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Review Article

TRACKING PRECURSOR LESIONS OF ANAL SQUAMOUS CELL CARCINOMA IN INDIVIDUALS WITH HIV

Rastreamento de lesões precursoras do carcinoma espino-celular anal em indivíduos portadores do HIV

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ABSTRACT - ***Introduction*** - squamous cell carcinoma of the anal canal is a disease that affects the middle-aged adults and accounts for 4% of cancers of the gastrointestinal tract below. In the general population the incidence is 1 in 100,000, and among men who have sex with men the incidence is 35 per 100,000 inhabitants, those with HIV have doubled this risk (70 per 100,000 inhabitants). ***Methods*** - We performed literature review in consultation with periodic Medline / Pubmed, Lilacs and Scielo crossing Trackingm, Precancerous conditions, Anus neoplasms and HIV descriptors. Besides the review,was added to this work the authors' personal experiences, and obtained at the Department of Gastroenterology - Surgical Division, in ICESP - Cancer Institute of the State of São Paulo Octavio Frias de Oliveira, in Department of Diseases Infectious - House of AIDS and in the Department of Coloproctology, Hospital das Clinicas, University of São Paulo, Brazil. ***Conclusions*** - HIV + is a major risk factor in developing squamous cell carcinoma anal in individuals infected with HPV. The evaluation of these patients should not restrict itself to the eradication of warts, but mainly include the screening of subclinical dysplastic lesions potentially neoplastic. Despite the screening methods are still not ideal, the great benefit of screening is based on the fact offer closely monitored, making possible the prevention or detection of increasingly early anal squamous cell carcinoma.

HEADINGS - Tracking. Premalignant lesions. Anus neoplasms. HIV.

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RESUMO – ***Introdução*** – O carcinoma espino-celular do canal anal é doença que atinge os adultos de meia idade e corresponde a 4% dos cânceres do trato gastrointestinal baixo. Na população geral a incidência é de 1 em 100.000 habitantes, e entre os homens que fazem sexo com homens essa incidência atinge 35 por 100.000 habitantes, sendo que os portadores de HIV têm esse risco duplicado (70 por 100.000 habitantes). ***Método*** – Foi realizada revisão da literatura com consulta nos periódicos das bases Medline/Pubmed, Scielo e Lilacs cruzando os descritores Rastreamento, Lesões pré-cancerosas, Neoplasias do ânus e HIV. Além da revisão bibliográfica, foi adicionada a este trabalho a experiência pessoal dos autores, e a obtida no Departamento de Gastroenterologia - Divisão Cirúrgica, no ICESP – Instituto do Câncer do Estado de São Paulo Octávio Frias de Oliveira, no Departamento de Moléstias Infeciosas – Casa da AIDS e no Serviço de Coloproctologia do Hospital das Clínicas da Universidade de São Paulo, SP, Brasil. ***Conclusões*** - HIV+ é um grande fator de risco no desenvolvimento de carcinoma espino-celular anal em indivíduos infectados por HPV. A avaliação desses pacientes não deve se restringir à erradicação de condilomas, mas principalmente incluir o rastreamento de lesões displásicas subclínicas potencialmente neoplásicas. Apesar dos métodos de rastreamento ainda não serem ideais, o grande benefício do rastreamento baseia-se no fato de oferecer acompanhamento rigoroso, tornando possível à prevenção ou detecção cada vez mais precoce do carcinoma espino-celular anal.

DESCRITORES - Rastreamento. Lesões pré-cancerosas. Neoplasias do ânus. HIV.

INTRODUCTION

The squamous cell carcinoma (SCC) of the anal canal is a disease that affects the middle-aged adults and accounts for 4% of cancers of the gastrointestinal tract below. In the general population the incidence is 1 in 100,000, and among men who have sex with men the incidence is 35 per 100,000 inhabitants, those with HIV have doubled this risk (70 per 100,000)[1].

The SCC is closely associated with chronic infection with human papilloma virus (HPV), a state of immunosuppression (HIV positive individuals in transplant using immunosuppressive drugs, etc.), receptive anal intercourse and personal history of cancer or dysplasia of high-grade cervical and / or vulva[7].

In analogy to cervical cancer, cancer of the anal canal is preceded by precancerous lesions termed anal intraepithelial neoplasia (AIN) or simply anal dysplasia. The cytological examination of the anal canal identifies and classifies these lesions in low grade dysplasia (corresponding to an AIN) or high grade (corresponding to AIN 2 and 3). The greater the degree of dysplasia, the greater the risk of injury to develop cancer[13].

METHOD

Literature review was conducted in consultation with periodic Medline / Pubmed, Lilacs and Scielo crossing Tracking, Premalignant lesions, Anus neoplasms, HIV descriptors. Besides the review, was added to this work the authors' personal experiences, and obtained at the Department of Gastroenterology - Surgical Division, in ICESP - Cancer Institute of the State of São Paulo Octavio Frias de Oliveira, in Infectious Diseases Department - House and AIDS Services of Coloproctology, Hospital das Clinicas, University of São Paulo, Brazil.

In a prospective study performed by the authors, 250 male subjects with mean age 41 years and HIV positive were consecutively subjected to a screening program, regardless of their symptoms. The frequency of anal dysplasia observed was 70%, being higher in those who had condyloma compared to those without (82.7% vs 55.2%, p <0.001), as well as between the group of patients practicing intercourse receptive anal intercourse (89% versus 10%, p = 0.004), standing out, so these two factors as high risk for the presence of anal dysplasia.

The role of HPV in carcinogenesis of anal cancer

HPV is a DNA virus belonging to the family *Papovaviridae*, genus *papillomavirus, human papillomavirus* species. Its genome consists of coding regions and regulatory regions. Studies of molecular oncogenic HPV types showed that the carcinogenic activity of this virus can be attributed mainly by the action of E6 and E7 proteins. These proteins cause mutations in the p53 gene and the gene encoding the protein Rb.P53 encodes a protein p53, which is an important tumor suppressor, as well as acting in cell cycle arrest by preventing the progression of mitotic division, also induces apoptosis of mutated cells. The Rb protein, while the state hipofosforilado, prevents further cell cycle, regulating its inception. Mutations in the genes encoding these proteins confer ownership of the tumor initiating and progressing through the cell cycle independently of growth signals[8,10,25].

There are over 100 different types of HPV, at least 40 types can infect the anogenital region, of which approximately 15 are oncogenic. Types 16 and 18 are the most common oncogenic types [17,26].

HPV is the most common sexually transmitted agent in the world, with 75% of sexually active adults contract one or more of 40 types during his life[19]. In Brazil, HPV infection has come to represent 23.4% of sexually transmitted diseases reported to the Department of Health The main risk factors for HPV transmission are the number of sexual partners, marital status and sexual habits[2,22].

It is known that persistent HPV infection is a major cause of development of SCC of the cervix. He resembles the anal canal to the cervix according to their histopathologic feature, and therefore, studies suggest that HPV infection may also be an important risk factor for this cancer.Patients with anal dysplasia have an increased incidence of HPV in the anogenital region and the incidence is even higher when associated with HIV co-infection [19,27]. The types 16.18, 33 and 35 can be found in up to 85% of cases of anal carcinoma and 80% to 90% of cases of tumors of the cervix[18,28,29].

In services for authors, 64 random patients with positive serology for HIV were tested for HPV infection in the anal canal by the method of in situ hybridization and were stratified into 3 groups: 1. not infected with HPV 2. HPV-infected non-oncogenic, 3. infected with oncogenic HPV. All patients underwent an examination of anal swabs for cytologic examination, as well as the anuscopy with magnified for biopsies of suspicious areas to search for anal dysplasia. According to the examination of in situ hybridization, 19 patients showed no infection, 21 showed infection by non-oncogenic types and 23 patients had infection with oncogenic types of HPV. The presence of anal dysplasia was statistically significant both in patients infected by oncogenic HPV types [relative risk of 9.5 (2.3-36.7, 95%, p = 0.002)] and not by oncogenic types [RR 6.4 (1.6-

24.8, 95 % p = 0.007)] when compared with patients without HPV infection. These results demonstrated that HPV infection by both oncogenic and for not oncogenic, characterized as an important risk factor for anal dysplasia in patients with HIV. However, discussions are still in the routine performance of this literature review, since some authors found no benefit in their performance[5].

HIV and anal cancer

HIV infection leads to intensification of the action of oncogenic HPV. The decline of the immune response caused by the decrease of CD4 + cells, and reduction in local immunity, facilitate viral replication and allow the emergence of more severe lesions that may progress to dysplasia and cancer[19]. Moreover, the HIV virus increases the expression of E6 and E7 proteins of HPV. Typically, the HPV DNA present in our body as a circular episomes. In this way the virus can not express oncogenic proteins (E6 and E7). HIV infection reduces the expression of E2 protein, which is responsible for maintaining the circular shape of viral DNA, and therefore increases the expression of E6 and E7, increasing its power carcinogen[4,14].

The introduction of treatment with highly active antiviral therapy has significantly contributed to improving the immune status of patients infected with HIV, significantly reducing viral load and contributing to increased levels of CD4 +[6]. Increased immunity contributed to the decline in the prevalence of various opportunistic infections such as cytomegalovirus infection, herpes simplex and molluscum contagiosum, as well as contributed to the decline of HIV-related malignancies such as Kaposi's sarcoma and non-Hodgkin lymphomas[6]. However, the incidence of anal intraepithelial neoplasia and anal cancer remained on the rise[6]. It is assumed that the increased survival of HIV-infected individuals allows more time for anal dysplasia progress to invasive carcinoma.

The prevalence of anal cancer in HIV patients is higher than the general population[2,21]. Likewise, the HPV prevalence is also increased, with the majority of seropositive patients in the group of MSM are infected with the virus and often there is contamination with multiple HPV types.

Despite strong evidence, the literature still lacks studies that definitively prove the interaction HIV, HPV and anal cancer. Nationally, there are virtually no data on the subject. The definition of the degree of interaction of these entities may allow a greater number of early diagnoses of anal cancer and its precursor lesions, improving the prognosis and even reducing its incidence.

Clinical and sub-clinical anal HPV infection

HPV infection may present condyloma lesions or subclinical present framework without any noticeable change, a sign or symptom.

The clinical lesions are represented by the condyloma, commonly known as "cockscomb". These are lesions that may vary in number and size, but that in general end up leading the patient to seek medical attention for fear, discomfort, difficulty in local hygiene after bowel movement, itching, fear, and mainly because their sex life committed to the rejection the partner.

Moreover, the present framework oncogenic silent (subclinical) which results from changes in the epithelium of the anal canal does not cause any macroscopic lesion, a sign or symptom. For this reason, the patient often is unaware of their infection, their sex life has not compromised, and thus do not seek medical attention, promoting persistence of infection and increased risk for developing cancer.

For these reasons, the authors have been conducting routine screening in the following risk groups: 1. immunocompromised (HIV positive or other causes, regardless of the practice of anal intercourse), 2. Practitioners of anal intercourse (including men and women, regardless of immune status), 3. individuals with genital dysplasia (diagnosed by vaginal smear, colposcopy or biopsy peniscopy) 4. individuals with the presence or history of anal warts and / or genitals

Tracking modes of precursor lesions anal SCC

In relation to HIV positive individuals, there is still no consensus regarding the best method and schedule that must be done tracing, as least with respect to HIV-negative population (there are no algorithms established by Brazilian companies with colorectal or American). However, there is an algorithm proposed by some American authors that is more accepted today. It starts from the anal swabs, reserving the anuscopy with magnified for those individuals with abnormal result (any result suggestive of HPV infection or dysplasia).

Screening tests

a. Shaved anal (cytology)

The shaved anal can be harvested through a standard cervical brush to collect cells (Vagispec R, Adline Plastics Ltd., SC, Brazil) for 3 cm into the anal canal, turning it clockwise three times across the wall of the anal canal to obtain cells. The brush is applied in a conventional glass slide for microscopic reading that will be immersed in a solution of 70% ethanol for fixation of the material.

b. Guided biopsy anuscopy magnification

Begins the exam with digital touch followed the introduction of anoscope to enable the insertion of a gauze soaked with 3% acetic acid.Anoscope The

gauze is removed and stays for 40 seconds to ensure the absorption of acid by the mucosa. After removing the gauze, the anoscope is re-introduced and then starts the examination with the apparatus of image magnification. The anal canal is examined at different magnifications. Areas of the epithelium of the anal canal that stain with 3% acetic acid (areas "acetowhite positive") and irrigation have abnormal vascular epithelium that gives a speckled appearance of fine or coarse, are considered suspicious for dysplasia and are therefore biopsy. The anuscope is removed and the perianal area is also analyzed after application of a gauze with 3% acetic acid. Areas highlighted by the acid, or change in pigmentation or consistency, or presence of ulcers should be biopsied.

Accuracy of screening methods

To date, six studies evaluated the effectiveness of anal cytology by calculating the sensitivity and specificity of the test through a comparison with histological findings obtained by biopsy guided by anuscopy with magnified [5,9,11,20,23,25]. In these studies, the sensitivity of cytology ranged from 69% to 93% and specificity of 32% to 59%. Moreover, these studies have reported variable agreement between the two methods, not surpassing the 74% (with weighted k = 0.36)[11]. These results are similar to those found in comparative studies of cervical cytology and cervical biopsies, which showed concordance of 64% to 91% (with k = 0.18 to 0.65)[3,12].

Based on these, is being held services in a prospective study of the authors in order to assess the correlation between smear cytology and biopsy for anuscopy magnification guided by the use of acetic acid 3% in the diagnosis of dysplasia in patients with anal HIV. The study is still ongoing, but preliminary results with 222 consecutive HIV-positive patients underwent a total of 311 anal swab examinations period of 12 months revealed the following results: 1. most patients were male (85%), with education above the 2nd grade (80%) engaged in receptive anal sex (82%) in antiretroviral use (79%) and HIV viral load undetectable (67 %) 2. biopsies (gold standard) showed a prevalence of 46% (CI 95%: 40% - 51%) of anal dysplasia, 3. the anal swab had a sensitivity of 61%, specificity 60%, positive predictive value of 56% and negative predictive value of 64%. The weighted kappa index of agreement between two methods (smear and biopsy) was 0.20 (95% CI: 0.103 to 0.292).

From these results, the use of anal swabs alone was not sufficient to exclude anal dysplasia. Therefore, it has been recommended that biopsies guided anuscopy with magnified as a complementary test in screening for anal dysplasia in high risk patients.

Remember that screening should not be limited exclusively to the anal canal, but also the perianal region, where relatively frequently since there is slight changes in pigmentation of the skin, flat warts, even persistent ulcers that may mimic herpes infections or syphilis, but which actually represent high-grade dysplastic lesions, including foci of microinvasive containing a few millimeters[16]. In a recent review of 52 HIV positive patient who went to Memorial Sloan Kettering Cancer Center for anorectal complaints, 19 (37%) had abnormalities noted in the perianal region to anuscopy with image magnification and were biopsied. Among them, 11 patients (21% of total) had high-grade dysplastic lesions or microinvasive. That number could be even higher considering that only individuals were biopsied with suspicious lesions, thus emphasizing the importance of thorough examination of the perianal region[15].

CONCLUSIONS

HIV + is a major risk factor in developing anal SCC in individuals infected with HPV. The evaluation of these patients should not restrict itself to the eradication of warts, but mainly include the screening of subclinical dysplastic lesions potentially neoplastic. Despite the screening methods are still not ideal, the great benefit of screening is based on the fact offer closely monitored, making possible the prevention or detection increasingly early anal SCC.

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