presence of this finding stimulated a broad statistical analysis that showed its impact on anal warts. Other factors were not statistically different, such as HIV viral load in relation to presence of anal warts; and CD4 T lymphocyte count in relation to Pap smear results.

It has been suggested that prolonged administration of HAART provides long-term protection against the development of anal dysplasia [17]. Only one patient had a residual anal lesion after the topical treatment, and this patient then underwent surgery. This patient could have had HAIN or ASCC, as described by Schlecht et al. but fortunately this did not happen [18]. We did not find ASCUS in our sample.

Use of 5% imiquimod for 12 to 16 weeks had regressive action on anal dysplasia, decreased recurrence after treatment and had anti-HPV action. Our data showed better results from treatments using 5% imiquimod than reported in the literature: previous data showed that the expected clinical response would be around 48% [19].

The incidence of HAIN and LAIN on Pap smears from MSM has not been described as high, but this was not found in our study. For all that, we had a senior pathologist reviewing our entire sample and the technique performed for the swab was the same as described in the literature [1,2,11]. The common factor found was that all HIV-positive patients should be screened for anal lesions [2] and that, if available, hybrid capture data for HPV should also be gathered [20,21]. Recent studies have elucidated that detection of HPV oncogenes could be specific for detection of HAIN and LAIN [22].

Alterations seen on Pap smears and through high-resolution anoscopy, and presence of HPV infection, are known to be the major predictive factors for HAIN and justify screening for these patients [23]. High-resolution anoscopy provides additional evaluation even for patients with negative Pap smears. One of the possible reasons for the high frequency of findings of negative Pap smears in our study is that the samples were not collected under direct viewing, as performed in cervical cytological evaluations, for which the screening programs are well-established [24-27].

Conclusion

In conclusion, the low serum CD4 T lymphocyte counts were an important factor in relation to the presence of anal dysplasia and warts in HIV-positive patients.

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References

1. Arain S, Waits AE, Thomas P, Bose S (2005) The Anal Pap Smear: Cytomorphology of squamous intraepithelial lesions. Cytology J 2: 4.
2. Weis SE, Vecino I, Pogoda JM, Susa JS, Nevoit J, et al. (2011) Prevalence of anal intraepithelial neoplasia defined by anal cytology screening and high-resolution anoscopy in a primary care population of HIV-infected men and women. Dis Colon Rectum 54: 433-441.
3. Gervaz P, Calmy A, Durnishi Y, Allal AS, Morel P (2011) Squamous cell carcinoma of the anus-an opportunistic cancer in HIV-positive male homosexuals. World J Gastroenterol 17: 2987-2991.
4. Nadal SR, Cruz SHA (2009) Seguimento dos doentes soropositivos e soronegativos para o HIV com carcinoma espinocelular anal. Rev Bras Coloproct 29: 404-407.
5. Munoz-Bongrand N, Poghosyan T, Zohar S, Gerard L, Chirica M, et al. (2011) Anal carcinoma in HIV-infected patients in the era of antiretroviral therapy: a comparative study. Dis Colon Rectum 54: 729-735.
6. Abramowitz L, Mathieu N, Roudot-Thoraval F, Lemarchand N, Bauer P, et al. (2009) Epidemiologic cancer prognosis comparison among HIV+ and HIV- patients. Aliment Pharmacol Ther 30: 414-421.
7. Hessol NA, Pipkin S, Schwarz S, Cress RD, Bacchetti P, et al. (2007) The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. Am J Epidemiol 165: 1143-1153.
8. Gimenez F, Costa-e-Silva IT, Daumas A, Araujo JD, Medeiros SG, et al. (2011) The value of high-resolution anoscopy in the diagnosis of anal cancer precursor lesions in HIV-positive patients. Arq Gastroenterol 48: 136-145.
9. Lam JM, Hoch JS, Timnouth J, Sano M, Raboud J, et al. (2011) Cost-effectiveness of screening for anal precancers in HIV-positive men. AIDS 25: 635-642.
10. Park IU, Palefsky JM (2010) Evaluation and Management of Anal Intraepithelial Neoplasia in HIV-Negative and HIV-Positive Men Who Have Sex with Men. Curr Infect Dis Rep 12: 126-133.
11. Moscicki AB, Hills NK, Shiboski S, Darragh TM, Jay N, et al. (1999) Risk factors for abnormal anal cytology in young heterosexual women. Cancer Epidemiol Biomarkers Prev 8: 173-178.
12. Bakotic WL, Willis D, Birdsong G, Tadros TS (2005) Anal cytology in an HIV-positive population: a retrospective analysis. Acta Cytol 49: 163-168.
13. Walker P, Dexeus S, De Palo G, Barrasso R, Campion M, et al. (2003) International terminology of colposcopy: an updated report from the International Federation for Cervical Pathology and Colposcopy. Obstet Gynecol 101: 176-177.
14. Manzione CR, Formiga FB, Nadal SR (2010) Uso do Imiquimode tópico no tratamento da infecção anal pelo papilomavírus humano. Rev Soc Bras Coloproct 30: 92-94.
15. Fox PA, Nathan M, Francis N, Singh N, Weir J, et al. (2010) A double-blind, randomized controlled trial of the use of imiquimod cream for the treatment of anal canal high-grade anal intraepithelial neoplasia in HIV-positive MSM on HAART, with long-term follow-up data including the use of open-label imiquimod. AIDS 24: 2331-2335.
16. Wooldridge JM (2010) Econometric analysis of cross section and panel data. MIT Press, Cambridge.
17. de Pokomandy A, Rouleau D, Ghattas G, Trottier H, Vézina S, et al. (2011) HAART and progression to high-grade anal intraepithelial neoplasia in men who have sex with men and are infected with HIV. Clin Infect Dis 52: 1174-1181.
18. Schlecht HP, Fugelso DK, Murphy RK, Wagner KT, Dowekio JP, et al. (2010) Frequency of occult high-grade squamous intraepithelial neoplasia and invasive cancer within anal condylomata in men who have sex with men. Clin Infect Dis 51: 107-110.
19. Steele SR, Varma MG, Melton GB, Rosa HM, Rafferty JF, et al. (2012) Practice parameters for anal squamous neoplasms. Dis Colon Rectum 55: 735-749.
20. Guimarães MD, Grinsztejn B, Melo VH, Rocha GM, Campos LN, et al. (2011) Anal HPV prevalence and associated factors among HIV-seropositive men under antiretroviral treatment in Brazil. J Acquir Immune Defic Syndr 57 Suppl 3: S217-S224.
21. Indinnimeo M, d’Ettorre G, Fiore A, Cецcarelli G, Ciardi A, et al. (2011)
Diagnosis of anal human papillomavirus infection: polymerase chain reaction or cytology? Int J Infect Dis 15: e232-235.

22. Silling S, Kreuter A, Hellmich M, Swoboda J, Pfister H, et al. (2012) Human papillomavirus oncogene mRNA testing for the detection of anal dysplasia in HIV-positive men who have sex with men. J Clin Virol 53: 325-331.

23. Swedish KA, Lee EQ, Goldstone SE (2011) The changing picture of high-grade anal intraepithelial neoplasia in men who have sex with men: the effects of 10 years of experience performing high-resolution anoscopy. Dis Colon Rectum 54: 1003-1007.

24. Lee EQ, Goldstone SE (2011) Predictors of anal dysplasia in men who have sex with men with benign cytology. Dis Colon Rectum 54: 347-351.

25. Darragh TM, Winkler B (2011) Anal cancer and cervical cancer screening: key differences. Cancer Cytopathol 119: 5-19.

26. Bean SM, Chhieng DC (2010) Anal-rectal cytology: a review. Diagn Cytopathol 38: 538-546.

27. Koppe DC, Bandeira CB, Rosa MR, Cambruzzi E, Meurer L, et al. (2011) Prevalence of anal intraepithelial neoplasia in women with genital neoplasia. Dis Colon Rectum 54: 442-445.