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Mini Review

The Screening, Diagnosis, Treatment, and Prevention of Anal Intraepithelial Squamous Lesions in HIV-Infected Persons

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Abstract

Human Papilloma Virus (HPV) is the most common sexually transmitted infection in the world. It has been associated with multiple malignancies, in particular, anal cancer. Patients with HIV are more prone to developing HPV-associated anal lesions and are at higher risk for progression to anal cancer. Aggressive screening and diagnosis of intraepithelial anal lesions using anal cytology and high resolution anoscopy is necessary to avoid progression to anal cancer. This is particularly necessary in HIV-positive men who have sex with men (MSM) as they are a group with high rates of anal neoplasia. Treatment is typically directed toward high-grade lesions using a variety of modalities. Prevention can be achieved with administration of the HPV vaccine.

Keywords: HIV infection; AIDS; Human papilloma; Analsquamous lesions; AIN; Anal Cancer

Abbreviations

HPV: Human Papilloma Virus; HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome; MSM: Men who have Sex with Men; ASC-US: Atypical Squamous Cells of Undetermined Significance; ASC-H: Atypical Squamous Cells, Cannot Rule Out HSIL; LSIL: Low-Grade Squamous Intraepithelial Lesions; HSIL: High-Grade Squamous Intraepithelial Lesions; AIN: Anal Intraepithelial Neoplasia; HGAIN: High-Grade Anal Intraepithelial Neoplasia; HRA: High Resolution Anoscopy; IRC: Infrared Coagulation; cART: Combination Antiretroviral Therapy; ACIP: Advisory Committee on Immunization Practices; HPV: Quadrivalent Vaccine (HPV4)

Introduction

The Centers for Disease Control and Prevention (CDC) estimates that about 79 million Americans are currently infected with Human Papilloma Virus (HPV), making it the most common sexually transmitted infection [1]. HPV infection is associated with a multitude of malignancies, including anogenital cancers. In patients with Human Immunodeficiency Virus (HIV), the incidence of HPV infection is increased compared to the general population. Prevalence of anal HPV has been reported to be as high as 93% in HIV positive men who have sex with men [2]. Persistence of HPV results in intraepithelial squamous lesions, some of which may ultimately progress to anal cancer. This persistence of HPV and resultant dysplasia is likely due to the profound immunosuppression seen with HIV. In addition, HIV may promote the oncogenic potential of HPV [3]. Furthermore, though anal cancer is not an AIDS-defining illness, it appears to be AIDS related [3]. Here, we will review the diagnosis, screening, treatment, and prevention ofanal intraepithelial squamous lesions in patients with HIV.

Screening and diagnosis

There are no definitive guidelines for the screening of anal cancer. Certainly, a digital anorectal examination seems to be appropriate and cost effective to feel for any masses that might be suggestive of advanced disease. Controversy lies in who should receive screening by anal cytology. Chin-Hong and others have proposed anal screening guidelines [4]. They and other authorities recommend screening all HIV-positive patients for anal dysplasia if adequate resources are available for management, treatment and follow-up. New York State AIDS Institute guidelines recommend screening for men who have sex with men (MSM), women with a history of abnormal cervical or vulvar histology, and persons with a history of anogenital warts [5,6]. The rationale for this is largely based on targeting high risk groups, in particular, MSM who are known to be at 80 times the risk of anal cancer compared to the non-HIV-infected population [6].

Further assessment is based on the findings of the initial screening test. Screening is simple to perform and can be done in an office setting and no special preparation is required. The techniques used are similar to those used for obtaining cervical PAP smears. The health care provider simply inserts a water-moistened Dacron swab approximately 2 inches past the anal verge, rotates the swab 5-10 times to swab the squamo-columnar junction (and, therefore, maximize cellular yield), and rinses the swab in specimen solution [7,8].

Anal cytology is classified using the 2001 Bethesda System terminology for reporting results of cervical cytology. The categories are: negative for intraepithelial lesions, Atypical Squamous Cells of Undetermined Significance (ASC-US), atypical squamous cells, cannot rule out HSIL (ASC-H), Low-Grade Squamous Intraepithelial Lesions (LSIL), and high-grade squamous intraepithelial lesions (HSIL) [9]. LSIL can also be classified as Anal Intraepithelial Neoplasia (AIN) 1 and HSIL classified as AIN 2/3 [10]. It is important to remember that there is strong evidence to suggest that high-grade anal intraepithelial lesions are the precursors to anal cancer, as

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opposed to low-grade lesions, and screening and treatment is typically directed toward these high-grade lesions [11,12]. Multiple studies show that cytology appears to be a good predictor of High-Grade Anal Intraepithelial Neoplasia (HGAIN). A large review found that cytology detected ASC-US or higher in 69-93% of patients ultimately found to have HGAIN [12,13]. Although anal cytology is a good screening tool, cytological grade of disease does not correlate well with histological grade [8,14,15]. This may be due to multiple factors such as method of sample collection, cytologists' lack of familiarity with anal cytology, and incorrect sampling of lesions seen on High Resolution Anoscopy (HRA) [14]. Based on these findings, it is recommended that all patients with ASC-US or higher on cytological examination undergo HRA with biopsy [16]. That being said, some experts have argued that particular populations which have a high prevalence of AIN (i.e. HIV-positive MSM) proceed directly to HRA as the primary screening modality, in lieu of anal cytology [16].

HRA can be performed in the outpatient setting in a manner similar to cervical colposcopy. A high-resolution binocular microscope and anoscope are used to identify suspicious lesions. The addition of 3% acetic acid to identify "acetowhite" lesions which may harbor HPV as well as Lugol (iodine) solution to determine abnormal cells helps the operator better identify lesions that may need to be biopsied. The role of HPV testing for high risk types is uncertain at this time, in large part because of the high prevalence of high risk HPV in the HIV-positive MSM population [14]. Berry and colleagues have shown that the combination of cytology and high risk HPV typing has high sensitivity, but poor specificity, for detecting HGAIN in both HIV-positive and HIV-negative MSM and that it may be most useful in the HIV-negative MSM patient [17].

Treatment

The primary goal is to treat HGAIN to prevent progression to anal cancer, though whether treatment prevents progression to cancer is controversial [4,18]. This can be accomplished by various means such astopical therapy, physical destruction using ablation/infrared coagulation, and surgery. No consensus exists as to which is the best modality for treatment of AIN [19].

Topical therapy appears to be most effective in patients with small, localized lesions [4,11]. Some common modalities employed in topical treatment include podophyllotoxin, 80% trichloracetic acid, imiquimod, and liquid nitrogen. Response rates for HGAIN of ~ 70% and overall efficacy in clearance of AIN in MSM HIV-positive and HIV-negative patients have been shown with the use of trichloracetic acid [20]. Immunomodulatory treatment utilizing imiquimod 5% cream has been shown to very effective (especially for multifocal disease) and is recommended "as a safe effective topical treatment" in guidelines issued by the Association of Coloproctology of Great Britain and Ireland [21-23].

For larger lesions that are not amenable to topical therapy, infrared coagulation (IRC) and electrocautery ablation have been used with success [24-27]. IRC involves the delivery of short (1.5 sec) bursts of visible infrared light through a contact tip resulting in thermal coagulation and necrosis of tissue [28]. Although not FDA-approved for the treatment of AIN/SIL here in the USA, Goldstone and colleagues have shown IRC ablation to be quite effective for managing anal HSIL and found no patients that progressed to anal squamous cell cancer in long-term follow-up [24]. Electrocautery has also shown to be a successful treatment modality and, like IRC, can be performed in an in-office setting. One study examining 232 MSM HIV-positive and HIV-negative patients showed cure rates of 75% and 85%, respectively, with recurrences being more common in HIV-positive individuals [27].

Finally, local surgical excision is occasionally used for extensive disease. However, careful consideration should be taken when excising wide/large lesions as excision is fraught with post-op complications such as stenosis, pain, bleeding, and infection [16,23].

The effect of Combination Antiretroviral Therapy (cART) on HPV incidence and persistence as well as the incidence of AIN is controversial. More recent studies appear to show that cART may lower the prevalence of AIN and/or anal HPV in HIV-infected MSM [29,30]. Further study will be required to confirm or refute these findings.

Prevention

The primary method to prevent anal intraepithelial lesions and, ultimately, anal cancer, is directed toward the prevention of HPV infection. This is largely achieved through the use of HPV vaccines. Currently, there is a bivalent and quadrivalent vaccine available for the prevention of HPV. Both vaccines afford protection from HPV16 and HPV18, with the quadrivalent providing additional protection against HPV6 and HPV11, which have been implicated in causing anogenital warts [32]. The HPV quadrivalent vaccine (HPV4) was shown to reduce the incidence of persistent anal infection with the above four types and prevented HPV-related AIN, though the study was too short in duration to show efficacy in preventing anal cancer [32]. The Advisory Committee on Immunization Practices (ACIP) recommends that girls and boys be vaccinated at age 11 or 12 years based on the benefit of these vaccines to prevent cervical, vaginal, vulvar, and anal cancer precursors [31]. In addition, the ACIP recommends vaccination of all MSM and bisexual persons through 26 years of age [31].

Conclusion

Given the prevalence of HPV and its relationship to anal intraepithelial lesions and anal cancer, providers need to be vigilant and aware of this ubiquitous virus. In particular, patients with HIV who are infected with HPV are at higher risk for AIN and need to be screened, diagnosed and treated in a timely fashion to prevent further progression of these lesions. The lack of specific consensus on screening, diagnosis and treatment of AIN should encourage more research in this area. Finally, vaccination for HPV serves an important role in the prevention of AIN and, ultimately, anal cancer.

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