

LOS ANGELES

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ANAL INTRAEPITHELIAL NEOPLASIA—AIN HUMAN PAPILLOMA VIRUS—HPV

An alphabet of diseases—
some bothersome and some ominous

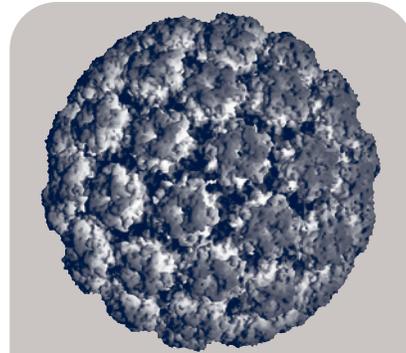
The term Anal Intraepithelial Neoplasia (AIN) describes the microscopic finding of dysplastic, non-malignant cells in the anal canal. AIN has been subdivided into AIN I, II, and III, representing low, moderate, and high-grade dysplasia. This dysplasia has been thought to arise as a result of local infection with the Human papillomavirus. The Human papillomavirus is a small double-stranded DNA virus with a diameter of 55 nm. and is encased in a protein capsid. The term

AIN has gradually replaced other descriptive terminology such as atypical squamous cells of indeterminate significance (ASCUS), low-grade squamous intraepithelial lesions (LSIL), or high-grade squamous intraepithelial lesions (HSIL).

One third of all cases of newly diagnosed sexually transmitted infections are related to HPV. Five million new cases of HPV are diagnosed each year, and at any given time in the United States, twenty million men and women have an active infection. Many patients will progress to the development of anal condyloma acuminata (genital warts). In addition, HPV is strongly associated

with the development of squamous cell carcinoma of the anus. Hence, this ubiquitous virus has taken on a more menacing significance. It is no longer

considered to be simply an inconvenient sexually transmitted disease. Many people have a genital HPV infection without exhibiting any signs or symptoms. Even when asymptomatic, the disease can be transmitted and complications of the infection may become manifest.



Atomic model of the
papillomavirus capsid.

THE MICROSCOPIC PROBLEM: Anal Intraepithelial Neoplasia (AIN)

With the development of cervical PAP smears, the relationship between cervical HPV and cervical cancer has become well-established. The relationship between anal HPV and the development of anal cancer from AIN is less well-defined. The anal canal, like the cervix, is a transition zone, transitioning from a squamous epithelium to a columnar epithelium. Anal cytology, via anal PAP smears, has been accepted as a screening tool to identify patients with anal dysplasia. There is no

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“Prevention of disease transmission is the goal in any illness... Many people have a genital HPV infection without exhibiting any signs or symptoms.”

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widespread acceptance of a particular specific screening algorithm however. This is due to variability in interpretation of AIN and limitations of our understanding of the exact relationship between HPV, AIN, and anal cancer.

Serotypes 16, 18, 31, 33, and 35 are associated with malignant potential. Transmission most commonly occurs as a result of anoreceptive intercourse. However, the virus can pool at the base of the penis, scrotum, or vagina and extend to the anal area. Infection with oncogenic serotypes can persist and result in a progression from low- to high-grade dysplasia and anal cancer.

While non-HIV infected individuals may harbor HPV and be at risk for the development of anal squamous cell carcinoma, recent studies have suggested a permissive role of HIV infection in the development of anal cancer in HIV-infected men and women. HIV-positive patients are more likely to have AIN III and are more likely to progress from AIN I to AIN III, especially with CD4 counts <200 cells/mm. With the widespread use of highly active antiretroviral therapy (HAART) in increasing the length of survival of HIV-positive individuals, we may soon see an increase in the rate of development of anal cancer in outwardly healthy but immunocompromised individuals.

THE ANAL PAP SMEAR

Many physicians have begun to use cytological testing to aid in the early diagnosis of pre-malignant or malignant changes in the anal epithelium. The anal area is brushed and the specimen is sent for cytological evaluation. This is similar to Pap smear testing for pre-malignant changes of the cervical epithelium in women. The results may be normal or may show any of the three grades of Anal Intraepithelial Neoplasia. AIN I is the earliest manifestation of dysplasia, while AIN III is associated with severe dysplasia (Bowen's disease). It is not yet clear that progression of AIN necessarily leads to carcinoma of the anus, and, it is also unclear as to whether or not eradication of these affected areas of the anal canal will lead to the prevention of carcinoma. Extrapolation from the gynecological literature and cervical dysplasia studies has prompted further research into evaluating the natural history of Anal Intraepithelial Neoplasia.

If squamous cell carcinoma of the anus is diagnosed, the standard treatment of intravenous 5-FU, mitomycin-C and radiation is used. Five year cure rates approach 84%. Follow up biopsies may be used to examine the treated area. In patients experiencing an incomplete response, or in those patients exhibiting a recurrence of the disease, an abdominoperineal resection may be used as a salvage technique.

THE MACROSCOPIC PROBLEM:

Condyloma Acuminata, A Major Nuisance

The most common clinical manifestation of HPV is that of genital warts. Sometimes called condyloma acuminata or venereal warts, these lesions are the most easily recognized sign

of a genital HPV infection. Human papillomavirus serotypes 6, and 11 comprise the major cause of cutaneous papillomas in the general population.

Genital warts are soft, moist, flesh colored and appear in the genital area within weeks or months after infection. They sometimes appear in clusters that resemble cauliflower-like bumps, and are raised or flat. In women, genital warts may present on the vulva or cervix, and inside the vagina or anus. In men, genital warts may appear on the scrotum, penis or in and around the anus. There are cases where genital warts have been found on the thigh and groin.

Oftentimes, patients are unable to relate the appearance of genital warts to any specific activity. However, genital warts are contagious and may be spread during oral, vaginal or anal sexual contact with an infected partner. They may be transmitted by skin-to-skin contact during sexual activity. Two-thirds of people who have sexual contact with a partner with genital warts will develop warts, usually within 3 months of contact.

The diagnosis of warts is easily made by visual inspection. Topically applied disclosing agents such as acetic acid may disclose otherwise invisible lesions.

There are many forms of treatment for anal warts. These include chemical methods such as podophyllin ointment, trichloroacetic acid, 0.5% podofilox solution (Condylox®), and 5% imiquimod cream (Aldara®). Common side effects of treatment include burning, redness and itching. These medications should be utilized only by physicians trained in their use. Podophyllin, podofilox and 5-FU should not be used during pregnancy.

While chemical methods may be curative, treatment may ultimately require some form of physical removal or destruction. This can be accomplished through freezing, electrodesiccation (cautery) or laser ablation. Surgical excision offers the most thorough and complete means of eradication. Subdermal injection of Interferon, more commonly used in the past, may be used to augment the treatment. Even with the best of treatments, recurrence is common and long term surveillance is necessary in order to spot recurrences as soon as they arise.

PREVENTION IS THE CURE

Prevention of disease transmission is the goal in any illness. Latex condoms are helpful but not completely protective as lesions may arise in covered areas. Misuse or failure to cover all exposed areas can also lead to the spread of disease. Regular examinations of susceptible individuals may aid in the control of early disease. The larger the load of condyloma, the more difficult is the treatment. Cytological swabbing and testing with early diagnosis may one day enable the practitioner to treat HPV while it is in the microscopic stages. Further research is necessary to clarify this issue.

Prevention remains the best cure.