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ANAL CANCER IN PEOPLE LIVING WITH HIV: THE IMPORTANCE OF THE SCREENING AND OF EARLY DIAGNOSIS

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Abstract – *Objective:* *HIV-positive patients suffer from higher cancer-related mortality compared to the general population. Anal cancer (AC) is considered as a rare form of neoplasm, accounting for 4% of all cancers of the lower gastrointestinal tract in the general population. Approximately 88% of AC cases are associated with human papillomavirus (HPV) infection. This paper purpose is the diagnostic and therapeutic management of AC in HIV infect people.*

KEYWORDS: *Anal Cancer, PLWH, HIV, ART, HPV, Screening.*

INTRODUCTION

Over the last decades, because of the broad use of combination antiretroviral therapy (cART), the life expectancy of patients living with human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) improved. This brought to a continuous increase in the total number of people living with HIV (PLWH) worldwide, a population who bears the burden of associated health conditions that complicate long-term HIV infection[1-23].

Among them, a constantly growing incidence of non-AIDS defining cancers (NADCs) such as hepatocellular carcinoma (HCC), lung cancer and anal carcinoma accompanied the decrease of AIDS defining cancers (ADCs) such as Kaposi's sarcoma and Hodgkin's lymphoma[1,24-26].

HIV-positive patients suffer from a higher cancer-related mortality than the general population. Studies have shown that this higher mortality is caused by the degree of immunosuppression, irrespectively of whether the tumor is infection-associated or not. NADCs are burdened by a poorer outcome compared to AIDS-associated malignancies, which might be positively influenced by the application of cART[27,28] before the onset of acquired immunodeficiency syndrome (AIDS.

The aim of this paper is to comprehensively review the literature about the diagnostic and therapeutic management of anal cancer (AC) in HIV-infected people.

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EPIDEMIOLOGY

AC is considered a rare form of neoplasm in the general population, accounting for 4% of all cancers of the lower gastrointestinal tract. Approximately 88% of AC cases are associated with human papillomavirus (HPV) infection, with HPV 16 being the most commonly detected type, followed by HPV 18, 32 and 34. In AC, two major morphologic kinds are highlighted: squamous cell carcinoma (SCC), accounting for 70% of the cases, associated to HPV in 80% of the cases, and adenocarcinoma (ADC), less frequently related to HPV[29-32].

PLWH have elevated rates of AC, because of a higher rate of sexually transmitted infections, especially infection by high-risk type of papillomavirus. The incidence of AC is elevated in PLWH when compared to the general population and it is especially high in the HIV-positive males who have sex with males (MSM) population, as it has been demonstrated in several studies[33-36]. Some authors reported that the rates of AC are in HIV+ MSM 135 per 100,000, in HIV+ non-MSM of 45 per 100,000, and in HIV negative non-MSM of 2 per 100,000. The same study also found AC rates of 30 per 100,000 in HIV positive women and the authors highlighted how there were no cases of AC in the HIV-negative women[37].

PATHOGENESIS

Recent data shows that the majority of the squamous cell ACs are apparently linked to HPV. It is often a persistent high-risk HPV (HR-HPV) genotype, most commonly 16 and 18, infecting the squamous epithelium and causing a neoplastic transformation in the rectal mucosa. As we can observe in the case of other HPV associated tumors, it exists a sequence from persistent infection to invasive cancer. An important role in this process is played by the dysregulation of autophagy[30,38-46].

An explanation of the higher risk for AC among PLWH might be that HIV is associated with a higher incidence of HR-HPV infection, which can promote the development of AC. Moreover, both HIV and AC are associated with inability to clear HPV infection and simultaneous infection with multiple strains of HPV[43].

The mechanism of tumorigenesis has been found to be the inactivation of tumor suppression genes. Mutations in the p53, DCC, and/or APC tumor suppressor genes have been identified as antecedent events. Much like the development of colorectal adenocarcinoma, a pattern of chromosomal instability is evident in the genesis of the ACs. Some author proposed the microsatellite instability rather than chromosomal instability to be the possible pathway for rapid progression towards invasive carcinoma in HIV positive cases[24,47,48].

DEFINITION AND CLASSIFICATION OF AC

AC is defined as cancer arising from the squamous epithelium of the anus, making it distinct from colorectal cancer. The anal canal consists of stratified squamous epithelium originating outside the body and extending into the anus up to the dentate line, the point where it intersects the columnar epithelium of the rectum. AC, as cervical cancer, may be HPV-associated and arise from precursor lesions defined dysplasia or intraepithelial neoplasia (anal intraepithelial neoplasia, AIN). Due to the concordant histopathological characteristics, in 2001 Bethesda classification revised the nomenclature for anal dysplasia, making it similar to the one utilized for cervical lesions. Cytology plays an important role in the diagnosis of anal lesions[49-51].

The cytological examination follows to distinguished from low- and high-grade dysplasia and lesions with undetermined significance. Low-grade squamous intraepithelial lesion (LSIL) cytology corresponds to the histological diagnosis of anal intraepithelial neoplasia grade 1 (AIN1) while the high-grade squamous intraepithelial lesions (HSIL) correspond to intraepithelial neoplasia grade 2/3 or anal carcinoma *in situ* (AIN2/3). The role of low-grade AIN for tumor progression is controversial, seen that these may sporadically demonstrate spontaneous regression, while AIN2 and AIN3 are potential precursor lesions of AC. The most recent version of TNM staging of AC is showed in Table 1.

Screening

Similar to cervical intraepithelial neoplasia (CIN) and cervical cancer, these cancers may be preventable by an early diagnosis, which could be reached thanks to mass screening[25].

However, despite the high-incidence of AC, the screening is not currently routinely effected, not even in HIV-infected MSM, who are burdened by the highest risk and could actually benefit from an early diagnosis and early therapy.

Similarly to what happens for cervical neoplasia, cytology has been proposed to screen for AC in high-risk population[52,53]. This kind of screening has not been studied and is not currently recommended in the general population[37,41,53-58].

DIAGNOSIS (FIG. 1)

Incidence of AC has dramatically risen in several parts of the world, including Europe and the United States, in the general population. It is even more significant among MSM, for whom where the incidence rates up to 37 per 100,000, to rise up to 135 per 100,000, in

TABLE 1 . Clinical Staging of Anal Cancer, according to AJCC Cancer Staging Manual, 8th edition.

AJCC Stage	*Stage definition*	*Stage description**
0	**Tis** **N0** **M0**	***Tis:*** High-grade squamous intraepithelial lesions (previously named carcinoma in situ, Bowen diseas, anal intraepithelial neoplasia II-III, high-grade anal intraepithelial neoplasia). It describes a situation where the cancer is limited to the epithelium layer (the most external) of the mucosa. ***N0 & M0:*** Neither lymph nodes nor distant sites are involved.
I	**T1** **N0** **M0**	***T1:*** The lesion is 2 cm (about 0.8") or smaller. ***N0 & M0:*** Neither lymph nodes nor distant sites are involved.
IIA	**T2** **N0** **M0**	***T2:*** The cancer is larger than 2 cm (0.8") but smaller than 5 cm (about 2") across. ***N0 & M0:*** Neither lymph nodes nor distant sites are involved.
IIB	**T3** **N0** **M0**	***T3:*** The cancer is larger than 5 cm (2"). ***N0 & M0:*** Neither lymph nodes nor distant sites are involved.
IIIA	**T1** **N1** **M0**	***T1:*** The lesion is 2 cm (about 0.8") or smaller. ***N1:*** Metastasis in inguinal, mesorectal, internal iliac or external iliac nodes (N1a: limited to inguinal, mesorectal or internal iliac nodes; N1b: limited to external iliac nodes; N1c: N1a + N1b) ***M0:*** No involvement of distant sites
	OR	
	T2 **N1** **M0**	***T2:*** The cancer is larger than 2 cm (0.8") but smaller than 5 cm (about 2") across. ***N1:*** Metastasis in inguinal, mesorectal, internal iliac or external iliac nodes (N1a: limited to inguinal, mesorectal or internal iliac nodes; N1b: limited to external iliac nodes; N1c: N1a + N1b) **M0**: No involvement of distant sites.
IIIB	**T4** **N0** **M0**	***T4:*** The cancer is any size and is growing into nearby organ(s), such as the vagina, urethra (the tube that carries urine out of the bladder), prostate gland, or bladder. ***N0 & M0:*** Neither lymph nodes nor distant sites are involved.
IIIC	**T3** **N1** **M0**	***T3:*** The cancer is larger than 5 cm (2"). ***N1:*** Metastasis in inguinal, mesorectal, internal iliac or external iliac nodes (N1a: limited to inguinal, mesorectal or internal iliac nodes; N1b: limited to external iliac nodes; N1c: N1a + N1b) ***M0:*** No involvement of distant sites.
	OR	
	T4 **N1** **M0**	***T4:*** The cancer is any size and is growing into nearby organ(s), such as the vagina, urethra (the tube that carries urine out of the bladder), prostate gland, or bladder. ***N1:*** Metastasis in inguinal, mesorectal, internal iliac or external iliac nodes (N1a: limited to inguinal, mesorectal or internal iliac nodes; N1b: limited to external iliac nodes; N1c: N1a + N1b) ***M0:*** No involvement of distant sites.
IV	**Any T** **Any N** **M1**	***Any T:*** The cancer can be any size and may or may not have grown into nearby organs. ***Any N:*** It may or may not have spread to nearby lymph nodes. ***M1:*** Presence of distant sites involvement, either macro- (cM1) or micro-scopic (pM1).

HIV+ MSM[29,54,55,59]. The burden of this cancer continues to rise, with only 10% of patients with metastatic disease surviving more than 2 years[60].

Moreover, 95% of HIV+ MSM are seropositive for the related viral pathogen, HPV (subtypes 16, 18, 32 and 34).

The most important diagnostic methods for AC are anal cytology with histology staging and radiological techniques.

Anal Cytology

Anal cytology is currently applied to screen for dysplasia or intraepithelial neoplasia. It is performed inserting a water-moistened polyester fiber swab into the rectum until encountering the rectal wall, then removing the swab with a twisting motion while applying lateral pressure. This technique allows gathering samples of the transitional zone and anal canal. The swab is then processed using a liquid cytology technique older than Papanicolaou staining. The sample obtained is then analyzed by a pathologist[61].

Some authors reported that, in HIV negative MSM, anal cytology sensitivity was between 47-70% for the detection of intraepithelial neoplasia of any grade. Performing a HPV molecular test, such as polymerase chain reaction (PCR), on the same specimens may help improving the diagnostic sensitivity.

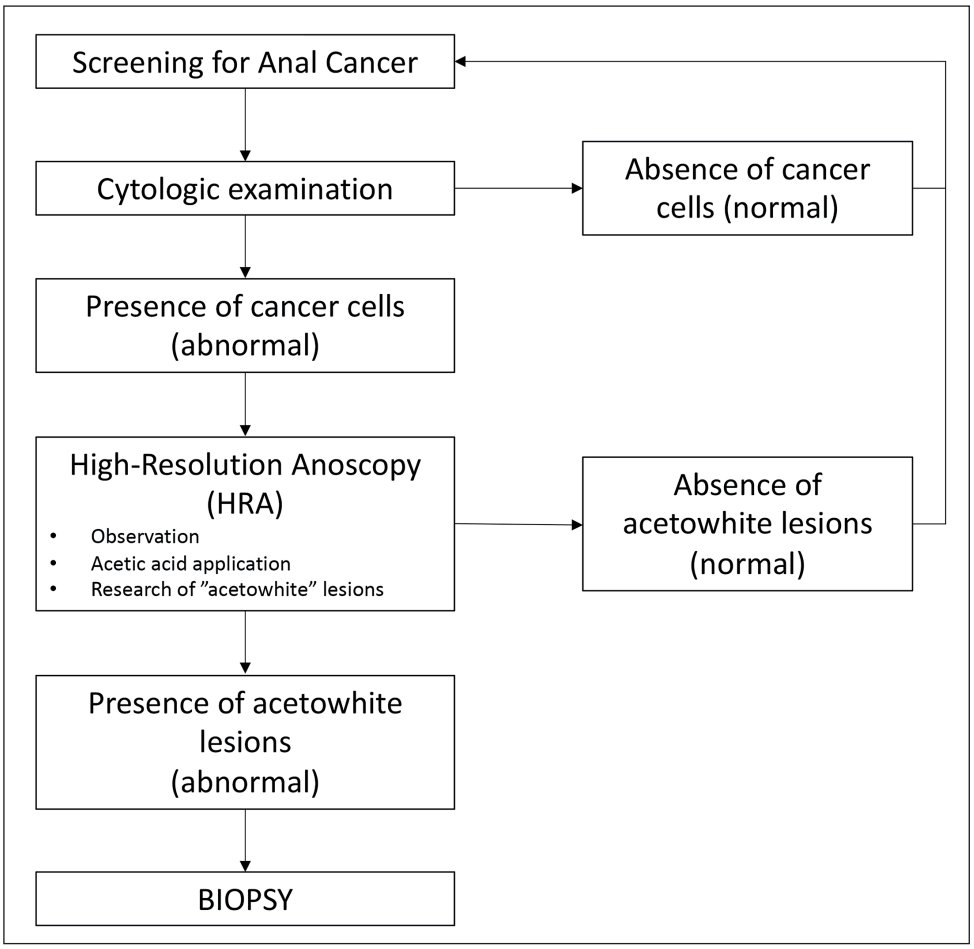

Fig. 1. Screening diagram for anal cancer.

If the cytologic examination comes out positive, the next step consists in localizing the source of those atypical cells with High Resolution Anoscopy (HRA). HRA consists of a direct examination of the squamo-columnar junction between the anus and the rectum, of the anal canal and of the perianal skin under magnification using a colposcope. During a first phase examination when the anoscope is placed into the anus with lidocaine lubrication, a direct observation is performed. The anoscope is then removed, and a swab soaked in 3-5% acetic acid solution is placed into the anal canal for two minutes. The acetic acid application helps distinguishing the epithelium infected by HPV from the healthy one, creating "acetowhite" areas, which can be observed at the anoscope.

The latest and final step is the biopsy of the suspected zone[56, 61-64].

Radiological staging

A number of imaging techniques can be used for the diagnosis and the staging of the AC. Computerized tomography (CT), Magnetic Resonance Imaging (MRI), Endo-Anal Ultrasound (EUS) and Positron Emission Tomography (PET) scanning are combined to allow an assessment of the local and distant spreading, including involvement of other organs and nodes. MRI is currently the gold-standard to assess loco-regional disease, but EUS is more specific for small lesions. PET/CT has been recommended because of high sensitivity in identifying involved lymph nodes[65-67].

TREATMENTS

Several therapies are nowadays possible for intraepithelial lesion or an invasive neoplasia. Despite its growing incidence, AC remains a rare condition and requires a high level of expertise to correctly diagnose and treat; all individuals found to have positive anal cytology should be referred to expert centers for treatment and therapy[68].

Topical therapy

Topical therapy consists in the direct application of a medication on the specific lesion or the entire anal canal. Available medications include trichloroacetic acid (TCA), 5-flurouracil, and the immune modulator imiquimod[69, 70].

However, several studies showed that the efficiency of local eradication of HPV-associated anogenital lesions with electrocautery was superior to that of local chemotherapy in HIV-positive MSM[69, 70].

Electrocautery constitutes a first-line treatment for intraepithelial neoplasia. A possible advantage of surgical excision is the chance to perform a histopathological examination of the tissue removed. Despite being ineffective on a high percentage of the patients, topical therapy appears to be generally well tolerated[69,70].

Surgical therapy

Surgery for AC is associated with significant morbidity, often requiring a large excision of healthy tissue around the cancerous lesion, and yet it is associated with a variable rate of recurrence. A local resection, which removes only the tumor plus a small margin (edge) of the normal tissue around the tumor, is mostly used to treat cancers of the anal margin when the tumor is small, and it has not spread to nearby tissues or lymph nodes. Abdominoperineal resection is a major operation, which consists in the complete removal of the anus and the creation of a colostomy. Surgical therapy is a common treatment for rectal cancer when the cancer is spread well above the anus. This technique consists in the resection of the entire rectal cancer with the adjacent normal rectal tissue and surrounding lymph nodes through an incision made in the lower abdomen. Local resection may be an option for early stage AC that has not spread to the lymph nodes or surrounding tissue[71-75].

PREVENTION

HPV infection can be currently prevented thanks to the introduction of a vaccination against the virus. Three kinds of vaccine against HPV are available: the quadrivalent Gardasil, against HPV-serotypes 6, 11, 16 and 18; the nine-valent Gardasil-9, against HPV-serotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58; and the bivalent against HR-HPV-serotypes 16 and 18.

The quadrivalent HPV (qHPV) vaccine has been demonstrated to prevent persistent anal HPV infections as well as anal intraepithelial neoplasia grades 2-3 in young MSM not previously infected; however, some recent studies showed that the quadrivalent HPV vaccine was not effective in preventing new anal infections or improving high-grade squamous intraepithelial lesions in adults aged older 27 years with HIV[40,51,76-78].

CONCLUSIONS

AC is often associated with HPV, arising from the squamous epithelium of the anus. In some groups, such as PLWH and especially MSM, it shows a high progression risk. Despite its low frequency in the general population, the incidence of this cancer is constantly increasing, especially in PLWH, who represenst an optimal target population for mass screening.

It is essential to acquire new data about the effects of the vaccination campaign on the incidence of AC. Further studies are needed to achieve these outcomes.

Conflict of Interest

The Authors declare that they have no conflict of interests

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