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Anal Intraepithelial Neoplasia

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Key Concepts

- Anal intraepithelial neoplasia is a dysplastic condition of squamous tissue and is considered to be a premalignant stage of anal cancer.
- The histological findings and cellular abnormalities mirror cervical dysplasia.
- Anal cytology is a useful method to identify anal neoplasia in high-risk groups.
- When cytology is concerning, the evaluation of anal neoplasia can proceed with anal cytology and high-resolution microscopy, a technique similar to colposcopy.
- A targeted approach to dysplasia ablation through microscopy is more sparing than historically practiced wide local excisions and flap advancements.
- Treatment should be tailored to the patient's degree of dysplasia, risk factors, immune status, continence, symptoms, and likelihood of progression.

Introduction

Anal intraepithelial neoplasia is a dysplastic condition of the squamous tissue and is considered to be a premalignant stage of anal cancer. Anal intraepithelial neoplasia (AIN) is further stratified into three grades: AIN I, AIN II, and AIN III, defined as low-, moderate-, and high-grade dysplasia, respectively (Figure 20-1). The histological findings, including the cytologic changes, mitotic activity, nuclear membrane changes, and cellular abnormalities [1, 2], mirror cervical dysplasia grading. Terminology can be confusing as anal intraepithelial neoplasia is referred to by many names including anal dysplasia, intraepithelial carcinoma, intramucosal carcinoma, squamous cell carcinoma in situ, and Bowen's disease. In addition, recently the terms high-grade anal intraepithelial neoplasia (HGAIN) and low-grade anal intraepithelial neoplasia (LGAIN) have been proposed that correspond to AIN III/II and AIN I, respectively [1]. In this chapter we will use the terms anal intraepithelial neoplasia which parallel the pathophysiology of cervical intraepithelial neoplasia, vulvar intraepithelial neoplasia, and perineal intraepithelial neoplasia.

Symptoms

The vast majority of individuals will experience no outward manifestation of human papillomavirus (HPV) infection, and similarly most patients with AIN have no clear symptoms. A small subset of patients will describe occasional rectal bleeding, and an even smaller group will experience pain with bowel movements. As AIN progresses to anal cancer, symptoms become more frequently reported. In fact, 50 % of patients with invasive cancer describe pain and bleeding [3, 4]. A minority of patients with anal intraepithelial neoplasia describe a palpable lesion on the non-hair-bearing portion of the anal skin, but the majority have no outward sign of disease. However, those patients with signs of external genital warts and immunosuppression have a very high risk of AIN.

Epidemiology

Anal intraepithelial neoplasia develops from HPV contact generally through direct exposure [1, 5, 6]. It is estimated that there are more than 100 subtypes of HPV but not all have been implicated as disease causing. In fact, as stated in the prior section, most patients who come into contact with HPV have no actual symptoms and experience no untoward effects. For those who come into contact with the virus, about 90 % of all patients remain asymptomatic and those that have infection resolve without any treatment within 2 years [7]. A small number develop persistent asymptomatic infections, while a smaller number of patients will develop condyloma. It is unclear why a fraction of patients develop neoplasia in the form of AIN that then may progress to squamous cell cancer.

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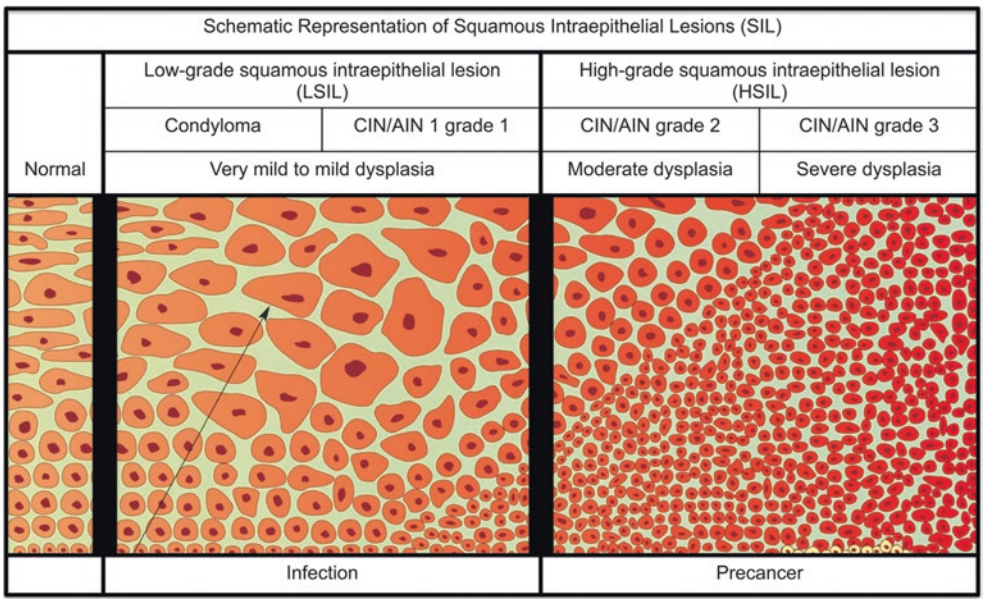

FIGURE 20-1. Schematic representation of squamous intraepithelial lesions (SIL). As shown in this illustration, with increasing severity of SIL of the anus, the proportion of the epithelium replaced by immature cells with large nuclear-cytoplasmic ratios increases. Invasive cancer probably arises from the one or more foci of high-grade SIL (HSIL) as depicted in the drawing by epithelial cells crossing the basement membrane below the region of HSIL. With permission from Brickman C, Palefsky JM Human papillomavirus in the HIV-infected host: epidemiology and pathogenesis in the antiretroviral era Curr HIV/AIDS Rep 2015;12:6–15. Copyright Springer [73].

Explanations for why the virus causes condyloma or neoplasia in some patients but not in others are speculative. It is likely related to patient immune function, subtype of HPV, repetitive inoculation, and/or potentially concomitant infections such as other sexually transmitted infections. For example, among HPV subtypes, types 6 and 11 cause 90 % of genital warts [8] as compared to those subtypes that are associated with cancer (i.e., types 16, 18). We do know that almost all patients with anal squamous cell cancer, and presumably AIN, have been exposed to HPV at some time in their life. The HPV exposure was likely years prior to the development of actual squamous tissue changes.

HPV, the causative exposure to AIN, is quite prevalent in both the developed and developing world. Estimates indicate that at any point in time, one in ten women worldwide harbors the HPV virus [9]. Prior to the introduction of the HPV vaccine, there had been a steady rise in the rate of HPV infections across the nation and the globe. However, with the introduction of the HPV vaccine, the prevalence of HPV types 6, 11, 16, and 18 identified by cytology specimens decreased by over 50 % among teens and young women. In addition and as expected, HPV prevalence has not been declining in older women who would not have received the vaccine [10]. Data from the National Disease and Therapeutic Index suggest that although cases of genital warts as measured by initial visits to physicians' offices increased during the late 1990s through 2011, genital wart cases appear to have decreased since 2011 [11], presumably because of increased vaccination (Figure 20-2).

Incidence data characterizing trends of HPV infection and condyloma are easily obtainable, yet it is unclear whether the rate of AIN has changed in the last several years. There are no public records and cancer surveillance data do not record incidence or treatment of dysplastic lesions. National cancer incidence data do reveal that the rate of anal cancer has been increasing for several years. Using statistical models for analysis, rates for new anal cancer cases have been rising on average 2.2 % each year over the last 10 years [12]. The number of new cases of anal cancer was 1.8 per 100,000 people per year based on 2007–2011 cases, and the cancer is still slightly more common in women than in men [12].

Much of what is known regarding the transformation of AIN to squamous cell cancer has been extracted from the cervical cancer literature. A recent review of medical records of men who developed anal cancer revealed a common history of precursor high-grade squamous intraepithelial lesions, i.e., anal intraepithelial neoplasia [13]. Because the virus has been detected in many asymptomatic patients, it is likely that viral persistence after integration of the viral genome into the host [14] occurs in order to produce genetic change. Viral oncogenes are then ultimately responsible for directly coupling to oncogenic enhancers and promoters permitting continued expression through integration and immortalization [14]. A number of genetic changes are proposed to

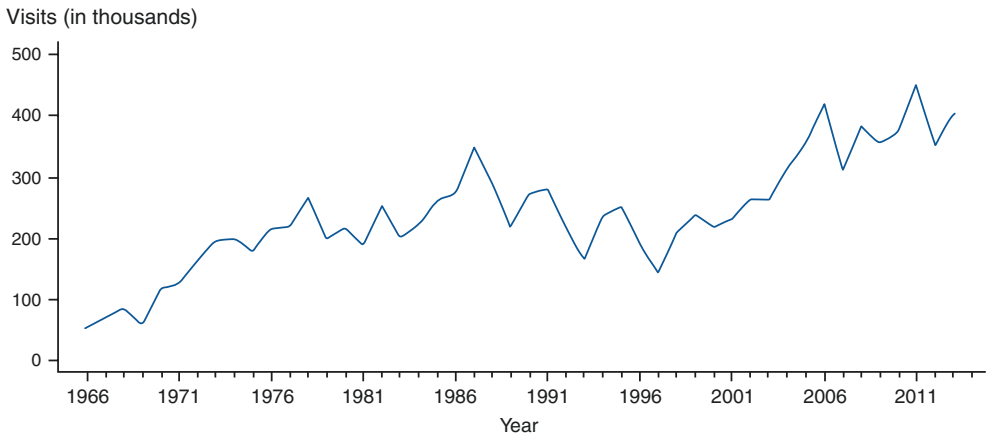

FIGURE 20-2. Genital warts. Initial visits to Physicians' Offices, United States, 1966–2013 http://www.cdc.gov/std/stats13/figures/49.htm. *Source*: IMS Health, Integrated Promotional Services™. IMS Health Report, 1966–2013.

occur after viral integration leading to phenotypic changes of the squamous epithelium. Abnormalities to chromosomes 1, 3, 7, 8, 11, 15, and 20 have all been reported with varying frequency [15, 16]. One of the most frequently reported changes in chromosomal structure is a gain in the long arm of chromosome 3q [17], which is also reported to occur in the transition from low-grade to severe cervical dysplasia and/or cervical cancer [15]. Although it is unclear which gene mediates this transformation, the mechanism may be through phosphatidylinositol 3-kinase, an oncogene on chromosome 3 that phosphorylates other proteins involved in cellular growth. This oncogene has been similarly implicated in the tumorigenesis of ovarian [18] and cervical [19] cancer but not in anal cancer at this time.

Following incorporation of the viral genome into host DNA, cellular changes and atypia of squamous tissues occur [1, 13, 20]. Ultimately these changes correspond to AIN I which then can progress to AIN II and AIN III and ultimately dedifferentiate into squamous cell cancer. It is unclear whether the development of anal neoplasia must traverse all these steps or if squamous cell cancer can skip one or more phases, i.e., from AIN I directly to AIN III. The degree of cellular abnormality and the level of cellular changes correspond to each phase; AIN I has minor changes to the epithelial cells and AIN III corresponds to full-thickness changes to the epithelium with aberrant structure and cellular atypia (Figure 20-1). Ultimately, the oncogenetic pathway is similar to the pathway described in cervical cancer, which degenerates from cervical intraepithelial neoplasia.

Screening/Surveillance

Most patients at risk for anal neoplasia undergo screening with digital rectal examination, anal cytology, and anoscopy. Anal cytology is akin to cervical cytology, providing cellular material for review of intraepithelial lesions. The technique is performed as part of a full physical examination and generally includes a digital rectal examination and anoscopic examination. The cytology must be performed before any instrumentation of the anus and before lubrication is used. The procedure is performed with a moist swab in the anal canal and without any preparation. Following completion, a digital rectal examination and anoscopy can be performed. Obvious condylomatous lesions are concerning if found, particularly in immunosuppressed patients, and should be removed or treated topically with close follow-up.

The anal cytology smear is graded by a cytologist with the same classification used in gynecologic samples. Anal cytology may return as insufficient, normal, atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, or anal cancer. Based on these results and prior medical history, the recommendation is either continued surveillance or more detailed evaluation with high-resolution anoscopy. Lesions classified as atypical squamous cells of undetermined significance or higher are generally referred for high-resolution anoscopy. However, a large number of patients have abnormal cytology results leading to a considerably large population of patients to evaluate in microscopy. In addition, given that the sensitivity of anal cytology ranges from 69 to 93 % and specificity ranges from 32 to 59 % [21–23], results can be difficult to interpret. It is important to remember that anal cytology in high-risk cohorts such as men who have sex with men has false-negative rates of up to 23 % in HIV-negative patient and 45 % if HIV positive [24]. Therefore, close follow-up of all high-risk patients is likely to be the best strategy (see Figure 20-3).

Defining the population that is high risk and requiring evaluation is challenging because of societal and other behavioral concerns. Overall, the risk of anal neoplasia is highest in immunosuppressed individuals as they appear to have great difficulty in clearing the virus from their body. Rates of anal dysplasia in HIV-infected patients of all sexual

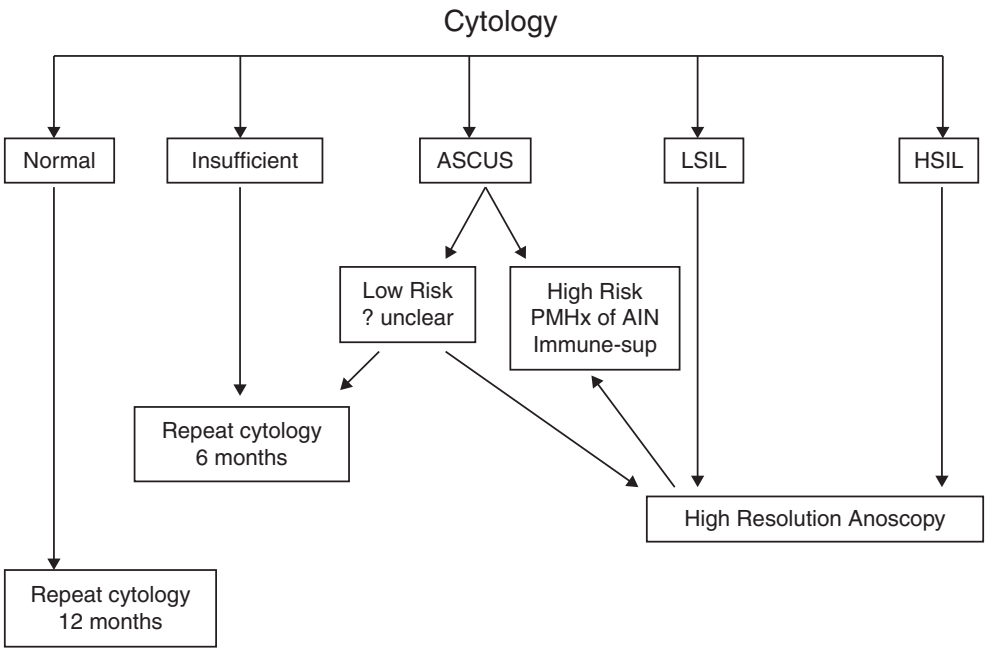

FIGURE 20-3. Management algorithm for anal cytology results. General guidelines provided. Individual case management is based on many factors, which may increase or decrease the interval of evaluation.

risk groups are substantial indicating some value for anal cancer screening in all HIV-infected patients regardless of sexual practices [25, 26]. The immunosuppressed group should also include those with organ transplants [27, 28], as well as other medically induced suppressive conditions. Men who have sex with men and a concomitant diagnosis of HIV pose the greatest risk of HPV-related illnesses and thus anal neoplasia [29]. Patients with prior history of HPV infection are also likely to be at high risk for anal dysplasia and cancer as well as those patients who practice anal receptive intercourse or persons with a high lifetime number of sexual partners [30].

One of the highest-risk groups is women with a past history of cervical, vulvar, or perineal neoplasia. A number of population-based studies report an increase in anal neoplasia risk among women with a history of invasive cervical cancer [31, 32]. In addition to invasive cervical cancer, a recent review of Surveillance, Epidemiology, and End Results data identified a significant association between gynecologic neoplasm and anal cancer for both in situ and invasive cancers of the cervix and vulva and in situ neoplasm of the vagina. In that study, the highest risk for anal cancer was identified in those women with evidence of either in situ or invasive squamous cell cancer of the vulva [33]. The proximity of the anus to the vulva may explain why patients with vulvar neoplasia were at highest risk for anal cancer, yet the increased risk with in situ neoplasia was also remarkable. Thus, patients with gynecologic neoplasia, and especially vulvar neoplasia, should be followed closely for potential anal cancer development.

Individuals with a past history of sexually transmitted infections may also represent an important screening population. A past history of condyloma is generally a sign of prior contact with human papillomavirus. At this time, it is unclear whether those individuals who tend to develop condyloma (without any sign of dysplasia) have a tendency to develop benign warts rather than cancer. Further studies are needed to investigate the link between prior history of condyloma and anal neoplasia. In addition, it is difficult to prove any synergy between human papillomavirus and other sexually transmitted infections that might act in an additive way to speed up transformation to AIN. However, the presence of HIV with anal coinfection with syphilis, gonococci, Epstein-Barr virus, cytomegalovirus, or herpes simplex was identified as an independent risk factor for dysplasia and cancer [34]. These data point to association between the herpes virus and HPV, yet the effect of these infections on anal neoplasia pathogenesis is certainly unclear.

The value of anal cancer screening is difficult to quantify. There are several studies using computer models to determine the benefit of these tests. Screening HIV-positive homosexual and bisexual men for anal dysplasia with anal cytology offers quality-adjusted life expectancy benefits at a cost comparable with other accepted clinical preventive interventions [35]. Others have not come to the same conclusion indicating that many of the criteria for assessing the

need for a screening program were not met for anal neoplasia screening and that cost-effectiveness remained unacceptable [36]. The lack of concordance for these models may be related to the lack of agreement with uncertainties in modeling clinical scenarios in the face of poor evidence. For those patients with a past history of high-grade dysplasia and immunosuppression, a role for surveillance is likely to be of some benefit given the high rate of recurrent disease in this population [17]. It is thought that a combination of surveillance high-resolution anoscopy and anal cytology at 6 and 12 months is cost-effective after treatment of anal neoplasia in HIV-infected men who have sex with men [37].

At this time, a review of 30 regional and national guidelines for screening in HIV patients revealed that only two societies recommended digital and anorectal examination [38]. The "European AIDS Clinical Society Guidelines" recommends digital examination every 1–3 years for HIV-positive men who have sex with men. In New York State, the Department of Health has recommended annual anal cancer screening for HIV-positive men who have sex with men, HIV-positive patients with history of condyloma, and HIV-positive women with a history of gynecologic neoplasia. However, the US Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents recommended only an annual digital examination for the HIV-positive population in general [38].

Diagnosis

Most patients are diagnosed with anal neoplasia through investigation with digital rectal examination, anal cytology, anoscopy, and/or endoscopy. The sensitivity of digital rectal examination in identifying anal neoplasia is fairly low as many AIN lesions are not palpable. Anoscopy is routinely performed by colon and rectal surgeons and can be used to identify macroscopic areas of AIN, which often appear to be benign condylomata, but may return with AIN on biopsy (Figure 20-4). In addition, endoscopic identification of AIN occurs quite commonly particularly during the retroflexed view of the anus. A biopsy of the lesion should lead to a consult with a surgeon who has experience with these lesions. Last, a large number of patients are identified with anal dysplasia on cytologic evaluation during routine screening. These patients are best evaluated with microscopic examination and referred to a facility with appropriate knowledge and capacity.

During diagnostic evaluation, it is imperative to remember that patients with AIN should have a complete and thorough history and physical examination. It is important to remember the link between anal dysplasia and other HPV-related diseases such as oral cancer, gynecologic neoplasia [33], and other genital lesions. In our practice, we refer all female patients for gynecologic evaluation and inquire about dental examinations. The physical exam should include a head to toe evaluation for squamous cell lesions, considering the mouth and all lymph node basins. Referral to gynecology or a urologic service should also be considered when applicable based on findings and history.

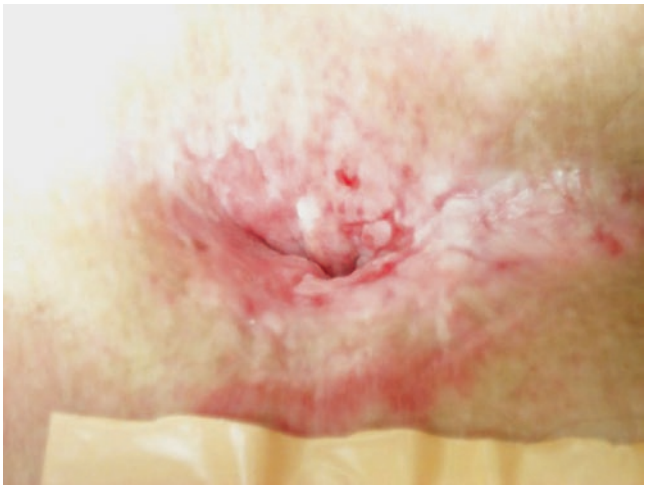

FIGURE 20.4. AIN 3. Courtesy of Richard Billingham, MD.

Following examination of the entire body, the evaluation of AIN can proceed with anal cytology and high-resolution microscopy, a technique similar to colposcopy of gynecologic neoplasia. In fact, the colposcopic appearance of variable grades of anal squamous intraepithelial lesions is similar to those described for the cervix [39]. In high-resolution anoscopy, a colposcope or another microscope is used to examine the anal verge and anal canal in close detail. The procedure can be performed in any position, but left or right lateral positioning provides greater visualization of difficult areas, such as under the prostate in men. No bowel or anorectal preparation is necessary and the procedure is most commonly performed without analgesia. After positioning, the tissues to be examined are swabbed with a 3–5 % acetic acid solution for 2–5 min. Some colposcopists choose to add an iodine-based Lugol's solution to further assist with detection of dysplastic tissue. The mechanism for Lugol's utility is that only healthy epithelial tissue absorbs the compound which causes normal tissue to appear wood-like. However, dysplastic tissues do not absorb the solution leaving these tissues with a yellowish hue. Although used by many colposcopists, our protocol is to avoid Lugol's solution as it interferes with proper dysplasia differentiation (i.e., AIN I versus AIN II or III).

For those who do not use Lugol's solution, the acetowhitening from acetic acid with microscopic assistance is sufficient to identify dysplastic tissues. The entire anal canal and anal verge should be examined, but we find that dysplastic tissues are most commonly found within the transition zone, as this area has the greatest area of susceptible and immature squamous tissues. The acetowhitening is particularly helpful in characterizing the degree of dysplasia. Dysplastic epithelium will absorb acetic acid and appear scaly white as

compared to columnar tissues. The characterization of dysplastic tissue and differentiation of AIN I, II, or III can then be performed without biopsies and in real time under high magnification. Dysplastic tissues are characterized by scaly white plaques and with greater disarray of vascular patterns, the higher the grade of dysplasia. We also find that high-grade dysplasia tends to be quite friable when in contact with the anoscope or a swab (Figure 20-5).

The equipment used for the evaluation of AIN is expensive and the high-resolution microscopy procedure is time intensive and difficult to learn. Others have taken to diagnose AIN with simple anoscopy or endoscopic methods. At this time, data have not demonstrated that high-resolution anoscopy is superior to other methods. However, a multicenter randomized trial is underway to demonstrate the value of close surveillance. Interestingly, a recent study from Ohio revealed no difference in anal cancer progression with simple observation versus high-resolution anoscopy [40]. However, the length of follow-up, diagnostic accuracy, and follow-up protocols were unclear as the study was underpowered to detect smaller outcome differences. Others have demonstrated a very low rate of anal cancer progression with an intense surveillance strategy involving anal cytology, digital anorectal examination, and oncogenic HPV testing in men who have sex with men. Abnormalities on screening lead to high-resolution anoscopy and ablation as indicated [41].

Treatment

It should be clear that there is no proven treatment for HPV infection. As stated earlier, the infection is self limited such that treatment is directed only to the macroscopic (i.e., genital warts) or pathologic (i.e., precancerous) lesions caused by infection [42, 43]. It is thought that all subclinical HPV infections resolve without treatment, and thus, any attempt at antiviral therapies is not indicated [43, 44]. When dysplasia is present, whether in the anus, vulva, or cervix, there are a number of methods to manage or treat these neoplastic tissues ranging from no intervention to very aggressive care. At this time there is no clear best treatment option for all types of patients and all degrees of anal dysplasia. Ultimately the best method of treatment must be efficacious in preventing the progression of anal intraepithelial neoplasia to cancer while reducing the morbidity of treatment and preserving function. In addition, one other consideration in treatment should be reducing the rate of virus transmission to others (Table 20-1).

Observation may be the best option for patients with low-grade dysplasia. In particular, this may be the least difficult technique for patients with no symptoms and with low likelihood of conversion to anal cancer. Management would consist of surveillance every 4–12 months [45]. Supporters of this "watch and wait" strategy cite overall low rates of disease progression and malignant potential (especially for low-grade disease) and the increased morbidity associated with excision and repeated focal destruction [1]. Certainly, the risk of progression is fairly low in patients with low-grade dysplasia with evidence indicating that some proportion of patients will exhibit regression of disease without treatment [45, 46]. It is our practice to recommend observation in select cases depending on risk factors, comorbidities, and available resources. In a recent review of cases observed for anal neoplasia, patients followed with expectant management or high-resolution anoscopy rarely develop squamous cell cancer if they were compliant with treatment protocols [40].

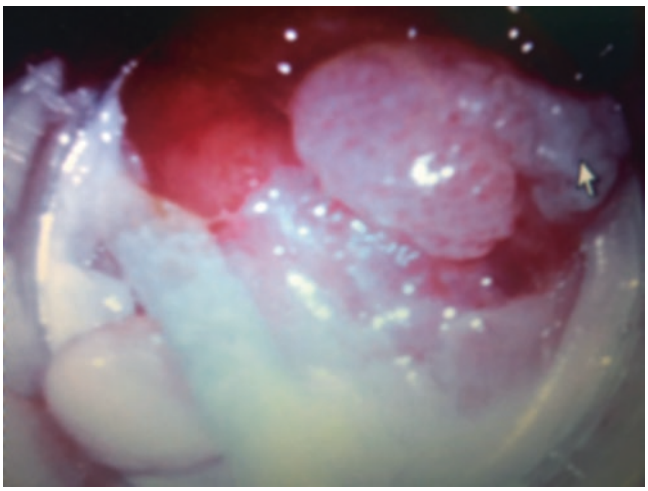

FIGURE 20.5. AIN on high-resolution anoscopy. The *pointer* denotes area of high-grade dysplasia. Courtesy of Rocco Ricciardi, MD.

Topical treatments have demonstrated effectiveness for both high- and low-grade dysplasia. These agents include imiquimod and 5-FU. Imiquimod is one of the most tested agents [47–49] and is considered to be efficacious by those who use it regularly. Despite its effectiveness in both immunosuppressed [47] and immunocompetent patients, there is a high rate of recurrence when treatment is discontinued [47, 48]. Many of the recurrent lesions are unrelated to the primary dysplastic lesion but rather due to undetected HPV types [48]. Interestingly a recent meta-analysis failed to demonstrate any statistically significant effect of imiquimod in the management of anal intraepithelial neoplasia, but there was a trend for imiquimod to downgrade high-grade AIN to a lower-risk stage [50]. As compared to imiquimod, 5-FU has fewer trials but is similarly effective in reducing dysplasia with complete response in 39 % [50]. Unfortunately, patients treated with 5-FU similarly had high rates of recurrence (50 %) and even higher rates of side effects [50, 51]. There are a smattering of reports demonstrating efficacy for other topical agents such as trichloroacetic acid [52], cidofovir [53], as well as photodynamic therapy [54].

Surgery is an effective option to treat anal neoplasia. Data reveal that electrocautery is highly effective in inducing complete response of AIN especially in immunocompetent

Table 20-1. Common options used in treatment of anal dysplasia

Treatment	Advantages	Disadvantages	Cure	Recurrence
Observation	Cost cheap No side effects	Low cure rate Time intense	Poor	High
Imiquimod	Minimal pain Easy to use	Burning Moderate cost	Poor	High with DC
5-FU	Easy to use	Burning Moderate cost	Poor	High with DC
Infrared coagulation	Clinic use	Need equipment	Good	Moderate in immunosuppressed
Ablation	One application	Painful Costly	Good	Moderate in immunosuppressed
Wide local excision	Removes all tissue	Disfiguring Painful	Good	Low

individuals (72 %) as compared to immunosuppressed individuals (51 %) [55]. Ablation is generally performed in the operating room with electrocautery in conjunction with high-resolution anoscopy; yet, others perform the procedure in the clinic with local anesthesia. The technique is highly selective with targeting of only those areas with evidence of dysplasia. The operating surgeon should remember that the disease is limited to the epidermis and does not require destruction of deeper dermal tissues. In addition, margins are unnecessary with ablation, so the electrocautery can be highly targeted without damage of healthy neighboring tissues. In fact, healthy skin bridges should be preserved as much as possible. During ablation, the surgeon should be mindful of potential scarring, stricture formation, and the need to preserve as much healthy tissue as possible. The preservation of the patients' gastrointestinal function and continence is critical. In addition, the patient will likely require further observation, and limiting electrocautery burns will lead to reduced scarring and ease of further examination in microscopy clinic.

In addition to ablation or excision, infrared coagulation can also be used to destroy lesions. Infrared devices use a beam of infrared light delivered through a light guide covered with a disposable plastic sheath to ablate tissue and coagulate blood in the immediate surface area in contact with the tip [56]. The infrared beam can be pulsed at varying intervals to prevent trauma to deeper tissues. A 1 s pulse penetrates the tissue to a depth of approximately 1 mm targeting the epithelium and destroying dysplastic tissue [56]. The other advantage of infrared coagulation is the ability to perform the technique within the clinic setting and without general anesthesia [57]. The technique is reportedly as effective as electrocautery and considered to be associated with less pain [1].

In the past, mapping biopsies with wide local excision was recommended for patients with anal intraepithelial neoplasia. Unfortunately, much healthy and uninvolved tissue was removed with the dysplastic tissues, and this treatment option was associated with high rates of recurrence between 13 and 63 % [58–60]. In addition, because of the extensive tissue destruction, wide local excision was associated with high rates of local wound complications such as stenosis and incontinence [59]. Although anal mapping with wide local excision was once routinely performed [61], it is generally not required to treat even the most challenging and diffuse disease.

When selecting which of the above options is best for an individual patient, the physician should consider patient treatment goals, symptoms, history of immunosuppression, past history of dysplasia, and bowel function. At this time, it is unclear what role HPV subtype, concurrent sexually transmitted infections, and other concerns should play in selecting treatment options. There is one trial comparing imiquimod, topical fluorouracil, and electrocautery in HIV-positive men that revealed higher rates of complete response and fewer side effects in the electrocautery group [62]. However, an attempt at Cochrane review failed to provide guidelines for treatment in anal intraepithelial neoplasia because of lack of high-quality randomized controlled trials [50].

Management Strategies

For AIN I, a minimalist approach may be the most effective strategy. Again, in the cervical literature, a large number of patients will regress to normal epithelium but similar data are unavailable in the anus. Given the lack of data regarding progression of low-grade dysplasia in healthy immunocompetent patients, most clinicians would advocate observation. However, the high likelihood of cure after ablation or other interventions makes a surgical approach attractive, particularly if the patient does not wish to return to a microscopy clinic on a regular basis. Low-grade dysplasia in an immunosuppressed patient presumably has a higher likelihood of progression but a high likelihood of recurrence as well. Thus, repeated ablative attempts to the anus with the potential development of scarring, stenosis, bleeding, and chronic pain render an aggressive approach difficult for patients. For immunocompetent patients with high-grade dysplasia, the simplest method of treatment is ablation. There are some who would attempt topical therapy, but surgical ablation is efficient, is effective, and can be targeted with high-resolution

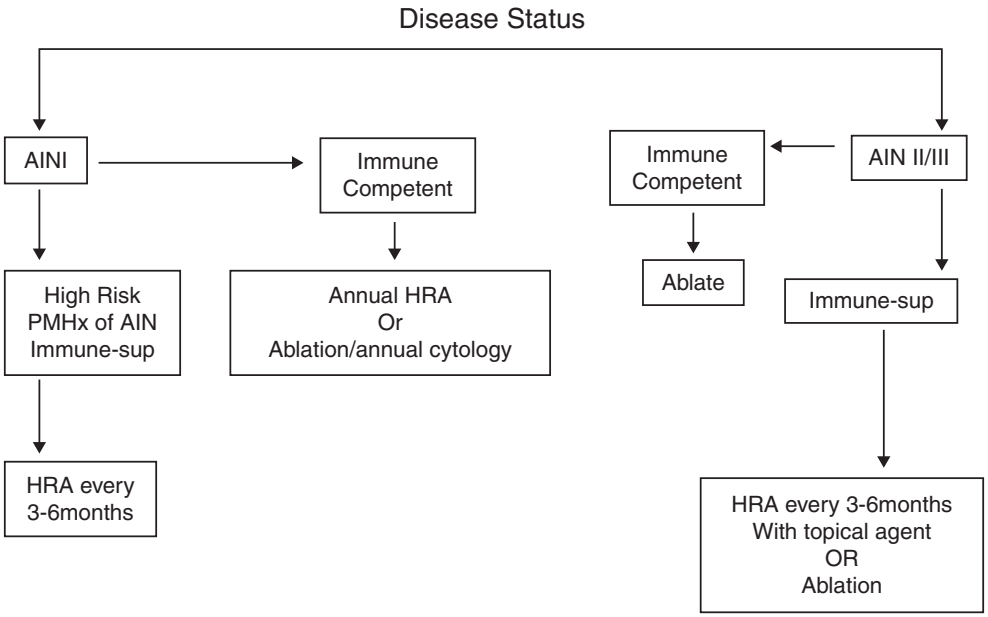

FIGURE 20.6. Algorithm for the treatment of AIN based on immune status and biopsy results.

anoscopy in the right hands. For immunosuppressed individuals with high-grade dysplasia, the best treatment is unclear (Figure 20-6). These patients have high likelihood of recurrence, multifocal disease, other comorbidities and health concerns, and other difficulties. Our approach is to combine therapies with topical therapy, close observation with high-resolution anoscopy, and ablation when the disease appears to be worsening or when patient follow-up is questionable. Our office chooses to limit the ablative interventions for these high-risk patients but follow closely and ablate only those areas that appear most ominous. In addition, the role of wide local excision in the surgical armamentarium is unclear.

Progression

Progression of anal intraepithelial neoplasia to squamous cell cancer of the anus parallels the pathway of cervical dysplasia to cervical cancer [63]. Once established in the anal epithelium, dysplasia of the anus rarely regresses [64] causing substantial concern for patients and their caregivers. The persistence of disease is particularly troubling for those with symptoms, but data proving persistence is incomplete as not all cases with anal dysplasia present for workup. In addition, it is unclear why anal dysplasia is thought to be more persistent than equivalent degrees of cervical dysplasia given the common pathogenic cause of these two conditions. In fact, it is estimated that approximately 60 % of low-grade cervical lesions will spontaneously regress in the cervix [45, 46]. Despite the favorable results in the cervix, similar anal disease is seen as prognostically worse. There are no natural history studies of untreated anal dysplasia, although case reports do detail a high rate of progression of the precursor lesions to anal cancer with lack of follow-up [65, 66]. The high rate of progression is particularly true for immunosuppressed patients as compared to immunocompetent patients [65].

Prevention

As with all infectious diseases that are transmissible by sexual contact, the best method of prevention is safe sexual practices or limiting sexual contact [67]. In addition to monogamy, proper and consistent use of prophylactic condoms has been shown to reduce the transmission of HPV [68]. Although latex condoms can prevent infection most of the time, the virus can still cause infection by infecting areas that are not covered by a condom. In addition to condoms, educational interventions targeting socially and economically disadvantaged women in which information provision is complemented by sexual negotiation skill development can encourage at least short-term sexual risk reduction behavior [69]. Thus, educational interventions do have the potential to reduce the transmission of HPV and possibly reduce the incidence of squamous carcinoma [69].

In addition to primary prevention techniques, vaccines have also been efficacious in reducing the incidence of HPV infection. In the general screening population, HPV vaccine efficacy was almost 100 % for cervical intraepithelial neoplasia, vulvar and vaginal intraepithelial neoplasia, and anogenital condyloma [70]. In men who have sex with men, the use of quadrivalent HPV vaccine significantly reduced the

rates of moderate and high-grade anal intraepithelial neoplasia [42]. Although the vaccinated populations were HPV naïve, there are some data indicating effectiveness of HPV vaccines in preventing reinfection or reactivation of disease [71]. Along the same reasoning, a nonconcurrent cohort study of HPV-vaccinated men who had been previously treated with high-grade anal intraepithelial neoplasia was noted to have a reduction in anal intraepithelial neoplasia recurrence [72].

Conclusions

Anal cancer incidence is rising in the United States indicating increased prevalence of AIN; therefore, screening programs are under development to identify disease earlier. There is a growing body of data indicating that high-resolution anoscopy with ablation leads to a low rate of anal cancer development [41]. However, optimal therapy of anal intraepithelial neoplasia is unclear. Multiple modalities exist and the clinician should balance factors such as symptoms, disease severity, dysplasia multifocality, immunosuppression, and past history of disease into account. Ultimately, the condition should be treated with the intent to preserve continence and reduce postoperative scarring and strictures while reducing the potential for disease progression to invasive cancer.

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