Anal Squamous Cell Carcinoma in the HIV-Positive Patient

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ABSTRACT

Epidermoid carcinoma of the anal canal is uncommon. The incidence of this disease has increased in HIV-positive men who have sex with men and the disease process is different from in HIV-negative patients. Modern therapy of HIV with highly active antiretroviral therapy (HAART) has improved the overall survival of HIV patients and allowed effective therapy for those who develop epidermoid carcinoma of the anal canal. This article describes the disease process and current treatment options.

KEYWORDS: Epidermoid carcinoma of the anus, HIV, anal cancer

Objectives: On completion of this article, the reader should be able to describe the relationship of HPV, HIV, and epidermoid cancer of the anal canal.

In the early years of the AIDS epidemic, many patients died of overwhelming infection due to their immunocompromised status. Only after the development of highly active antiretroviral therapy (HAART), in the mid-1990s, did HIV-positive patients begin to have longer life expectancies. In many cases, HIV infection became a chronic disease and new clinical phenomena began to become apparent. As patients lived longer with reconstituted immune systems, they began to manifest new phenotypes of HIV infection.

Cancer of the anal canal is still a relatively uncommon disease in the United States. The National Cancer Institute SEER statistics estimated just over 5000 cases of anal squamous cell carcinoma (SCC) in 2008.¹ The ratio of affected women to men is 3:2 and age-adjusted incidence rate was 1.5 per 100,000 men and women per year. However, there has been an increased incidence of anal SCC primarily seen in HIV-positive men who have sex with men (MSM).^{2,3} During the era of HAART, the incidence of anal cancer in HIV-

infected homosexual men has increased sharply, with ~70 new diagnoses per 100,000 patients.

ETIOLOGY

It is well understood that human papilloma virus (HPV) is the major causative agent for anal SCC.⁴ Although HIV is not the primary etiologic agent in anal SCC, infection with HIV is a marker for coinfection with other sexually transmitted diseases, including HPV.

HPV is a DNA virus, often sexually transmitted, that causes anal SCC. There are many viral subtypes; HPV 16 and 18 have the highest malignant potential.⁵ Understanding of anal carcinogenesis is based on cervical carcinogenesis, which is an identified pathway of HPV infection, persistence of infection, development of dysplasia, and progression to invasive carcinoma.⁶ HPV-infected anal mucosal cells undergo this temporal progression, with the stages of dysplasia graded as anal intraepithelial neoplasia (AIN). Reverse steps in this

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pathway can include clearance of HPV infection and regression of dysplasia.

A common mechanism of tumorigenesis is inactivation of tumor suppression genes via loss of heterozygosity (LOH). In patients who are HIV-negative, mutations in the p53, DCC, and/or APC tumor suppressor genes are identified as antecedent events. The genomic changes of LOH are most commonly seen at loci 11q23, 17p, 18q, and 5q.⁷ Much like the development of colorectal adenocarcinoma, a pattern of chromosomal instability is evident in the genesis of these cancers.

HIV infection attenuates the host response to HPV infection, and the HPV virus can integrate into the host genome. Patients with greater levels of immunosuppression, marked by lower CD4+ counts, have a higher incidence of persistent HPV infection and greater incidence of AIN.⁸ Research into the mechanism of carcinogenesis in HIV-positive patients suggests that immunosuppression may play a stronger role in the earlier stages of the pathway: persistence of HPV infection and development of dysplasia. However, the LOH seen in HIV-negative patients is not replicated in HIV-positive patients and an alternative pathway of microsatellite instability is postulated to contribute to the progression to actual invasive cancer.⁹

PRECURSOR LESIONS AND THEIR TREATMENT

Anal intraepithelial neoplasia (AIN) describes the dysplastic changes in the anal canal that are precursors to invasive anal carcinoma. AIN grades 1, 2, and 3 reflect low-, moderate-, and high-grade dysplasia. Grades 2 and 3 are often grouped together as high-grade squamous intraepithelial lesions (HSIL) and are associated with a higher risk of invasive cancer. Data shows that these lesions are most frequently identified in HIV-positive patients and MSM.¹⁰ They are also seen in other immunosuppressed individuals such as transplanted patients.¹¹ The natural history of AIN is not entirely known. In particular, the rate of progression of untreated AIN to cancer is not defined.

The assessment and treatment of these precursor lesions is extrapolated from the management of cervical intraepithelial neoplasia (CIN), given the biological similarities between AIN and CIN. Current screening practices include anal PAP smear and high-resolution anoscopy (HRA).

Anal PAP smear assesses for cytological abnormality in the anal canal. Traditional slide preparation of anal PAPs can have a high rate of technically unsuitable samples and requires consistent training of practitioners.¹² The sensitivity of this test using liquid medium is high for any cytological abnormality, but it has low specificity for high-grade disease.¹³ As recently as

2006, a systematic review of the current evidence for anal PAP screening in HIV-positive patients documents the increased risk of anal cancer in these patients, but could not support routine use of the test.^{14,15}

Currently, due to the low specificity for HSIL of anal PAP, any abnormality is referred for HRA (high resolution anoscopy). HRA is a direct modification of colposcopy. It has a steep learning curve and the results are operator dependent, but improve with experience. Reports of concordance between operator observation and pathology can have significant variability.

Again extrapolating from cervical cancer, screening programs have been initiated with the assumption that screening will have an impact. The progression from HSIL to invasive anal SCC is inferred from CIN progression. A meta-analysis recently predicted the 6-month rate of this conversion to be well under 0.01%.¹⁶ The rate of regression of CIN in older studies is higher than the rate of progression.¹⁷ Metrics for AIN progression are not documented, but it is inferred that immunosuppressed and HIV-positive patients will likely have a higher rate of progression than other patients. A recent evaluation of their own established anal dysplasia screening programs led the authors to not support a comprehensive screening program at this time based on available data and resources.¹⁸

Current published treatment regimens include ablative and topical therapies. Ablative therapies include surgical excision, infrared coagulation (IRC) and thermal ablation. Topical therapies include immunomodulators such as imiquimod, podophyllin, or 5-FU. There are no published controlled trials of these various treatment regimens to guide best practice. Current literature documents the effectiveness of some treatments on AIN. Infrared coagulation (IRC), laser, and imiquimod are treatments reported to clear or resolve AIN in affected patients.^{19–21} However, the impact of AIN treatment on anal cancer development has not been established. The appropriate screening for, and treatment of AIN, is a subject of ongoing debate and study.

PRESENTATION, DIAGNOSIS, AND STAGING EVALUATION

Before the HIV epidemic, Caucasian women in their sixties had the highest incidence of anal SCC. After HIV infection became prevalent and the introduction of HAART, a different population of patients was identified that had an increased risk of anal SCC. As previously noted, HIV-positive MSM are at the highest risk of developing anal cancer. The mean age of presentation in this population is in the 4th decade of life.²² Therefore, patient age at disease onset is earlier in HIV-positive patients than non-HIV-positive patients. Pre-HAART, the diagnosis of anal SCC often fairly quickly followed the diagnosis of HIV disease. In

HAART-treated patients, there is substantial delay from the time of diagnosis of HIV disease to diagnosis of anal SCC, which averages 10 years or more. Lower CD4+ counts have been linked to increased risk of anal SCC correlating with increased immunosuppression.³

The clinical presentation of anal SCC in non-HIV-positive patients is typically rectal bleeding and/or pain, and the primary physical exam finding is a rectal mass. HIV-positive patients can have a variable clinical presentation. HAART patients can present with anal masses or erosive perianal ulcerations or fistulae-in-ano.²³ Like non-HIV-positive patients, rectal pain and bleeding were the primary symptoms pre-HAART. After HAART, other nonspecific anorectal symptoms, such as mucus drainage and pruritus, became more prevalent in the presentation of anal cancers.

Definitive pathologic diagnosis is made, of course, by biopsy. Because of the erosive or burrowing nature of these neoplasms, traditional incisional biopsy can be insufficient to make the diagnosis even when performed in the operating room. Superficial biopsies may reveal only nonspecific ulceration, dysplasia, or necrosis. Core biopsies (such as Tru-cut or laparoscopic liver biopsy needle) through the lesion to the deeper layers of the anal canal can be helpful in conclusively demonstrating the presence of invasive cancer.

Variations in clinical presentation do not alter the staging work-up of anal cancer. Local and distant tumor is assessed by imaging studies. Pelvic magnetic resonance imaging (MRI) or anal ultrasound is used for T staging. Local and regional lymph nodes are evaluated by MRI or pelvic computed tomography (CT). A CT scan of the chest, abdomen, and pelvis is performed to evaluate for metastatic disease.

TREATMENT

Prior to Nigro's landmark article in 1974, the standard treatment for anal SCC was an abdominoperineal rectal resection (APR) with permanent end colostomy, with expected 5-year survival rates of 50 to 70%. The Nigro protocol of radiation therapy to the pelvis and tumor combined with systemic chemotherapy results in a cure rate of 80 to 90%, and has replaced the APR as the standard of care.²⁴ Surgical treatment has been relegated to cases of persistent or recurrent disease, or when a patient has a contraindication to chemotherapy or radiation.

HIV-positive patients with anal cancer are likewise treated with chemoradiation. Initial reports of HIV-positive patients who were not on HAART, albeit small patient studies, were discouraging, with inability to complete treatment and absent disease control.²⁵ Other studies compared HIV-positive with HIV-negative patients and found a significant worsening of acute

treatment toxicity for HIV-positive patients and decreased tumor response to treatment.²⁶

After the development of HAART, HIV-positive patients fared better with combined chemoradiation. Recent studies show reasonable tolerance of therapy in these patients, but with a consistent trend to greater dermatologic, gastrointestinal, and hematologic acute toxicity. In some studies, two-thirds of patients required treatment breaks. Reports of long-term local control are also still lower than that seen in HIV-negative patients.²⁷⁻²⁹

As databases have matured, results of chemoradiation for HIV-positive patients appear to have improved and in some cases are equivalent to HIV-negative patients.³⁰ These results may reflect better immune-reconstitution and better supportive management of expected toxicities during therapy. A large Veteran's Administration (VA) database study reported that survival was equivalent between HIV-positive and HIV-negative patients in the era of HAART and concluded that no patient should be denied treatment based on HIV status.³¹

All cancer patients undergo surveillance after completion of treatment to assess for recurrent disease. It is important for the colorectal surgeon to remain involved in patient follow-up to assess for local recurrence. There is no documented role for routine posttreatment biopsy in the anal cancer patient. However, posttreatment biopsy is essential for persistent abnormality 8 to 12 weeks after treatment is completed. Surveillance assesses for local, regional, and metastatic disease. HIV-positive patients may be at increased risk for recurrent or new cancers in the treatment field as the underlying promoter of carcinogenesis, that is HIV and HPV coinfection, is not eradicated by chemoradiation.

Heretofore, patients who have recurrent or persistent disease after chemoradiation are treated with salvage surgery with abdominoperineal resection. Recent data corroborates earlier reports that ~30 to 35% will achieve long-term survival.³² However, significant morbidity is associated with this procedure, and there are no studies of salvage surgery in the HIV-positive population.

CONCLUSIONS

Anal SCC in HIV-positive patients is a different disease process than anal SCC in non-HIV patients. Prolonged coinfection with HIV and HPV collaborates in creating an increased risk of neoplasia over patients without coinfection. The carcinogenic pathways may be different than in non-HIV patients.

Patients at highest risk are MSM. The clinical presentation of these patients differs from others: they present in their 40s and there are multiple clinical disease

presentations. Fistulae and ulcers are equally common presentations as anal masses in these patients.

Chemoradiation is the standard of care for all patients, regardless of HIV status. Treatment of anal SCC should not be modified based on HIV status, although additional treatment supports and breaks may be necessary. HIV-positive patients who are on HAART clearly fare better during treatment; acute toxicity and local control of disease remain challenges. Treatment modifications may enhance tolerance and effectiveness of treatment.

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