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OPINION ARTICLES

Early Detection of Anal Intraepithelial Neoplasia in High-Risk Patients☆

Detección precoz de la neoplasia intraepitelial anal en pacientes de alto riesgo

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Screening tests are applied systematically to an asymptomatic population in order to detect abnormalities, establish an early diagnosis, provide early treatment, and avoid the consequences of delayed diagnosis.[1] Screening programs are particularly effective in the detection of common cancers for which good, cost-effective tests are available, affordable, acceptable, and accessible to the majority of the at-risk population. Examples are cervical cancer and breast cancer in women. This issue of *Actas Dermo-Sifiliográficas* includes an article that reviews the need for early detection of anal intraepithelial neoplasia (AIN) in high-risk patients, a topic that has received much attention in the literature in recent years, mainly because of the steadily rising incidence of this disease.

Until the early 1990s anal cancer was not considered a major public health concern because the frequency was low and patients were usually of advanced age; AIN was more common in women and accounted for 5% of cases of gastrointestinal neoplasia.[2] The incidence began to rise in Europe and North America in the 1990s, however, and interestingly, the prevalence was higher in young men. It soon became clear that most of the patients were homosexuals infected with human immunodeficiency virus (HIV), among whom the incidence was much higher than expected. At present, despite the introduction of highly active antiretroviral therapy, anal cancer is the most common non–AIDS-defining neoplasia in HIV-infected patients and the incidence has increased most in this population.[3]

To understand the pathophysiology of anal cancer and its similarity to cervical cancer, it is essential to understand the anatomy of the area. The anatomical anal canal extends from the dentate line to the anal verge. The dentate line, at the point where the squamous epithelium and the columnar epithelium of the rectum meet, is the most important macroscopic reference point of the anal mucosa because tumors located above or below it have distinct drainage patterns. Above this line, tumors drain to the perirectal and paravertebral lymph nodes and below it they drain to the femoral and inguinal lymph nodes. The perianal space surrounds the anal canal to a distance of 5 cm. Because anal tumors originate in the squamous epithelium of the perianal space or of the anal canal, over 80% of these cancers are of the squamous cell type.

Like cancer of the cervix, penis or vulva, squamous epithelial dysplasia of the anal canal (known as AIN) is considered a carcinoma in situ. Also like cancer of the cervix, penis or vulva, AIN is classified into 3 grades of dysplasia, defined by the degree of the cytologic atypia and the degree of epithelial involvement. AIN grade 1 refers to a low-grade squamous lesion, whereas grades 2 and 3 are

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high-grade squamous cell or in situ carcinomas.[4] These tumors typically occur in the squamous epithelium below the dentate line and their diagnosis always requires a biopsy for pathology.

The pathogenesis and clinical course of anal cancer are also very similar to those of cervical cancer. Both mucosas have a transition zone between the columnar and squamous epithelia. In both cases intraepithelial neoplasia always precedes the appearance of an invasive carcinoma and the transition period may be very long. Furthermore, as occurs in cervical cancer, over 90% of anal cancers are associated with human papillomavirus (HPV) infection, a major oncogenic stimulus; HPV-16 and HPV-18 are the most common genotypes.[5] However, we know that AIN progresses much more slowly and less frequently towards invasive anal cancer than cervical intraepithelial neoplasia progresses, suggesting that there are relevant factors in addition to HPV.

The rising incidence of anal cancer has made it necessary to establish early detection programs. Because systematic screening for cervical cancer reduces the risk of invasive cervical cancer, early diagnosis and treatment of AIN should also reduce anal cancer. However, before establishing a program for early diagnosis of anal cancer, we must first determine the target population for screening, the optimal screening intervals, the long-term recurrence rates, and whether we have effective treatments that improve the prognosis. Our current lack of knowledge of the pathogenesis and natural history of anal cancer makes it difficult to answer these questions.

In general, AIN screening programs reveal higher incidences than cervical cancer screening programs do. In principle, AIN screening programs should be applied to groups at risk for this disease. The results of screening programs have shown that groups at high risk include not only HIV-infected men who have sex with men (MSM) but also non-MSM patients who are HIV-infected and MSM who are not HIV-infected; thus, the target population for screening has broadened.[6] The range of at-risk patients has now been extended to chemically immunosuppressed patients, such as recipients of solid-organ transplants, women infected with HIV, and women not infected with HIV who have a history of genital cancer. In a study in which women with HPV infection in the genital area underwent screening of the anal canal, 12% of biopsies revealed AIN.[7] The common denominator of these groups is the practice of anoreceptive sex or the extension of the HPV infection from the genital zone to the anal canal because of immunosuppression or a high viral load. However, HIV-infected MSM are very clearly the group with the highest incidence of AIN and should therefore be the main targets for AIN screening programs.

The main objective of AIN screening is to detect anal dysplasia early and to eradicate it, thus preventing progression to invasive lesions such as squamous cell carcinoma. Fortunately, more and better techniques for diagnosing and treating anal dysplasia and anal cancer are emerging and will undoubtedly reduce the morbidity and mortality of this disease. Anal cytology has been proposed as a method for AIN screening in high-risk patients.[8] The test must be done by an expert, so as to ensure that a sufficient number of cells representing the whole anal canal are obtained and to avoid, as far as possible, contaminants such as fecal remains. It is not necessary to prepare the colon, but the rectal vault must be emptied before the sample is obtained. As explained in an article in this issue of *Actas Demo-Sifiliográficas*, the cytology brush must be inserted into the anus, advanced 2 to 3 cm, and then removed with a rotary motion to obtain cells representing the whole anal canal; the sample must be fixed immediately. Several studies have shown good cost-effectiveness in HIV-infected patients screened every year and in HIV-uninfected MSM screened every 2 or 3 years, but there is no clear consensus in international guidelines on whether systematic anal cytology for AIN screening should be recommended in HIV-infected MSM.[8] This technique is imperfect, however, because it gives false positives and false negatives. Therefore, molecular techniques for improving the sensitivity and specificity of AIN screening are being tested. Another problem of cytology is that it does not always indicate lesion severity, so in patients with an abnormal cytology, high-resolution anoscopy-guided biopsy should be used to identify dysplastic lesions.[9] Though anoscopy is similar to colposcopy, specific training is required to become an expert in the technique. At present, the lack of experts in anoscopy limits the creation of new screening programs. In our hospital an anal dysplasia screening department has been functioning for just over a year and in one year it dealt with 200 MSM and HIV-infected patients. During this period we detected 58 patients with condylomata and 11 patients with AIN 2 and 3, who were treated successfully.

What we do have today is excellent primary prevention of HPV infection. All young girls in Spain are currently being vaccinated before their first sexual relations and the US Food and Drug Administration has also approved the use of the tetravalent vaccine in males aged 9 to 26 years in order to reduce the incidence of condyloma acuminata associated with the genotypes covered.[10] However, it is not clear what subgroup should be vaccinated because it is best to vaccinate before sexual relations begin and vaccination has not been proven to reduce the incidence of anal cancer.

In some population groups anal carcinoma is a common tumor and it has a premalignant period that can be detected by simple cytology. The cytologic diagnosis has reasonable sensitivity and high specificity, and histologic confirmation by high-resolution anoscopy is easily obtained if trained staff are available. The therapeutic arsenal for treating intraepithelial lesions is large, encompassing topical treatments such as imiquimod and 5-fluorouracil in addition to infrared coagulator, carbon dioxide laser therapy, and surgery. However, no optimal treatment for AIN has been established: the approach should be tailored according to the characteristics of the lesion, the patient, the availability of a treatment center, and its experience with AIN. Having a large therapeutic arsenal usually means that none of the treatments is optimally effective with minimal adverse effects. In my opinion, screening for anal cancer should be managed as screening for cervical cancer is: it should target selected populations, such as HIV-infected MSM. However, many studies are still needed to answer a series of questions. Can AIN screening reduce the incidence and mortality of anal cancer? What patient groups should screening target and how often should tests be done? Should high-resolution anoscopy be performed in all patients with a diagnosis of carcinoma of the cervix, vulva, or vagina? What about transplant patients with genital lesions caused by HPV infection? And what

about MSM not infected with HIV? Whatever the answers may be, I think that dermatologists should join multidisciplinary teams specializing in the management and early diagnosis of these patients, so that we can contribute our opinion as experts in skin cancer and venereology.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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