VIROLOGICAL AND EPIDEMIOLOGICAL ASPECTS OF ANAL CARCINOMA: CURRENT AND FUTURE CHALLENGES

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ABSTRACT

Human papillomavirus infection, a sexually transmitted disease studied mainly in women due to its link to uterine cervical carcinoma, has become a health problem in men also, mainly by the significant increase of the prevalence and incidence of anal intraepithelial neoplasia and anal carcinoma in specific groups, such as men who have sex with men, HIV-seropositive and immunocompromised. The anal carcinoma, as cervical cancer, is associated with high-risk oncogenic HPV in 90% of cases, with HPV 16 as the predominant, followed by HPV 18. This fact occurs in a moment when there are no management protocols for HPV infection in the anal area, either preventive, diagnostic or therapeutic, and without an unique specialty that embraces the problem of HPV anogenital infection in men as does the gynecology for women, causing a dispersion of expertise. Added to this, there are still many doubts in the medical and general population about prophylactic vaccination for HPV in boys, and the absence of its distribution in a public health scale in most countries that still wait for statistical calculations to justify its use.

Keywords: HPV, anal carcinoma, HIV, STD, intraepithelial neoplasia

INTRODUCTION

The infection by the human papillomavirus (HPV) results of one of the main sexually transmitted diseases (STDs) at present time. In recent years, the male infection has increasingly become a research object after the awareness that sexual transmission is the main way of dissemination to women and that men also take the consequences of anogenital HPV infection in the form of anogenital warts (AGW), penile intraepithelial neoplasia (PIN) and anal intraepithelial neoplasia (AIN) and carcinoma invader, added to the development of prophylactic vaccination for both genders.

Although benign, AGWs take on the psycho-social stigma character, often leading to depression and loss of quality of life, with a high social cost.

Penile carcinoma often occurs in men in their 60’s, with incidence ranging from 0.3 to 4.2/100,000, depending upon socioeconomic differences and religious conditions, reason why this pathology studies have low priority. However, anal carcinoma, which until recently were thought to arise as a result of chronic inflammatory intestine disease, has today on HPV infection its primary etiologic agent, being the high-risk types associated with approximately 90 cases of anal squamous cell carcinoma, and most of these associated with HPV 16, followed by HPV 18. Its incidence has been increasing in the general population around 2% per year, however, in some specific groups, such as men who have sex with men (MSM), HIV-seropositive men for the human immunodeficiency virus (HIV) and immunosuppressed, rates are more alarming – a recent study in San Diego shows the incidence of 224 per 100,000 individuals/year. To better understand this figure, we should mention that the incidence of UCC before the introduction of routine Pap smear examination was around 37/100,000 individuals/year.

Sorting through cytology, similar to Pap smear, has been proposed for anal carcinoma, however there is still no consensus on the reliability of the method. Physical examination with biopsy and histopathologic study is still considered a good option, although the visualization of sub-clinical lesions (anal intraepithelial neoplasias) most time is only possible with a set up view by a high resolution videocolposcope, a kind of examination not yet well known by other experts than Gynecologists.

The tests for the detection of viral nucleic acid have high sensitivity and specificity – like the polymerase chain reaction (PCR) and the capture of the hybrid (not available in all health services, mainly in public health) – and require knowledge about the viral behavior and the pathology in question, so that the interpretation of the results have a practical significance and not be just another inconvenience, with a waste of time and money.

ANAL INFECTION BY HPV

Transmission and epidemiology

HPV transmission occurs by direct contact of two surfaces, i.e., through the skin or mucous membrane microtrauma, exposing the epithelial basal layer. The main route of transmission is the sexual contact without the exclusive need for penetration, followed by episodes in which microtraumas may also occur. As the HPV are quite resistant to heat and drying, it is still possible a reduced transmission via contaminated fomite. HPV transmission does not occur through blood, since it doesn’t make viremia, or through ejaculate, except in the presence of urethral injury by HPV. Although it has already been detected in sperm, it has not been possible to prove its infectious potential in this circumstance. The potential transmission of HPV through seminal fluid raises the question of what might be possible for the transmission of HPV via sperm donation.

There is still no accurate HPV acquisition and elimination rates data, nor the incidence and duration of infection nor the production of antibodies in response to HPV infection in man. In Giuliano et al. study, the prevalence among men and women in the same age group would be between 52.8% and 53.8%, respectively. Also Giuliano et al. in a recent prospective study, with heterosexual men aged between 18 and 44 years, points to the probability of 0.29% HPV infection per year.

According to Burd and Frisch et al., following are the main factors predisposing individuals to a greater risk of infection: pri-
The high-risk HPV’s, particularly HPV 16, are etiologically associated with virtually all cervical carcinomas, and types 16 and 18, alone or in association, are present in 78% of all anal carcinomas\textsuperscript{(24,25)}. HPV 16 is present in 65% to 75% of anal carcinoma samples analyzed, followed by HPV 18\textsuperscript{(26)}. The populations considered high-risk for anal carcinoma are HIV-seropositive women and men, MSM, women with uterine cervical or vulvar carcinoma history and immunosuppressed. Anal cytology, like the annual or biannual Pap smear, is being studied as an alternative for the prevention of anal carcinoma in high-risk groups\textsuperscript{(27)}.

Chin-Hong et al.\textsuperscript{(28)} demonstrated that anal HPV infection in MSM may probably be associated with HIV acquisition. The mechanisms are not yet clear, however an important factor would be that the HPV-induced lesions are often brittle and susceptible to breakage of mucosal integrity during intercourse, with blood loss.

Anal carcinoma screening aims to identify and treat high-grade AIN and invasive squamous carcinoma. Following the cervical model, anal cytology can be used to detect precursor lesions, and in case of detection of atypical cells, be followed by a high-resolution videoanaloscopy with directed biopsy. However, most clinicians and cytopathologists still have little experience of collecting and reading anal specimens respectively. Anal cytology should cover the entire anal canal, including mainly the transformation zone. The cells sample should be collected through a long swab of synthetic fiber, in circular motion, inserted into the anal canal and taken up after the dentate line and the distal rectal wall, always with firm pressure to touch all the anal wall. Conventional smears may be used, but the liquid-based preparation increases the efficiency of the sample, reducing fecal contamination and desiccation by air, which cause common artifacts in this type of examination.

Data published by the College of American Pathologists (CAP), in its annual disclosure of 2009, indicate that the categorization of anal HSIL cytology specimens is still problematic. In a recent study, only 61% of the blades showing anal HSIL were recognized by the specialists and compared with cervical cytology more than 85% of HSIL blades were correctly classified. It is worth mentioning that for the anal cytology reading, cytomorphology of gynecological lesions associated with HPV is used, and the employed terminology is that of Bethesda’s\textsuperscript{(27)}.

A retrospective Australian study examined the presence of AIN in all excised condylomatous lesions of most of HIV-seronegatives male patients during a period of 9 years in a clinic. HSIL lesions were present in the anal canal in 44% of 27 HIV-seropositive men (of these, 26 MSM), and 18% of 88 HIV-seronegative men (half supposedly heterosexual). The authors concluded that most HIV-seropositive men with untreated anal warts can develop anal carcinoma, a view that seems alarmist, but completely supported by epidemiological data available. This study clearly underlines the importance of anal warts treatment\textsuperscript{(29,30)}.

Anal carcinoma screening routine is still a quite controversial topic. There is no randomized clinical trials to validate the effectiveness of any kind of selection, the target groups are limited, the effectiveness and the methodology have yet to be clearly determined and the long-term effects are not yet possible to be perceived. However, without any doubt, it is possible to observe that sorting is important and should be established in higher-risk groups.
**HIV infection in HIV-seropositive men**

The prevalence of HPV infection with higher viral load and the presence of multiple types are greater in HIV-seropositive patients, resulting in a higher incidence of pathological conditions of worse prognosis. These patients also have lower resolution rate of latent infections by HPV or increased reactivation, with higher risk for all kinds of low and high intraepithelial neoplasia grades and carcinomas.

HIV-associated immunosuppression seems to play an important role in the pathogenesis of HPV in HIV-seropositive men, as the organic defense against HPV infection requires a competent cellular immunity, which is reduced during HIV infection. Other interaction mechanisms between HIV and HPV have been postulated, such as: the increased expression of cytokines (e.g., interleukin-6) known to modulate the expression of HPV genes that would allow its reactivation in keratinocytes when there is a latent infection; the increase of growth factors; the effect of HIV-1 Tat protein, which would intensify the E6 and E7 expression, and the activity of lymphocytes CD4+ T, also in E6 and E7, similar to that observed in other immunosuppressive conditions, leading to a decreased ability to retain HPV, which consequently will have its replication increased, keeping intact its epithelial proliferation. Low CD4+ T-lymphocyte count is associated with a statistically significant risk to increased incidence of invasive carcinoma, by infection with HPV among HIV-seropositive women and men.

Although there are no well-controlled studies demonstrating the latent infections reactivation, this seems to occur when immunocompetent patients move to conditions of immunosuppression, occurring during the use of steroids for long periods or in chronic diseases. It was observed that in celibate HIV-seropositive women, the count of lymphocytes CD4+ T was strongly associated with the detection of new types of HPV, presumably by reactivation of latent infection previously acquired. Low CD4+ T-lymphocyte count is associated with a statistically significant risk to increased incidence of invasive carcinoma, by infection with HPV among HIV-seropositive women and men.

Treatment of anal lesion associated with HPV

Smaller lesions and perianal warts are usually easier to treat than larger lesions or anal canal. For the anal region, the common and well known therapies, such as the use of trichloroacetic acid 70%, electroatenuation, imiquimod or podophyllotoxin gel can be used for all injuries smaller than 1 cm² at the base. Larger lesions, especially in HIV-seropositive men have a higher rate of recurrence feature and evolution with high-grade lesions, and a study is usually necessary with an additional biopsy so the type of injury can be known.

All patients with perianal lesions and obligatorily HIV-seropositive immunosuppressed patients should always be referred for an evaluation by the coloproctologist. If injuries to anal canal are detected, they must be treated by this expert. Due to the local anatomical challenges, such as the presence of hemorrhoids and crypts, it can be much more difficult to treat AIN, compared to CIN. As occurs in the cervical disease, the histology, the size of the lesion and its location are the determining factors that influence the type of treatment to be chosen. The AIN I, which probably does not advance directly to the invasive carcinoma, aims to reduce the risk of progression or increase of the injury in its early treatment, which would prevent the use of topical agents and would require a wider resection with greater morbidity.

Recent guidelines have been published for the treatment of AIN in the presence of HIV co-infection, which can always be treated in any grade. And in all patients, AIN II and III should be treated for prevention of invasive carcinoma.

In 2007, the New York State Department of Public Health AIDS Institute recommended the digital anorectal touch and cytological examination during first appointment of HIV-seropositive MSM, and also of any patients with a history of AGW and in women with abnormal histopathological result in cervix and vulva too. Most early stage anal invaders carcinomas are easily palpable to the touch, even when asymptomatic, and are marked by the presence of hardening or thickening in the anal canal. Despite the low cost and the unnecessary technology, digital anal touch is unfortunately underused. Suspicion and search for anal carcinoma must be adopted by professionals as part of the routine clinical care in MSM and in people with AGW.

The self-examination without prior guidance can lead to an excessive fear due to patient’s non-acquaintance of prominences that can be part of his/her anatomy, as pilcomas and hemorrhoids. Therefore, first examination should be performed by a doctor, so that a parameter can be established by them both. Those who are unable or reluctant to self-examination should delegate the task to their doctors routinely. Proctoscopy, although desirable, is not strictly necessary, unless a nodule is detected.
Prophylactic vaccination

Sexual abstinence, mutual long-term fidelity and use of condoms were the only possible actions in the primary prevention of anogenital HPV infections until recently. Currently, the more effective weapon in primary prevention of HPV infection is the vaccination aimed at viral types most frequently responsible for anogenital lesions. Today there are two safe and effective vaccines for infections and diseases caused by HPV types contained in the products. Both of these use vectors that express the L1 gene of the virus, used successfully to generate VLP, that induce high titer of specific antibodies(33).

The quadrivalent vaccine approved by ANVISA (Brazilian Health Surveillance Agency) has four VLPs: 6, 11, 16 and 18 – viral types associated with AGW and carcinomas. In Brazil, it is released for use in women and men from 9 to 26 years of age(10).

The vaccine induced protection mechanism seems to be mediated mainly, if not entirely, by high concentrations of neutralizing antibodies (or ten times higher than the concentrations after natural infection). Prophylactic vaccination with L1 VLP has shown to be very effective in the prevention of primary infection, latent infection and associated diseases. However, serum concentrations of antibodies necessary to grant protection against this infection are unknown, therefore the period of protection given by vaccines continues to be indeterminate(33). In the Australian study to evaluate the quadrivalent vaccine, from a randomized double-blind trial with 1,781 males and females aged 9-15 years, 99.5% or more patients had high rate of antibodies in the serum in the seventh month after applying the third dose, a rate also above the natural infection(42).

So far the effectiveness of prophylactic vaccination against HPV infection in men is still unknown and results from various studies are expected to occur in a near future(43). Farley et al. study in Australia, in 2009(44), observed a sharp reduction of AGW among women in the target age group in the year following the implementation of a national programme of vaccination against HPV, a decrease that clearly differed from previous trends in clinical diagnostics. Another subgroup which showed a modest decrease of AGW presented by this same study was the heterosexual men group, and remarkably there was no difference in the AGW diagnosis in the studied period between gay men or women outside the age range eligible for free vaccination. The quadrivalent vaccine has also shown efficacy against infection in heterosexual men and MSM between 16 and 26 years of age. In a randomized trial with 4,065 people, the quadrivalent vaccine efficacy against AGW was of 89.4%. Further analysis of effectiveness of the vaccine in MSM (n = 602; age: 16-26 years) confirms the benefits of HPV vaccination in reducing the burden of anogenital HPV infection and incidence of AGW (79.0%). However, the most anticipated data are about the impact both of the vaccine on AIN and the inclusion of men in a routine programme for children of 12 years of age and duration of human papillomavirus infection among a cohort of 290 US men. J Infect Dis. 2008b;198:827-835.

It is obvious thinking that the incorporation of men in a routine vaccination against HPV will probably reduce the burden of the disease not only in men, but also in women, and would help eliminate the stigma that focuses on the disease in women. However, considering public health, we recognize that the cost-benefit analysis is necessary to determine the effectiveness of these programs for the general population. Such analyses shall be fundamental in guiding the conception, acceptance and implementation of those programmes in clinical practice(42).

REFERENCES


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