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ANAL INTRAEPITHELIAL NEOPLASIA: DIAGNOSIS & TREATMENT
Case

- 49 HIV positive male
- 6 months history of pruritus ani, rectal bleeding associated with a skin lesion at the left side of the anal verge,
- Patient is a male having sex with men
- Highly active antiretroviral treatment (HAAR) over the last 15 years,
- In good general health
Case

- PR & Anoscopy: A single lesion, 1 cm diameter with white plaques. Anoscopy did not reveal additional lesions @ anal canal.
- Excisional biopsy: Foci of Squamous Cell Carinoma *in situ* arising on background of condylomatous lesion,
- Repeat random biopsies circumferentially at the anal verge showed same pathology of SQUAMOUS INTRAEPITHELIAL NEOPLASM.
ANAL INTRAEPITHELIAL NEOPLASIA

Introduction

- The anal and cervical canal share embryologic, histologic, and pathologic characteristics.
- Both develop from the embryonic cloacal membrane, and are sites of fusions of endodermal and ectodermal tissue to form a squamocolumnar epithelial junction.
- Both areas may display normal metaplastic change and abnormal dysplastic change related to infection with human papillomavirus (HPV).
Introduction

- The biologic consequences of anal intraepithelial neoplasia (AIN), also termed anal squamous intraepithelial lesions (ASIL) and anal dysplasia, are considered analogous to those of cervical dysplasia.
- AIN may be further subdivided into low-grade AIN (LG-AIN) and high-grade AIN (HG-AIN).
- Anal HG-AIN is considered premalignant and may progress to cancer, similar to the progression of cervical HG-CIN to cervical cancer.
Risk Factors in the development of AIN

- HPV infection
- receptive anal intercourse
- HIV infection
- lower CD4 levels
HPV infection of the anal canal and perianal region

- may be latent, subclinical, or clinically apparent as condylomata
- Latent infection may last eight months or longer
- some individuals never develop clinically apparent lesions
- Subclinical anal infections, such as the presence of HG-AIN
  - high-resolution anoscopy (HRA)
- Condylomata clinically obvious and often have a plaque-like appearance
HPV

- (PCR) technology - 29 individual HPV types
- men who have sex with men (MSM), both with and without HIV infection - high incidence of HPV infection and anal cancer
Anal condyloma

Photograph shows the characteristic verrucous, pink or skin-colored, papilliform appearance of anal condyloma acuminata. In contrast, anal squamous cell carcinoma has a smooth and pearly appearance and may contain areas of hemorrhage and necrosis.

*Reproduced by permission from the American Society of Colon and Rectal Surgeons.*
HIV infection

- HPV infection is associated with an increased risk of incident AIN in HIV-positive individuals
  - high-risk sexual behavior
  - infection with multiple HPV types
  - impaired mucosal immune response that facilitates HPV replication
- The current incidence of anal cancer among HIV-positive MSM has been estimated to be at least twice that of HIV-negative MSM
HIV & highly active antiretroviral therapy (HAART)

- reduces the incidence of HIV-associated malignancies such as Kaposi’s sarcoma
- HAART does not appear to alter the prevalence of AIN
- HAART may facilitate the progression of HG-AIN to anal cancer due to its increasing life expectancy
High-risk sexual behavior

- The prevalence of anal HPV infection in MSM is high at all ages between 18 and >50 years and ranges between 50 and 60 percent.
- In women, risk factors for AIN include a history of receptive anal intercourse and presence of HPV DNA.
- HIV-positive women with abnormal cervical cytology have an increased risk of concurrent abnormal anal cytology.
Other risk factors

- In men:
  - history of rectal discharge
  - history of genital warts
  - injection drug use
  - current cigarette smoking

- In women:
  - current cigarette smoking
  - vulvar cancer
  - high-grade CIN or vulvar intraepithelial neoplasia
  - iatrogenic immunosuppression, such as following solid organ transplantation
The anus consists of a mucosa-lined anal canal and an epidermis-lined anal margin. The proximal end of the anal canal begins anatomically at the junction of the puborectalis portion of the levator ani muscle and the external anal sphincter, and extends distally to the anal verge, a distance of approximately 4 cm. The anal canal is divided by the dentate line, which overlies the transition from glandular (columnar) to squamous mucosa that is often referred to as the transitional zone. The anal margin begins approximately at the anal verge, which corresponds to the introitus of the anal orifice. It represents the transition from the squamous mucosa to the epidermis-lined perianal skin, and extends to the perianal skin.
PATHOLOGY

- HG-AIN
  - histologic grades AIN 2 and 3
  - abnormal basaloid cells, characterized by an increased nuclear to cytoplasmic ratio, replace more than one-half of the epithelium

- LG-AIN
  - histologic grade AIN 1
  - 20 to 25 percent of the epithelium is replaced by abnormal cells

- Lesions showing evidence of LG-AIN may spontaneously regress

- Lesions showing evidence of LG-AIN may spontaneously regress - true precursor of invasive anal squamous cell carcinoma
Schematic presentation of different grades of anal squamous intraepithelial neoplasia (ASIL). ASIL grade I is characterized by 20 to 25 percent replacement of the epithelium with immature cells with high nucleus:cytoplasm ratios. Approximately 50 percent of cells are replaced with immature cells in ASIL grade 2, and complete or nearly complete replacement occurs in grade 3. Microinvasion, shown at the bottom, occurs when the cells traverse the basement membrane. Although microinvasion can occur in conjunction with ASIL grade 1, it is more likely to occur in conjunction with grades 2 or 3. The increasing risk of invasive cancer with increasing severity of dysplasia is depicted by the size of the tumor underneath the basement membrane at various stages of disease. Invasive cancer rarely if ever progresses directly from condyloma or mild dysplasia. Reproduced with permission from Ferenczy, A., Winkle, B. Cervical intraepithelial neoplasia and condyloma. In: Blaustein’s Pathology of the Female Genital Tract, 3rd ed., Kurman, R (Ed). Springer Verlag, New York 1987, pp.177-217. Copyright © 1987 Springer-Verlag.
CLINICAL MANIFESTATIONS

- Mostly asymptomatic,
- Pruritus,
- Bleeding,
- Discharge,
- Irritation,
- Tenesmus,
medical history

- History of clinical HPV infection and other sexually transmitted infections
- Sexual history including specific inquiry about receptive anal intercourse
- HIV serostatus and markers of infection (CD4+ level and viral load)
- Previous anal/gastrointestinal conditions
- Local symptoms (pain, itch, bleeding, discharge, irritation, tenesmus)
- Smoking history
The physical examination

- The physical examination,
- Digital and high-resolution anoscopy examination of the anal canal,
- Anal cytology,
- Examination of the inguinal lymph nodes,
Anal squamous intraepithelia neoplasia

(A) Bowenoid anal intraepithelia neoplasia.
(B) Erythroplakic anal intraepithelial neoplasia.
(C) Leukoplakic anal intraepithelial neoplasia.
(D) Verrucous anal intraepithelial neoplasia.

Perianal pigmented anal intraepithelial neoplasia III lesion (black arrow) and associated white plaque (white arrow).
TREATMENT

- **Topical therapy**
  - For small lesions (<1 cm² at the base)
  - Local application of bichloroacetic or Trichloroacetic acid
  - Topical 5-fluorouracil

- **Immune modulation**
  - Imiquimod (ALDARA) - can result in pathological resolution of AIN in HIV positive MSM on HAART

- **Infrared coagulation:**
  - For lesions that are too large for TCA
  - Direct application of a 1.5 second pulse of irradiation in the infrared range to dysplastic anal epithelium
  - Results in tissue destruction to depth of approximately 1.5 mm
TREATMENT

- Anoscopy-directed lesion ablation
  - Large or circumferential lesions
  - Electrocautery ablation
  - The use of high-resolution anoscopy, rather than mapping biopsies, may minimize complications
  - The high rate of local recurrence, even in patients initially thought to have been completely ablated with a single procedure, mandates careful surveillance following treatment
PERIANAL AIN AND CARCINOMA

- perianal dysplasia (Bowen's disease, squamous cell skin cancer in situ) is less well described and recognized
  - red or hyperpigmented, well-defined scaly plaques
  - Histologic examination shows HG-AIN without dermal invasion
  - Perianal HG-AIN is less often associated with HPV than those involving the anal canal
  - approximately 5 percent of these lesions progress to invasive squamous cell cancer
  - Treatment modalities for Bowen's disease include electrodessication and curettage, and excisional surgery
SUMMARY

- Rates of anal cancer are increasing in the general population and are particularly high in HIV-positive MSM.
- The biologic consequences of anal dysplasia or AIN are considered analogous to those of cervical intraepithelial neoplasia.
- Maintain a high index of suspicion for anal intraepithelial neoplasia in patients presenting with anal pruritus or discharge and a suspicious scaly lesion or condylomata.
SUMMARY

- Ask the patient about sexual history, previous diagnosis of HPV, cervical or vaginal intraepithelial pathology, HIV status, and previous excision of anal warts
A word of thanks...