Human Papillomavirus, Condylomata Acuminata, and Anal Neoplasia

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ABSTRACT

Genital human papillomavirus (HPV) infection is an increasingly common sexually transmitted disease. This virus causes condylomata acuminata and is associated with anal neoplasia. Management options are discussed.

KEYWORDS: Human papillomavirus, condylomata acuminata, anal neoplasia

Objectives: Upon completion of this article, the reader should be familiar with human papillomavirus and understand the management of condylomata acuminata.

HUMAN PAPILLOMAVIRUS INFECTION

Genital human papillomavirus (HPV) infection is increasingly common and affects an estimated 24 million Americans.¹ It is the most common sexually transmitted disease and is second only to human immunodeficiency virus (HIV) infection in causing morbidity and mortality. Perianal HPV infection produces a wide range of disease presentations, from asymptomatic infection to benign genital warts to invasive cancer.

Human papillomaviruses are members of the Papovaviridae family of epitheliotropic double-stranded DNA viruses and are considered tumor viruses because of their ability to immortalize normal cells. Currently more than 130 types of HPV have been identified, with more than 40 types infectious for the lower genital tract, of which ~15 are oncogenic.² These are generally characterized as “low-risk” types (6, 11, 42, 43, 44), which are primarily associated with genital warts and respiratory papillomatosis, or as “high-risk” types (16, 18, 31, 33, 35, 39, 45, 51, 52), which are associated with low-grade and high-grade squamous intraepithelial lesions (LSIL and HSIL) and invasive cancer.³⁻⁵

HPV infection is extremely common in the cervix and affects between 2% and 43% of the female population worldwide.⁶ In the United States, the prevalence is 22.5% overall and significantly higher among the young.⁷ The prevalence of HPV infection among 600 young women attending family planning clinics in an urban setting was 82%.⁸ In another study of over 2011 young women aged 15 to 19, the 3-year cumulative risk of acquiring HPV infection was 44%.⁹ Clearly, not all of these individuals go on to develop cervical cancer, and in fact HPV infection in most women demonstrates a pattern of regression or latency with HPV DNA becoming undetectable even by polymerase chain reaction (PCR) assays by 1 to 2 years.¹⁰ Only a small percentage of women develop persistent and progressive disease. Other cofactors such as smoking, history of sexually transmitted infections, and individual immune responses to HPV may be necessary along with oncogenic HPV infection for carcinogenesis.

The true prevalence of anal HPV infection in the general population is not currently known, but it is present in virtually all HIV-positive men who have sex

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with men (85 to 93%) and also in a high proportion of HIV-positive injection drug users who did not engage in anal-receptive intercourse (46%).¹¹ Anal HPV prevalence is more common in HIV-positive men, at more than 60%, versus 17% in HIV-negative men. Another risk factor for HPV infection is the number of sexual partners. Up to two thirds of sexual partners of patients with condylomata acquire HPV infection. Among HIV-negative homosexual men, the prevalence of anal HPV infection has been reported to be as high as 78% by PCR.¹² In an earlier study of 71 heterosexual male patients with anal fissure or hemorrhoids in a surgical outpatient department, the incidence of cytologic evidence of anal HPV infection was 25%. This figure rose to 98% in 225 men seen for anal condylomata.¹³ Additionally, infection by multiple HPV types is common and carries an increased risk for anal squamous intraepithelial lesions (SIL, also known as anal intraepithelial neoplasia or AIN) and progression to HSIL over time. Multiple HPV types were found in 73% of HIV-positive and 23% of HIV-negative homosexual men.¹⁴

Women with cervical HSIL are also at a high risk for anal HPV infection (51%) when compared with control women without cervical intraepithelial neoplasia (CIN) (14%). This control group is validated by a 24% prevalence of cervical HPV infection which is comparable to the general population.¹⁵ In a subsequent study of women with invasive vulvar cancer, histologic evidence of anal HPV-16 infection was identified in 48.5% of patients with vulvar cancer versus 13.7% of control women with no prior history of anogenital HPV infection or neoplasia.¹⁶ In a San Francisco cohort study of 319 at-risk young women (high-risk for HIV), the prevalence of anal HPV infection by PCR was 76% among HIV-positive women and 42% of HIV-negative women.¹⁷

The actual prevalence of anal HPV infection will depend upon the sum effect of risk factors such as smoking, number of sexual partners, sexual behavior, presence of other sexually transmitted diseases (STDs), and so on. But it may be in the range of 5 to 15% in women, with autoinoculation being a potentially significant mechanism, and the range may be somewhat lower in men. These figures would explain the reason for the higher prevalence of anal cancer in the general population of women than in men. Improving sensitivities of the tests for HPV DNA detection in recent years should be considered when examining the data prior to second-generation hybrid capture or PCR.

CONDYLOMA ACUMINATA

Genital warts, or condylomata acuminata, are now the most common virally transmitted STD, surpassing even genital herpes. Condylomata acuminata affects ~5.5 million Americans each year and is estimated

to have a prevalence of ~20 million.¹ It is the most common anorectal infection affecting homosexual men.¹⁸ However, it also frequently occurs in bisexual and heterosexual men and women. Although the most common mode of transmission is through sexual contact,^{19,20} nonsexual routes of transmission via fomites and nonsexual contact can also occur.^{21,22}

Anal lesions occur most frequently in men who engage in anal-receptive intercourse, where the association has been observed to be as high as 95% in patients.^{23–25} However, there is significant variability in this association and the presence of anal condylomata does not necessarily imply that a patient engages in anal-receptive intercourse. The virus pools in the vagina and at the base of the scrotum and penis from where it can track along the perineum to the anus. Patients who are immunosuppressed are also at higher risk. Following renal transplantation the anal condylomata incidence has been reported to be 2.4% to 4%.²⁶

In HIV-positive patients the HPV prevalence is 30%.²⁷ The effect of HIV infection on the course of HPV disease is unclear but may be influenced by the severity of immunocompromise and the use of antiretroviral therapy. Infection by high-risk HPV types is associated with SILs, which are the putative precursors to invasive cancer. The impact of HIV on HPV infection, as well as the associated biologic and behavioral risk factors in patients with HIV and HPV, may contribute to the 30- to 80-fold higher rates of anal cancer in HIV-positive patients versus the general population.^{28–30}

SYMPTOMS

Most patients with anal condylomata present with minor complaints. The most frequent complaint is that of perianal growth. Pruritus ani may be present and to a lesser degree, discharge, bleeding, odor, tenesmus, and difficult perianal hygiene may be noted.

DIAGNOSIS

Physical examination may reveal the classic cauliflower-like lesion (Fig. 1). The warts tend to run in radial rows out from the anus and may be surprisingly large at the time of presentation. Macroscopically the warts may vary from lesions invisible to the naked eye to pinhead-sized lesions to large cauliflower-like masses. The warts may be single or multiple, or coalesce to form polypoid masses. Individual warts can be sessile or pedunculated, isolated, or clustered. Anoscopy and proctosigmoidoscopy are essential because the disease extends internally in more than 75% of patients and in up to 94% of homosexual men.¹⁸ Lesions are often found on the perianal skin or within the anal canal and lower rectum. They are pink or white in color. Microscopically, anal warts show acanthosis of the epidermis with hyperplasia

Figure 1 Anal condylomata acuminata.

of prickle cells, parakeratosis, and an underlying chronic inflammatory cell infiltrate. Serologies and cultures for HPV and other venereal diseases may be taken from the penis, anus, mouth, and vagina and the PCR technique can be used to detect HPV DNA with high sensitivity.

The differential diagnosis includes condylomata lata and anal squamous cell carcinoma. Condylomata lata are the lesions of secondary syphilis. They are flatter, paler, and smoother than condylomata acuminata. Anal squamous cell carcinoma is generally painful and may be tender and ulcerated where condylomata are not tender or ulcerated.

TREATMENT

Due to the risk for communicability, as well as the risk for the development of squamous cell carcinoma, lesions should generally be treated. Many methods of treating condylomata acuminata have been described and are listed in Table 1. In general they can be separated into topical, immunotherapeutic, and surgical techniques. We prefer to examine the patient in the prone-jack-knifed position. But lateral decubitus, lithotomy, and knee-chest positions all provide adequate exposure. Excellent lighting is imperative and a magnifying device may be helpful.

Topical Chemical Agents

PODOPHYLLIN

Podophyllin is the best-known and most widely available topical chemical agent. First recommended for the treatment of condylomata by Culp and Kaplan in 1942,³¹ it is a cytotoxic agent derived from the resin of *Podophyllum emodi* and *Podophyllum peltatum* that contains biologically active lignin compounds, including

Table 1 Treatment of Condyloma Acuminata

Folklore	Charming
	Hypnosis
Topical Methods	Lime water
	Lemon juice
	<i>Podophyllin</i>
	<i>Podophyllotoxin</i>
	<i>Trichloroacetic acid</i>
	<i>Bichloroacetic acid</i>
	5-fluorouracil
	Dinitrochlorobenzene
	Fowler's solution
	Phenol
	Cochicine
	Dimethyl sulfoxide
	Tetracycline ointment
	Bismuth sodium triglycollamate
	Thiotepa
Immunologic Methods	Sulfonamide cream
	Ammoniated mercury
	Idoxuridine
	Bleomycin
	Cantharidin
	Solcoderm
	<i>Imiquimod</i>
	Interferon
	Bacille Calmette-Guerin
	Autovaccination
Surgical Techniques	<i>Excision</i>
	<i>Electrocautery fulguration</i>
	<i>Laser therapy</i>
	<i>Infrared coagulation</i>
	<i>Cryotherapy</i>
	Liquid nitrogen
	Carbon dioxide snow
	Liquid air

Currently utilized techniques are in italics.

podofilox, which is the best-characterized and most active component against genital warts.³² It is applied in a vehicle such as liquid paraffin or tincture of benzoin. Podophyllin has the advantage of being simple to use and it is inexpensive. Concentrations of 5 to 50% have been used without much difference in efficacy.^{33–36} Podophyllin is applied directly to the warts with care to avoid the adjacent normal skin because it is extremely irritating.

Several disadvantages, including application limitations, limited efficacy, and systemic toxicities, have led to podophyllin losing favor as a treatment modality for anal condylomata. It must be washed off after 6 hours because it is extremely irritating to the surrounding normal skin and causes a severe local reaction that can include dermatitis, necrosis, scarring, or fistula in ano.³⁷ It cannot be applied to internal lesions. It is rarely

effective after a single application and multiple treatments require repeated visits to the office. It also has poor penetration into keratinized warts, decreasing its efficacy. Response rates are variable but can be as low as 22% after 3 months of therapy.³⁵ Use of podophyllin during pregnancy has been associated with teratogenicity and intrauterine fetal death.³⁸ Systemic toxicities to virtually all of the organ systems can occur with application of large amounts of podophyllin.³⁹⁻⁴¹ Finally, the potential for oncogenicity cannot be overlooked.

Podophyllotoxin is one of the active compounds in podophyllin. It is effective in wart clearance in about one half of cases, but is associated with a high recurrence rate. Its advantage is that it is safer and can be self-administered.^{42,43}

BICHLORACETIC ACID OR TRICHLORACETIC ACID

Bichloroacetic acid is a powerful keratolytic and cauterant and has been successfully used for the management of condylomata.²³ Like podophyllin, it is inexpensive and easily applied. It has the advantage of being applicable to internal disease. However, it too can cause local skin irritation and often requires multiple office visits, generally at weekly intervals. In an uncontrolled study by Swerdlow and Salvati, bichloroacetic acid was compared with other modes of office-based therapy and noted to result in better patient comfort and decreased recurrence rates.²³

CHEMOTHERAPEUTIC AGENTS

Various chemotherapeutic agents used for the treatment of condylomata have been described, including 5-fluorouracil (5-FU) as a cream or salicylic acid preparation,⁴⁴⁻⁴⁶ thiotepe,⁴⁷ bleomycin,⁴⁸ dinitrochlorobenzene in acetone,⁴⁹ and idoxuridine cream.⁵⁰ Unfortunately, most descriptions are anecdotal for the treatment of anal warts and there are no meaningful reports of efficacy.

Immunotherapy

INTERFERON

Interferons are produced and secreted in response to viral infections. Thus interferon injection may be a practical way to treat refractory anogenital warts.⁵¹ Intramuscular, intralesional, and topical therapies have all been employed,⁵¹⁻⁵⁵ but it is generally felt that the systemic route is ineffective. The usual dose of intralesional interferon is 1 to 2 million units. Ten to 28 days of daily treatment have been reported.⁵⁶ However, the usual maximum dose per patient is 5 million units due to adverse effects such as fever, chills, myalgia, headache, fatigue, and leukopenia. Therefore the maximum number of warts that can be injected at one time is 5.⁴⁵ Multiple trials, including a randomized double-blinded multicenter

trial, demonstrate modest and variable efficacy when compared with placebo.^{51,53,55,57} Although complete remission rates of 82% have been reported,⁵⁶ the overall success and 6-month recurrence rates are ~50% and 25%, respectively.⁵⁸

Many authors have advocated the use of interferon in combination with other therapeutic modalities⁵⁹ for extensive, refractory disease and to improve wart clearance rates. Aside from the adverse effects noted above, interferon has the disadvantage of high cost and potentially decreased efficacy with concurrent HIV disease.⁶⁰ At this time, interferon has not gained wide acceptance for the treatment of anogenital condylomata and has widely been supplanted by the use of imiquimod.

IMIQUIMOD

Topical imiquimod is an immune modulator that induces interferon and cytokine release by the host tissues. Although it has no direct antiviral activity, it activates the host immune system to clear the HPV infection by both the innate and cell-mediated pathways. Applied as a 5% cream, external wart clearance can be achieved in 72 to 84% of women and a somewhat smaller percentage of men. It is well tolerated and safe, with the most frequent side effect of treatment being local erythema. Once the lesions have been cleared the local recurrence rate has been reported to be 5 to 19%.⁶¹ Although controversial, there may be a role for adjuvant imiquimod treatment following surgical therapy of condylomatous disease.

VACCINE

In 1944, Biberstein first described the use of immunotherapy with an autologous vaccine in the treatment of condylomata acuminatum.⁶² Although efforts have been made for a vaccine,²⁴ they have not been widely effective. More recently, HPV vaccines targeting the late structural proteins of the viral capsid (E6, E7) have shown more promise. The ideal vaccine engenders a cell-mediated immune response generating HPV-specific cytotoxic T-lymphocytes. Since cross-reactivity among HPV subtypes is low, newer approaches are geared toward generating polyvalent vaccines. In preclinical animal models, both prophylactic and therapeutic vaccines have effectively induced HPV-specific cell-mediated immune responses. Although safety and immunogenicity of vaccine preparations have been demonstrated in Phase I trials, few data exist on efficacy and there are multiple trials ongoing.^{63,64}

Surgical Therapy

ELECTROCOAGUATION

Electrocautery is an effective way to destroy both internal and external anal warts but this technique requires local anesthesia and is somewhat dependent on the skill

of the operator who must control the depth and width of the cauterization. The effect is a first- or second-degree burn. Controlling the depth of the wound is important to prevent scarring and injury to the underlying anal sphincters. Circumferential burns should be avoided to prevent anal stenosis. If the disease is extensive or circumferential, efforts should be made to preserve skin bridges. If this is not possible, treatment should be staged. In studies of electrocoagulation, complete clearance was achieved in up to 94% with a recurrence rate of 22%.⁴⁶ Close follow-up is needed to identify recurrent disease that can often be treated topically in the office. Representative biopsies should be taken at the time of electrocoagulation for pathologic evaluation for dysplasia or occult carcinoma.

LASER THERAPY

Carbon dioxide laser therapy to destroy condylomata was first reported by Baggish in 1980.⁶⁵ An overall success rate of 88 to 95% has been reported.^{66,67} This is similar to electrocautery, but laser ablation has a higher recurrence rate and is associated with as much or more postoperative pain.⁶⁶ With respect to treatment efficacy, laser therapy has no benefit over conventional electrocauterization⁶⁸ and is limited by higher equipment costs and the potential for aerosolization of virus in the laser plume,^{69,70} which can result in laryngeal papillomatosis in the operating surgeon.⁷¹

CRYOTHERAPY

Cryotherapy involves the topical application of liquid nitrogen, carbon dioxide snow, or liquefied air to the warts. This technique purportedly does not require anesthesia but this is not the general experience. Post-treatment pain levels are comparable to electrocautery and laser therapy. In head-to-head trials comparing cryotherapy to trichloroacetic acid⁷² or to electrocautery,⁷³ no difference in efficacy was found. Rates of success are reported to be 63 to 88% with recurrence of warts in 21 to 39% of patients.⁴⁶ These rates are inferior to those achieved with electrocautery.

SURGICAL EXCISION

Surgical excision has long been used to treat condylomata acuminata with superior rates of treatment success and recurrence. Patients are placed in the prone, jack-knife position and their buttocks taped apart for exposure. Classically a solution of 1:200,000 epinephrine in saline or lidocaine is injected subcutaneously and submucosally to separate the warts and facilitate the preservation of healthy skin and mucosa. The wart is grasped with a pair of toothed forceps and excised with fine scissors. Electrocautery may be used for hemostasis or as an adjuvant modality.

The combination of excision and electrocautery is considered to be the gold standard for the treatment of

condylomata. Care is taken to avoid injury to the underlying sphincter mechanism. Although most patients can have all of their disease removed in one procedure, patients with more extensive disease may require staged excisions at an interval of 1 to 3 months.⁷⁴ The advantage of this approach is that it allows for pathologic examination of the specimen. In prospective, randomized, controlled trials comparing simple surgical excision to 25% podophyllin for up to 6 weeks, rates of wart clearance and recurrence were significantly better with simple excision.^{33,75}

RECURRENCE

The problem of recurrence is a significant one in the treatment of condylomata and rates have been reported to range between 4.6% to over 70% depending on the treatment modality.^{23,24} Although current efforts are aimed at removing or destroying all visible warts, little is known about subsequent transmission or persistence of papillomavirus in the tissues. The problem of recurrence is a multifaceted one that must take into consideration surgical technique, surveillance, immunocompetence, and patient behavior. Incomplete treatment, particularly due to presence of internal disease or disease that is not visible to the unaided eye, causes self-inoculation and recurrence. Furthermore, warts are caused by the papillomavirus and eradication of virus from any tissue is problematic. For this reason, addition of immunotherapy after surgical ablation is an attractive concept that may gain favor as experience with immunotherapy grows.⁷⁶ In particular the treatment margins are at greatest risk for recurrence. In addition many patients are immunocompromised either from HIV or immunosuppressive agents. Adding to the complexity of this issue is the fact that sexual partners of patients with genital HPV are also likely to have genital HPV. Failure to treat a partner's lesions is also a cause of recurrence. It is generally felt that a 3-month disease-free interval is safe for resumption of sexual activity.

ANAL NEOPLASIA

Anal SILs are an increasingly prevalent condition associated with HPV infection and condylomata and can occur both externally and internally within the anal canal. SILs range from low- to high-grade and the progression to high-grade dysplasia (HSIL) may be an intermediate stage toward malignant transformation to squamous cell carcinoma of the anus.

The principle risk factor for anal neoplasia is the presence of HPV infection. Cofactors include anal-receptive intercourse and immunocompromise. It is now apparent that infection by oncogenic strains of the HPV may be causative for the development of anal cancer.^{77,78} HPV infection is also causative in the development of

anal SIL (also known as anal intraepithelial neoplasia or AIN) and there is also growing evidence that invasive anal cancer is preceded by the development of HSIL. These findings parallel observations in the cervix where HPV infection causes the development of CIN, the precursor lesion to invasive cervical cancer.⁷⁹ Although limited data exist on the natural history of anal HPV infection and the development of anal cancer, multiple epidemiological and associative studies have demonstrated an HPV/anal SIL/anal cancer relationship that appears to mimic that for cervical cancer.⁸⁰

The Cervical-Anal Analogy

The natural history of untreated anal SIL is unknown. However, there are many similarities between the cervix and the anus suggesting that the lessons learned from treatment of cervical dysplasia may be applicable to anal dysplasia. Anal cancer and cervical cancer are caused by HPV infection, and the observed relationship between HPV, HSIL, and squamous neoplasms of the anus is similar to that of the cervix where the etiologic relationship between HPV infection, cervical HSIL, and cervical cancer has been established.

Numerous similarities exist between the cervix and anus. Both tissues are exposed to trauma from activities such as defecation, receptive anal intercourse, and vaginal intercourse. Both cancers are histologically similar and have a tendency to arise from the squamous-columnar transformation zone. Both the anus and cervix have a similar anatomic feature, the transformation zone (the squamocolumnar transitional zone of the anal canal and the cervical transformation zone) where squamous metaplasia is found. The immature squamous metaplastic cells of these transformation zones are the most susceptible to oncogenic HPV, although the nonkeratinizing and keratinizing squamous epithelium of the surrounding tissues are also susceptible. HSIL in both tissues is associated with HPV infection ($\geq 61\%$ of anal HSIL have HPV DNA).^{17,28,81} Under the microscope, cervical SIL and anal SIL are virtually indistinguishable. There is also morphologic and histological similarity between cervical and anal cancer. Cervical cancer is preceded by a well-defined precursor lesion, CIN, or more generally SIL of the cervix.

Although there is a relative abundance of data on the benefits of screening and treatment of CIN, there are limited data about the natural history of HSIL and the effectiveness of ablative therapy.^{82,83} But cervical Pap smears and ablative therapy, although never subjected to trials, have proven effective for the prevention of cervical cancer. Prior to the implementation of these interventions, the incidence of cervical cancer was 36 per 100,000. But with the introduction of screening techniques, the incidence of cervical cancer has decreased by 78%.⁸⁴ The numerous similarities between the cervical

and anal disease processes support the argument that screening followed by directed ablative therapy may have a beneficial effect on anal cancer. Histological similarities between anal HSIL and cervical HSIL with regard to angiogenesis, increased cellular proliferation, and decreased apoptosis have been demonstrated.⁸⁴

As seen with CIN, anal LSIL can regress or progress to HSIL. However, HSIL does not typically revert to LSIL or normal without treatment. Moreover, although either LSIL or HSIL may be the presenting phenotype, LSIL does not directly go on to become invasive cancer without progressing to HSIL. In the cervix, 21% and 0.15% of CIN I lesions progress to CIN III and invasive cancer, respectively.⁸⁵ In the anus, 50% of HIV-negative homosexual men who had LSIL had regression of their lesions over a 2-year period. However, 62% percent of HIV-positive and 36% of HIV-negative men with LSIL progressed to detectable HSIL within the same time period. Anal SIL and HSIL developed within 2 years in 17% and 8% of HIV-negative men who had no evidence of lesions at baseline, respectively.^{86,87} The 4-year incidence of HSIL in HIV-negative men was 17%.²⁸ These numbers are consistent with findings from Seattle where HSIL developed in 15% and 5% of HIV-positive and HIV-negative men, respectively.⁸⁸ Factors in progression may include multiplicity of oncogenic HPV-type infection and HPV viral activity as well as cigarette smoking and host immunity. Thus, the similarities between anal and cervical neoplasia make the cervical SIL/cancer sequence a reasonable model for the study of anal carcinogenesis, and consideration must be given to screening and treatment for anal SIL as is done for cervical SIL.

Bowen's Disease and HSIL

Bowen's disease, squamous cell carcinoma in situ, is often an incidental finding discovered at the time of histological evaluation of an anal specimen obtained at surgery for an unrelated diagnosis. It is considered premalignant. It is generally treated by mapping with punch biopsies taken in a clock-face pattern at 1-cm intervals from the anus, as described by Strauss and Fazio in 1979.⁸⁹ Wide excision of affected tissue is performed based on intraoperative frozen section analysis of the punch biopsies, and skin flaps are often mobilized for closure of the skin defects. Large amounts of uninvolved tissue may be sacrificed to obtain clear margins because the lesions are not grossly apparent. The recurrence rate with wide excision is 23.1% and the cancer rates are less than 10%.^{90,91} Postoperative continence, stenosis, and resumption of sexual activity rates have not been reported.

Although Bowen's disease is surgically treated with wide excision of the perianal skin and anal mucosa, disease above the dentate line in the transformation zone

is often left untreated. The transformation zone is composed of variable amounts of transitional epithelium and rectal mucosa with squamous metaplasia. Metaplastic tissue is an immature tissue and may be particularly susceptible to HPV infection. Thus, the standard therapy for anal Bowen's disease may leave in situ the tissue most at risk for development of malignancy.

Within the treating community (surgeons, gynecologists, dermatologists, primary care physicians) there is considerable disagreement as to how Bowen's disease and HSIL should be treated, partly because they are considered by many to be different diseases. Therefore, we sought to establish how Bowen's disease might be distinguished from anal HSIL. In our series of 10 patients diagnosed with Bowen's disease at other institutions, histologic evidence of HPV infection was present in all 10 specimens. Moreover, they were otherwise histologically indistinguishable from HSIL.⁹² Further, upon immunohistochemical study, Bowen's disease and high-grade SIL both have statistically significantly increased microvessel density and show similar trends in apoptosis and proliferation rates when compared with normal tissue. Thus, Bowen's disease and HSIL are indistinguishable histologically and immunohistochemically. It seems reasonable to consider reviewing the terminology and standardizing treatment of the "two diseases" for consistency. Currently, histopathologists and dermatopathologists use the term Bowen's disease, a term that probably should be avoided, while cytopathologists label the same findings as HSIL. This leads to unnecessary confusion among treating physicians.

TREATMENT

Patients with anal SIL present with minor complaints and are typically identified during evaluation of anal condylomata or pruritus. They may demonstrate typical condylomatous lesions or simply abnormal-appearing anal canal mucosa. The perianal skin and the entire surgical anal canal, as defined by the American Joint Committee on Cancer and by the World Health Organization, extending through the length of the internal anal sphincter to the anal verge (2 to 4 cm in women, up to 6 cm in men) should be thoroughly examined.

Patients with low-volume disease and no history of dysplasia may be treated with topical agents in the office regardless of risk factors. The primary care physicians perform follow-up screening Pap smears. Patients with large-volume disease are treated in the operating room with a combination of excisional or incisional biopsy and cautery destruction under monitored anesthetic care with a standard perianal block as previously described.⁹³ The pathology is reviewed for evidence of dysplasia. The primary care physician performs a follow-up Pap smear at 3 months. Patients with a history of

Figure 2 Areas of dysplasia appear white and display characteristic vascular markings after the application of 3% acetic acid.

dysplasia, either from previous biopsy or Pap smear, are "mapped" in the operating room with the operating microscope, acetic acid, and Lugol's solution. The patient is positioned and a perianal block given as described earlier. The anal canal and perianal skin are painted with 3% acetic acid and examined with the operating microscope. Tissue infected with HPV becomes white (acetowhite) and demonstrates characteristic vascular patterns⁹⁴ allowing otherwise occult disease to be identified (Fig. 2). The tissues are next painted with Lugol's solution. Nonkeratinizing high-grade lesions of the anal canal do not readily take up Lugol's solution and stain either mahogany or yellow. Low-grade and normal tissues stain partially or completely black (Fig. 3). The high-grade-appearing lesions are biopsied and the lesion is destroyed with electrocautery. Electrocautery ablation

Figure 3 Normal tissues and areas of low-grade dysplasia take up Lugol's solution and appear black. Areas of high-grade dysplasia do not take up Lugol's solution and appear yellowish or light tan (here grayish or lighter).

is achieved by "painting" the lesion with needle tip cautery. The surgeon moves the needle tip quickly across the tissue trying not to burn deeply, as this damages the underlying tissues unnecessarily, potentially increasing scarring and hemorrhagic complications. The lesion and a small 2- to 10-mm rim of tissue are destroyed in this fashion. Care is taken to preserve normal-appearing tissues and to avoid creating an uninterrupted circumferential burn. Low-grade lesions may be biopsied and destroyed but may need to be left untreated if treatment of high-grade and low-grade disease would lead to a circumferential injury. The low-grade disease may be treated after an interval that allows healing, generally 3 months. Once all of the lesions have been treated, the patient returns to the primary care physician for follow-up anal Pap smear at 3 months. A repeat smear is performed after an additional 3 months and if both show no dysplasia, further follow-up can be tailored according to the patient's underlying risk factors.

This method of anal cartography is preferred to punch biopsy and mapping with local excision and flap procedures because it preserves tissue and function. This technique eliminates HSIL in the HIV-negative population. Recurrence rates, however, are high in HIV-positive patients. Retreatment in these patients is safe and well tolerated, and may be considered in patients with recurrent or persistent disease. Although post-operative pain may be a significant problem as with any anal surgery, there was no sphincter dysfunction or anal stenosis. In addition, patients have experienced no decrease in enjoyment of sexual activity after surgery. Most importantly, no cancers have occurred in treated patients regardless of HIV status.⁹³

CONCLUSIONS

Genital HPV infection is the most common STD and is responsible for a wide range of conditions from benign warts to anal cancer. Most patients exhibit a pattern of regression but persistence after HPV infection may occur. Persistent HPV infection is associated with high-risk subtypes, multiplicity of viral infections, certain high-risk behaviors, and host immunity. However, the true rates of disease progression are yet unknown and are the subject of further study. In recent years the incidence of anal cancer has increased to alarming rates among certain subpopulations of patients. Several different treatment modalities are available for treating anal condylomata and include topical, immunologic, and surgical techniques. Vaccine development is an area of active investigation and early data appear to show promise. HPV infection also leads to the development of anal SIL and subsequently anal cancer. Although important questions remain, much has been learned about the diagnosis and treatment of patients with anal SIL. High-resolution anoscopy with cautery ablation is a safe

and effective treatment for controlling HSIL in the general population and appears to be effective in the immunosuppressed patients as well, but multi-institutional trials may be needed to establish its impact on anal cancer.

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