

Anal intraepithelial dysplasia and squamous carcinoma in immunosuppressed patients

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Objective: To describe a treatment and follow-up protocol for HIV patients with anal dysplasia or warts, which are at risk of malignant change. **Design:** An ongoing study of highly selected patients referred to a single surgeon. **Setting:** The Colorectal and HIV/AIDS Clinics, University of Ottawa, General Campus. **Patients:** Nineteen young men who presented with suspicious anal lesions and were referred to the Colorectal Clinic by the HIV/AIDS Clinic, which sees approximately 800 patients per year. **Outcome measure:** Significance of dysplasia or carcinoma. **Results:** Of the 19 patients, 14 had dysplasia, carcinoma-in-situ or invasive carcinoma. All were treated with multiple mapped cold biopsies and local or wide excision as indicated. Two patients with invasive carcinoma received radiotherapy or chemotherapy, or both. **Conclusions:** The incidence of dysplasia or the sequence by which dysplasia progresses to invasive carcinoma is unknown. Surveillance of HIV patients, especially those with nodules or warts, by flexible sigmoidoscopy and Papanicolaou smears every 3 to 12 months is recommended, depending on the severity of the anal lesion.

Objectif : Décrire un protocole de traitement et de suivi des patients infectés par le VIH et ayant une dysplasie ou des verrues anales risquant de devenir malignes. **Conception :** Étude continue portant sur des patients sélectionnés de façon très rigoureuse et référés à un seul chirurgien. **Contexte :** Clinique colorectale et Clinique du VIH-sida, Université d'Ottawa, campus Général. **Patients :** Dix-neuf jeunes hommes présentant des lésions anales douteuses et référés à la Clinique colorectale par la Clinique du VIH-sida, qui reçoit quelque 800 patients par année. **Mesures de résultats :** Importance de la dysplasie ou du carcinome. **Résultats :** Sur les 19 patients, 14 avaient une dysplasie, un carcinome in situ ou un cancer envahissant. Tous ont été traités par biopsies à froid cartographiées multiples et par exérèse locale ou étendue, selon l'indication. Deux patients atteints d'un cancer envahissant ont été traités par radiothérapie, chimiothérapie, ou les deux. **Conclusions :** L'incidence de la dysplasie ou l'ordre dans lequel elle évolue en cancer envahissant sont inconnus. On recommande de surveiller tous les patients infectés par le VIH, particulièrement ceux qui ont des nodules ou des verrues, en procédant à une sigmoïdoscopie flexible et des frottis de Papanicolaou aux trois à 12 mois, selon la gravité de la lésion anale.

In 1986, Frazer and associates¹ reported a higher than expected incidence of anal intraepithelial dysplasia and carcinoma-in-situ in men who had HIV, with or without AIDS. Over the ensuing 13 years, several papers on the association of anal warts and carcinoma in HIV appeared.²⁻⁴ Currently, this syndrome is termed anal high grade squamous intraepithelial lesion (anal HSIL).

In the mid-1990s we noted a minor epidemic of anal HSIL at our institution. HIV patients now receive increasingly better treatment. Fortunately, this has resulted in the conversion of a formerly lethal condition into a chronic syndrome wherein patients live with their disease for extended periods, albeit requiring constant monitoring and pharmacologic treatment. The concept of anal

dysplasia in young men is not universally appreciated. Its management is vague and controversial. There are several reviews on the subject, but none are Canadian.^{2,3} This clinical syndrome presents in a typical and predictable manner. We report our experience with anal HSIL in a highly selected group of patients and suggest a treatment and follow-up protocol.

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Patients and methods

Patients

The General Site of the Ottawa Hospital has a large HIV-AIDS clinic, which sees approximately 800 patients annually. From this referral base, we collected 19 patients (age range 32–59 yr) whose clinical courses typified anal HSIL. The typical patient was a homosexual, immunosuppressed or HIV man referred to the senior author's Rectal Clinic for hemorrhoids, rectal bleeding, anal warts or vague anal nodularity. Data were stored in an ongoing manner using a conventional database.

Management protocol

For each patient a medical history was obtained, physical examination, digital rectal examination and sigmoidoscopy were performed. Those with classic hemorrhoids or other obvious anorectal conditions were excluded. Those without an obvious cause for their symptoms had examination under anesthesia. A complete bowel preparation was carried out at home. All patients were admitted and discharged on the day of surgery. They received preoperative intravenous hydration, antibiotics and indomethacin. In the operating room, sigmoidoscopy was repeated with rectal washout using a dilute povidone-iodine solution. The perineum was shaved, prepared and draped. A circular retractor with small hooks was used to evert the anal canal (Lone Star Medical Products, Inc., Houston, Tex.). The entire perineum and areas in question were infiltrated with a 0.5% bupivacaine and dilute (1/100 000) epinephrine solution. Hemorrhoids, warts or "nodules" were removed by sharp dissection or punch biopsy to avoid cautery artifact. Large-bore suction tubing aspirated the smoke. The excised lesions were mapped according to

location in the anal canal and quadrant. Each wart was then cauterized, its base scraped with a scalpel and re-cauterized to maximize destruction of intraepithelial viral particles. Then, a perineal block with 0.5% bupivacaine was repeated, followed by insertion of an indomethacin suppository and a hemostatic sponge into the rectum.

Two patients received radiation. One received 15 Gy in 5 fractions at 5 cm depth with cobalt 60 followed by 2 weeks of rest, then 15 Gy in 5 fractions at 5 cm depth with ⁶⁰Co using a direct perineal appositional beam (9 × 8 cm). Three weeks later, he received a 17 MeV boost of 16 Gy in 8 fractions. The other patient received 15 Gy in 5 fractions at 5 cm depth with ⁶⁰Co followed by 8 weeks of rest due to persistent induration and disease. This was followed by 15 Gy in 5 fractions at 5 cm depth with ⁶⁰Co, single beam and an iridium 192 implant (4 lines, each 5 cm, dose prescribed according to the rules of the Paris dosimetry system). This patient also received VP-16 and cisplatin for his small cell carcinoma.

All patients were followed up with outpatient flexible or rigid sigmoidoscopy and 4-quadrant random biopsy as well as biopsy of additional suspicious lesions every 3 to 6 months. These patients appreciate the comfort of intravenous sedation and a flexible rather than a rigid instrument. Vigorous bleeding may occur with the large biopsy forceps utilized during rigid sigmoidoscopy. All biopsy specimens were taken at or just above the dentate line. This may be painful. Such biopsies are facilitated by retroflexing the endoscope. In the past 18 months, we added brush cytology, similar to Papanicolaou smears. More recently, we added acetic acid staining to our screening protocol, but have yet to obtain sufficient data. Transrectal ultrasonography, which was unavailable until 1 year ago, is now also part of our surveillance protocol.

Results

Of the 19 patients, 15 were HIV positive (7 had AIDS) and the HIV status was unknown for 4 patients, 2 of whom were receiving immunosuppressive drugs (steroids for lupus erythematosus or renal transplant; 6-mercaptopurine for chronic hepatitis). Five patients had giant anal warts encompassing the entire circumference of the anal canal (Buschke–Loewenstein lesions) that were removed by wide local excision in 1 of 2 operations.

In 4 patients, all biopsy specimens were normal. Intraepithelial dysplasia was present in 8 patients, carcinoma-in-situ in 5 and invasive carcinoma in 2. These 2 patients had wide local excision followed by radiotherapy or chemotherapy, or both. Subsequently, both had severe radiation proctitis and 1 had a stricture. The latter required abdominoperineal resection for local recurrence and remains well. The former had metastatic disease. The most challenging management problems were in these 2 patients who received radiotherapy.

In no patient with benign disease has dysplasia developed. Also, dysplasia has not progressed to a higher grade or to invasive carcinoma. All follow-up endoscopic examinations gave normal results. Satisfactory Papanicolaou smears and biopsy specimens were obtained in 15 patients over a 24-month follow-up. Twelve specimens were negative on cytologic and biopsy examination; 3 were positive on both cytologic and biopsy examination; and only 1 was negative on biopsy but positive on cytologic examination.

Anal warts recurred in 2 patients at 6 and 9 months, respectively. Both were successfully treated with podophyllin. One patient with dysplasia had a stricture a year postoperatively. He had previously undergone anoplasty in our unit before dysplasia developed. Therefore, his stricture was more likely secondary to multiple intra-anal operations rather than to

the simple surgery for his anal warts.

We observed another recurrence in a 52-year-old HIV-positive man with giant anal warts, managed by a wide local excision. The recurrence was extremely rapid (<6 mo) and re-excision was performed. The second specimen showed anal warts with dysplasia and Bowenoid carcinoma-in-situ. The anal wounds healed without stricture after each operation.

All anal wounds healed primarily, and there were no instances of worsening incontinence. There were no other surgical complications. In fact, the most serious problems were in the 2 patients who required radiotherapy. The 4 patients lost to follow-up were contacted by telephone. Although they refused clinic appointments, they had no anal symptoms.

Discussion

There is a higher-than-expected incidence of dysplasia, carcinoma-in-situ and invasive carcinoma in young HIV men with or without AIDS who typically have minor anorectal complaints.⁵⁻⁷ Seemingly innocent warts, nodules or firm hemorrhoids can be capricious in this patient subset. Our data reveal an association between HIV infection, human papilloma virus (HPV) and dysplasia. Fourteen of 15 HIV/AIDS patients with minor anorectal complaints had underlying dysplasia, carcinoma-in-situ or invasive carcinoma. The presence of HPV anal warts, although relatively innocent in the general population, is associated with an increased risk of anal HSIL and carcinoma in HIV patients.⁸⁻¹⁰ We do not know if patients with invasive carcinoma initially had only dysplasia. However, our data suggest that dysplasia does not necessarily lead to cancer. Since infection with HPV increases in the presence of HIV, and since HIV patients are at increased risk for dysplasia or carcinoma, it seems logical to screen these patients to prevent adverse outcomes.¹¹ Men with HPV are analo-

gous to women with HPV and cervical dysplasia, in whom there is a known direct correlation between dysplasia, HPV and cervical cancer.¹⁰ There are similarities in viral type,¹² suggesting that the Papanicolaou smear, the standard for screening cervical cancer, may facilitate anal screening in men. We have not proven the necessity of mandatory screening or its frequency. Rather, we think of our protocol in terms of what must have existed when the association between HPV and cervical dysplasia was first noted. At that time, the management of female patients was not clearly understood, similar to the uncertainty surrounding anal dysplasia in men today.

Recently, Jay and associates¹³ described a colposcopic method for classifying potentially dangerous, "high-grade," intraepithelial anal lesions that may lead to squamous cell cancer. The strong light and magnification combined with the absorption of acetic acid into the anal canal, revealing colour, surface characteristics and vascular patterns, facilitate the diagnosis of dysplasia and the differentiation of low- from high-grade dysplasia. We have recently introduced acetic acid staining used in conjunction with flexible sigmoidoscopy.

Not only HPV warts but any anal lesion should prompt the physician to consider the possibility of squamous dysplasia or carcinoma in HIV or homosexual patients. Nine of our 18 patients had precancerous lesions yet they did not present with condyloma.

Only 1 of our patients had Kaposi's sarcoma, which affected his extremities not his anal canal. With better treatment, AIDS has become a more chronic disease. This seems to coincide with a decline in anal Kaposi's sarcoma and an associated increase in squamous cell dysplasia.

The association of immunosuppression with anal intraepithelial dysplasia, carcinoma-in-situ or invasive carcinoma in non-HIV patients is well known. This is exemplified by the high incidence of squamous car-

cinoma in immunosuppressed patients with giant anal warts. Interestingly, 4 out of 5 of our patients with giant warts did not have carcinoma.

Unfortunately, CD4 levels were unavailable in many of our patients. However, Palefsky and colleagues⁸ have also shown a high incidence of HSIL in HIV-positive men with warts. There was a higher prevalence of neoplasia in those who were immunosuppressed. Both of our patients with invasive squamous cell carcinoma as well as the patient with rapidly recurrent warts and Bowenoid carcinoma had very low CD4 counts.

Patients, who present with anal warts, require careful examination by a surgeon and usually examination under anesthesia. One would expect poor healing in these immunosuppressed patients, yet they tolerate anal surgery well. The importance of surgical technique cannot be underestimated. Most HIV patients require triple therapy, so diarrhea is common. Undue anal stretching or other damage to the sphincter can have devastating effects on fecal control. Herein lies the benefit of the Lone Star retractor.

Unquestionably, many of these patients have field defects. The entire anal canal may be involved in the dysplastic process. Therefore, mapping is valuable. On the other hand, a number of the patients (Table 1) presented with isolated nodules that contained in-situ or invasive carcinoma. If it can be established that dysplasia is truly significant with respect to progression to cancer, then ablation of the entire lining of the anal canal (extended "mucosectomy") can be considered. With our present knowledge, we cannot recommend aggressive therapy for mild to moderate dysplasia involving the entire anal canal.

We treated our 2 patients with invasive carcinoma with wide local excision and radiation, with or without chemotherapy. The diarrhea that inevitably accompanies triple therapy is

exaggerated by radiation proctitis, resulting in severe perineal discomfort. Diligent medical management is required. We believe a trial of chemoradiotherapy is an acceptable initial conservative treatment, but this issue is still in question. One of these patients had metastatic disease and the other required a technically very difficult abdominoperineal resection for a severe radiation stricture and recurrent disease.

Our patient population is highly selected and the common denominator is unknown. A busy HIV clinic referred only patients with suspicious lesions to our service. To determine the true incidence of dysplasia and carcinoma in the HIV population would be a Herculean task. Yuhan and associates⁵ found 4 cancers in 180 HIV patients. Only 1 was a squamous lesion. We found 14 HIV patients with dysplasia or carcinoma

(or both), all of the squamous type. This seems alarmingly high even though the denominator is unknown.

Our follow-up protocol of these patients has evolved over the past 4 years. Initially, serial sigmoidoscopy and biopsy were done every 3 to 6 months on all patients who initially had normal biopsy specimens, dysplasia or carcinoma-in-situ. More recently, we have been using flexible sigmoidoscopy with retroflexion, acetic acid staining, multiple biopsies and simultaneous anal Papanicolaou smears every 3 to 12 months. The preliminary brush cytology data correlated very well with the biopsy findings. Hence, brush biopsy, an easier and simpler screening tool, may eliminate the need for endoscopic biopsy. Cytologic examination also facilitates accurate sampling of tissues at the dentate line where squamous cell abnormalities are most

likely to occur.¹ Until more knowledge is garnered, we believe routine follow-up is necessary. Its frequency is determined by the severity of the initial biopsies and the presence or absence of anal warts, which are often associated with intraepithelial anal dysplasia or anal squamous cell carcinoma.^{13,14}

Recommended management

We suggest the following algorithm for all HIV-positive or immunosuppressed patients with suspicious anal nodules, particularly when anal warts are present. Initially, history taking, physical and digital rectal examination and sigmoidoscopy should be carried out. If the findings are normal, patients should be followed up yearly. If warts or other suspicious lesions are seen, the patient should have an examination under

Table 1

Summary of Data in 19 Patients Who Had HIV and Anal Lesions

| Age, yr | Diagnosis | Presenting symptom | Warts | Date of operation | Follow-up, mo | Treatment | Final diagnosis |
|---------|---------------------|------------------------------|-------|-------------------|---------------|---|--|
| 52 | HIV | Hemorrhoids | Yes | 7/99 | 6 | Excision, biopsy | Dysplasia |
| 33 | HIV (IV drug user) | Giant condyloma | Yes | 11/99 | <6 | Wide local excision | Normal |
| 36 | HIV | Condyloma | Yes | 10/99 | <6 | Excision | Dysplasia |
| 36 | HIV | Condyloma | Yes | 9/96 | 36 | Excision | Dysplasia |
| 44 | AIDS | Hemorrhoids | Yes | 1/96 | 48 | Radiation, excision, abdominoperineal resection | Invasive carcinoma (recurrent, 7/00) |
| 48 | AIDS | Condyloma | Yes | 3/98 | 18 | Excision | CIS |
| 37 | HIV | Hemorrhoids | Yes | 6/98 | <6 | Excision | Dysplasia |
| 33 | AIDS | Rectal bleeding | Yes | 6/98 | 18 | Excision | CIS |
| 44 | Hepatitis | Giant condyloma | Yes | 7/94 | 60 | Wide local excision | Normal |
| 44 | HIV | Rectal bleeding, anal nodule | Yes | 4/97 | 30 | Radiation, chemotherapy, excision | Invasive small cell carcinoma (metastatic disease, 7/00) |
| 59 | Lupus erythematosus | Giant condyloma | Yes | 3/99 | <6 | Wide local excision | Normal |
| 40 | HIV | Condyloma | Yes | 6/98 | <6 | Excision | Dysplasia |
| 45 | Unknown* | Giant condyloma | Yes | 7/96 | <6 | Wide local excision | Normal |
| 36 | AIDS | Hemorrhoids | Yes | 12/97 | 18 | Excision | CIS |
| 38 | Unknown* | Rectal bleeding | Yes | 10/98 | 6 | Excision | Dysplasia |
| 52 | AIDS | Hemorrhoids, giant warts | Yes | 4/99 | 6 | Wide local excision | CIS |
| 38 | AIDS | Condyloma | Yes | 1/99 | 12 | Excision | Dysplasia |
| 46 | AIDS | Anal nodules, hemorrhoids | No | 4/99 | <6 | Excision | CIS |
| 32 | HIV | Hemorrhoids | Yes | 4/98 | 12 | Excision | Dysplasia |

*Homosexual men not tested for HIV. CIS = carcinoma in situ.

anesthesia with mapped cold biopsies and cauterization. With normal findings, the patient should be followed up yearly. Patients with low- or high-grade dysplasia or carcinoma-in-situ require certainty of complete excision. They can be followed up every 3 to 6 months with flexible sigmoidoscopy, biopsy, cytologic examination, staining (with colposcopy where available) and transrectal ultrasonography. Those with invasive cancer may require repeat resection followed by chemoradiotherapy. Those cured by the latter treatment are followed up like those with dysplasia; those who have a recurrence require abdominoperineal resection.

The role of acetic acid staining and flexible sigmoidoscopy versus colposcopy remains to be determined. The latter permits superior visualization in those centres with sufficient numbers of patients to justify the cost. Differentiation of low- versus high-grade dysplasia may be inadequate without cytochemical and colposcopy. The magnification of flexible sigmoidoscopy with staining is as close as we can come to colposcopy.

Goldie and associates¹⁴ added another variable, suggesting that HIV patients with anal disease be treated on the basis of CD4 cell counts and the severity of intraepithelial lesions.

Thus, the factors that assist the surgeon in determining the risk of squamous carcinoma in young men with anal lesions include HIV status, suspicious anal nodules, cytologic and biopsy findings, acetic acid staining with flexible sigmoidoscopy or colposcopy, and possibly the CD4 count. The literature on anal dysplasia ranges from normal patients with coincidental dysplasia in hemorrhoids, to the higher-than-expected incidence in our patients.¹⁵ Each centre uses different diagnostic tests.

Further, individual surgical attitudes vary from active investigation and follow-up, to "cavalier" management. Further, the HIV status of many homosexual men is often unknown. The natural history of the disease and the relevance of the reviewed criteria are undetermined. A multicentre trial is required to enable clinicians to determine the most appropriate treatment and follow-up for these patients.

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