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Anal Squamous Intraepithelial Lesions and Cancer: An Underappreciated Risk in IBD

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INTRODUCTION

Anal squamous intraepithelial lesions (SIL) are precancerous lesions of the anal squamous epithelium that can progress to anal cancer. Anal cancer is rare in the general population. However, rates are markedly higher among specific risk groups and have been steadily increasing in the past two decades. Anal squamous cell carcinoma is thought to occur through progression of high grade squamous intraepithelial lesions (HSIL) via the effect of particular high-risk subtypes of the human papilloma virus (HPV). The risk of SIL and anal cancer are elevated in certain populations, especially in people living with human immunodeficiency virus (HIV). Identifying and treating these lesions reduces the risk of progression to anal cancer. Most recent society guidelines suggest screening for anal cancer in those with HIV. However, there are additional at-risk groups that may warrant consideration for screening.

The risk of anal squamous intraepithelial lesions and anal cancer is elevated in inflammatory bowel disease (IBD). Patients with IBD appear to have increased prevalence of high-risk HPV subtypes. In an uncontrolled cross-sectional study of forty-five sexually active male and female patients with IBD, 89.1% were positive for anal HPV, with HPV 16, the highest risk subtype, being the most prevalent strain. Four patients (8.7%) had HSIL present on biopsy, while twenty-four (43.5%) had low grade squamous intraepithelial lesions (LSIL).[1] Anal cancer risk is highest in Crohn's disease,

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particularly when perianal fistulizing disease is present. In a large cohort study, the incidence rate of anal squamous cell carcinoma (SCC) in patients with perianal Crohn's disease was 26 per 100,000 person-years, which was greater than their risk of colon adenocarcinoma by about two-fold. In this cohort, most anorectal cancers associated with Crohn's disease were adenocarcinomas, and were associated with fistulas.[2] In a review of sixty one anal cancers arising from fistulas, adenocarcinoma was responsible in 59%, and anal SCC was responsible in 31%.[3] This review will focus on anal cancer and HSIL to increase awareness among gastroenterologists who manage IBD.

Anal Squamous Cell Carcinoma

Anal cancer is a rare but increasingly more prevalent cancer that disproportionately affects certain population groups. SCC makes up the majority of anal cancers, comprising about two thirds of anal cancer cases in the United States.[4] While rare in the general population (about 1 per 100,000 person-years), certain risk groups carry a much higher risk of anal SCC. Anal SCC incidence is estimated at 85 per 100,000 person-years in men who have sex with men (MSM) living with HIV which is the group with the highest known risk. Among men who have sex with women (MSW) living with HIV, the risk is lower at 32 per 100,000 person-years. In women with HIV, the risk is 22 per 100,000 person-years. Other groups with risk above the general population include women with prior HPV related gynecological precancerous lesions, solid organ transplant recipients, and patients with immune mediated diseases such as IBD and lupus.[5] While other HIV associated cancers such as non-Hodgkin's lymphoma and Kaposi Sarcoma have fallen in incidence since the emergence of HIV/AIDS, anal cancer continues to rise in incidence, at 2.7% per year between 2001 and 2015.[6] This rise in anal cancer rates may be related to the aging population of persons living with HIV, as rates have increased the most in people above age fifty.[6]

Presenting symptoms of anal SCC are bleeding or anal pain, although twenty percent of patients with anal SCC are asymptomatic at presentation. On exam, patients may have a palpable mass or area of bleeding. Anal cancer is staged by Tumor Nodes & Metastases (TNM) classification. Prognosis for early stage (I or II) is good with five-year survival of 86%, while T4 cancers or node positive cancers have five-year survival rates of about 50%.[7] However, the prognosis for IBD patients is worse than in patients without IBD, as a systematic review of IBD patients with non-fistula associated anal SCC found an overall five-year survival of 37%.[8] A more recent analysis of over 61,000 patients with HPV-related cancers found that patients with IBD and anal cancer had a median survival of 46 months versus 61 months in non-IBD patients.[9] This difference in survival is thought to be due to more advanced malignancy at diagnosis and the presence of pelvic sepsis in Crohn's disease limiting the ability to use radiotherapy.[8]

Diagnostic evaluation includes physical exam with inguinal lymph node evaluation, biopsy of the lesion, chest and abdomen contrast-enhanced computed tomography (CT), pelvic CT or magnetic resonance imaging (MRI) with IV contrast, anoscopy, HIV testing (if unknown), gynecologic exam, and consideration of fertility risk counseling.[10] Treatment of T1, node negative, well differentiated tumors is with local excision, while more advanced tumors are treated with combination chemoradiation.[10]

Anal Squamous Intraepithelial Lesions

Anal cancer is preceded by changes in the epithelial layer of the anal canal mediated by HPV which parallel the types of changes seen in the cervical epithelium. This has led to the adoption of the same nomenclature and classification used in the care of cervical precancerous lesions. Often referred to as "anal dysplasia", these changes are now referred to as squamous intraepithelial lesions (SIL), with a two-tiered subdivision into LSIL and HSIL.[11] This replaces the prior system of classification that utilized the terminology anal intraepithelial neoplasia (AIN). While LSIL is associated with condyloma and not thought to be a direct precursor to anal SCC, HSIL carries a markedly increased risk of progression to anal cancer. In a large population-based study, the 5-year risk of progression from HSIL to anal cancer in MSM living with HIV was 14.1%, and in MSM not living with HIV was 3.2%. In the same study, a diagnosis of LSIL carried a 5-year risk of 0.15%, which is higher than the risk if no LSIL was present.[12] HSIL may spontaneously

regress, with regression rates between 20-30%.[13,14]

HPV is the major causative factor in inducing squamous intraepithelial lesions. Of the numerous subtypes of HPV, there are specific types that are most likely to cause ASIL. HPV 16 is the type most highly associated with HSIL and anal cancer.[15] Other oncogenic HPV types that affect the anogenital area are 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68.[16] HPV types 6 and 11 are responsible for benign genital warts. Overall it is estimated that high-risk HPV is a causative factor in over 90% of anal squamous cell carcinomas.[17]

HSIL is usually asymptomatic, although it can be associated with anal pain, pruritis, or bleeding.[18] Additionally, HSIL typically cannot be palpated during a digital anal rectal exam (DARE).[19] In contrast, LSIL cause condylomas or warts, which are more readily identified by patients and providers.[20] Methods of identifying underlying HSIL have borrowed from techniques used to identify cervical intraepithelial neoplasia, given their pathophysiologic similarities. Identifying the presence of HSIL involves both cytology and direct visualization techniques. Initial screening is with anal cytology, commonly referred to as an anal Pap smear. Using a moistened brush or nylon/polyester swab, epithelial cells are scraped from the surface and the swab is placed into a transfer medium as in cervical cytology testing. This is then examined under microscopy. Anal cytology has modest sensitivity and specificity, with pooled sensitivity of 85% and pooled specificity of 43.2% for the identification of HSIL, which is comparable to the performance of cervical cytology.[21,22]

As with in cervical cancer screening, if anal cytology identifies an anal squamous intraepithelial lesion, this should be followed by high resolution anoscopy (HRA), a procedure analogous to cervical colposcopy. In this procedure, the anorectal area is examined under high magnification by a colposcope. Acetic acid is applied to the anal epithelium along with lugol's solution. Areas with squamous intraepithelial lesions will display characteristic patterns of acetowhitening, which can then be sampled via biopsy for histology. HRA has been found to be well tolerated with most patients reporting acceptable pain levels and willingness to follow-up as recommended.[23]

At Risk Populations

Those living with HIV, and particularly MSM with HIV, are at markedly increased risk for anal premalignant lesions as well as anal cancer. This is felt to be due to the effect of HIV on the immune system leading to increased HPV activity and persistence.[24] HPV prevalence is highest in MSM with HIV, followed by MSM without HIV. People living with HIV are more likely to carry more than one oncogenic strain of HPV, which may also contribute to the higher risk.[15] Among those with HIV, low current CD4 count was associated with HPV16 infection, HSIL, and HPV16-positive HSIL. Anal cancer incidence rate (IR) in MSM with HIV has been estimated in a recent meta-analysis at 85 per 100,000 person-years, while IR in MSW with HIV was 32 per 100,000 person-years, and IR in women with HIV was 22 per 100,000 person-years. The IR for MSM with HIV who are age ≥ 60 was even higher at 107.5 per 100,00 person-years.[5]

MSM without HIV are also at increased risk. People identifying as MSM have a high prevalence of high-risk HPV subtypes, with about 14% prevalence of HPV16 versus 2% in men who are not MSM in a large meta-analysis. The pooled prevalence of HSIL in MSM patients without HIV in the same meta-analysis was 11.3%.[25] Anal cancer incidence rate in MSM not living with HIV is estimated to be about 19 per 100,000 person-years, a nearly 20-fold increase in risk from the general population.[5]

Women with prior cervical neoplasia are at particular risk for anal SCC. Numerically more anal SCC is diagnosed in women, particularly women above age 50.[26] Women with cervical high-risk HPV strains are likelier to have high-risk anal HPV strains.[27] In a cross sectional study of 324 women with prior cervical, vulvar, or vaginal high grade dysplasia or cancer, there was a 28% prevalence of anal high risk HPV and anal cytology was abnormal in 23%. In a large population-based cohort study involving 89,010 women with a diagnosis of cervical intraepithelial neoplasia grade 3 (CIN3)

matched to an equal number of healthy controls, those with CIN3 had increased risk of AIN3 (HSIL) and anal cancer with incidence rate ratio of 6.68 (95% CI, 3.64 - 12.25) and 3.85 (95% CI: 2.32 - 6.37) respectively.[28]

Other risk factors for anal SCC include solid organ transplantation, smoking, early sexual debut, multiple sexual partners, and receptive anal intercourse. Patients and providers should be aware that receptive anal intercourse is not required for the introduction of HPV to the anorectal region, and development of HSIL or anal cancer can occur without a history of receptive anal intercourse.[19]

Screening

Given the presence of a discrete precursor lesion and the identification of at-risk groups, programs have been proposed and developed for anal cancer prevention. The current available modalities for screening are physical exam with DARE, anal cytology, anal HPV testing, and HRA. Currently, only the New York State Department of Health AIDS Institute provides guidelines for anal cancer screening. In this algorithm, all patients with HIV ≥ 35 years old should receive annual physical examination and DARE. For patients with HIV above age 35 who are transgender or MSM, annual anal cytology should be performed. If results of cytology indicate the presence LSIL or HSIL, patients should be referred for HRA. If results indicate abnormal squamous cells of undetermined significance (ASC-US), testing for high risk HPV should be performed, and if present, the patient should be referred for HRA.[29] Other expert opinion suggests consideration of screening for additional at-risk populations, including: 1) MSM not living with HIV > age 40, 2) persons with a history of HPV-associated genital cancers, 3) solid organ transplant recipients, and 4) other immunocompromised people not living with HIV.[19]

The results of the Anal Cancer HSIL Outcomes Research trial (ANCHOR) published in 2022 have now demonstrated benefit to treating HSIL lesions in MSM with HIV above age 35 when compared with active monitoring, with a cumulative progression to anal cancer of 0.9% at 48 months in the treatment arm versus 1.8% at 48 months in the active monitoring group. While the trial showed benefit to screening, it also highlighted the need for better ways of preventing progression to anal cancer, as not all cancer was prevented even with treatment.[30] Treating HSIL when present in patients above age 35 has also been shown to be cost effective in a separate study.[31]

It is likely that screening patients with IBD would provide benefit, especially for those on long-term immunosuppression or with multiple risk factors for anal cancer. There is a paucity of data examining the effect of immunosuppressing medication use on anal cancer risk in IBD patients. In patients who receive immunosuppression for solid organ transplantation, the risk of anal SCC is estimated to be as high as 49.6 per 100,000 person-years, which is comparable to patients living with HIV. The risk was higher the further from transplantation. In a recent review of heart transplant recipients, the incidence rate for anal SCC was even higher, at 136 per 100,000.[5,32] IBD patients receive long term immunosuppression, often life-long, which may put them at a similar risk level. Although not currently recommended by published society guidelines, given the risks outlined, screening for anal cancer (including DARE, cytology, and HRA when indicated) should be strongly considered for IBD patients, and especially when multiple risk factors are present, such as MSM status, history of anal intercourse, or cervical dysplasia.

HPV Vaccination

HPV vaccination has been available since 2006 and offers the promise of decreasing the burden of HPV and its related cancers by preventing initial HPV infection. The current pentavalent *Gardasil 9* covers HPV 6 and 11, which cause genital warts, and HPV 16, 18, 31, 33, 45, 52, and 58 which are responsible for anogenital and head and neck cancers. Current Center for Disease Control guidelines recommend vaccination for persons between age 12 and 26, and can be initiated as early as age 9. Vaccination can be extended to age 45 if it is felt it would provide benefit after shared clinical decision making with the patient. A two-dose series is recommended between 9 – 15 years of age. A three-dose series is recommended after age 15 and in immunocompromised people.[33] Testing for HPV subtypes prior to administering the vaccine is not recommended, and administering the vaccine can

be beneficial even after sexual debut, especially in high-risk populations.[19]

HPV vaccination is approved only for preventive use and not for therapeutic use. Vaccination against HPV has been evaluated in MSM living with HIV as an adjunctive therapy to prevent HSIL recurrence after HSIL treatment, but data is limited. In a prospective study of MSM diagnosed with HSIL, vaccination with the quadrivalent HPV vaccine was associated with decreased recurrence of HSIL at one- and two-years post HSIL treatment but was non-significant at three years after treatment.[34]

In IBD patients, HPV vaccination is recommended following the same guidelines as for the general population.[35] No studies have looked at immunogenicity of HPV vaccination in IBD patients on immunosuppression. Studies in other immunocompromised groups show lower antibody titers in these patients compared to healthy controls, but the clinical significance of lower titers and impact on efficacy is unknown.[36] Adherence to HPV vaccination guidelines has not been studied in men with IBD. However, in women with IBD, knowledge of HPV vaccination and uptake is low, despite women being the initial population identified as benefiting from vaccination and the well-studied risks of cervical neoplasia in women with IBD.[37] Therefore, it is likely that knowledge of HPV vaccination and uptake is even lower in men with IBD.

CONCLUSION

Anal cancer is a rare but increasingly prevalent cancer that disproportionately affects at-risk groups including patients with IBD. Progression to anal SCC typically occurs through development of HSIL. This lesion can be identified by cytology or high resolution anoscopy, and treatment has been found to decrease progression to anal squamous cell cancer. IBD patients are at increased risk for anal cancer, and providers taking care of IBD patients should ensure all IBD patients regardless of sex are vaccinated for HPV and discuss screening with patients. Open discussion of sexual orientation and practices with IBD patients will help to risk stratify, as MSM patients and those participating in receptive anal intercourse are at further increased risk.

Anal cancer incidence has been shown to increase with age in immunocompromised populations, and as IBD patients age in the biologic era, the risk of anal SCC may increase further with time. Further data is needed regarding the differential risk of various IBD phenotypes and the impact of IBD medications on anal cancer risk. Established guidelines suggest screening in persons living with HIV who are older than 35, but these guidelines are likely to evolve as the evidence in favor of screening specific groups grows. Comprehensive care of IBD patients requires an awareness of anal cancer risk and initiating screening and prophylaxis when appropriate. ■

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Answers to this month's crossword puzzle: