Human Papilloma Virus Infection and Anal Squamous Intraepithelial Lesions

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Abstract

This article addresses the natural history of the human papilloma virus (HPV) infection to anal squamous intraepithelial lesions, and onto squamous cell carcinoma of the anus. This article provides overviews of the virology, pathophysiology, nomenclature, classification, historical terms, risk factors, clinical evaluation, differential diagnosis, and treatment of HPV infection and its sequelae.

Keywords

- HPV
- ASIL
- HIV
- PAIN
- AIN
- Bowen's disease
- Bowenoid papulosis
- squamous cell carcinoma

Human papilloma virus (HPV) is the most common sexually transmitted disease (STD) throughout the world.[1] The vast majority of sexually active adults are affected at some point in their lives. Most will have no symptoms or self-limited anogenital lesions. There are 150 genotypes. Forty can infect the anogenital organs.[2] HPV subtypes are categorized as low or high risk according to their propensity to progress to squamous intraepithelial lesions (SIL). SIL are also stratified into low- or high-grade SIL (LG-SIL and HG-SIL) based on their oncogenic potential of progressing to anal squamous cell carcinoma (SCC). LG-SIL is relatively innocuous. HG-SIL can progress to anal SCC in a minority of cases. However, 90% of anal SCC are attributable to HPV infections[3] (►**Fig. 1**).

HPV infection predominantly affects the anogenital regions but rare naso- and oropharyngeal infections do occur. Progression to intraepithelial neoplasia (-IN) can involve the cervix (CIN), vagina (VaIN), vulva (VIN), penis (PeIN), anus (AIN), and perianal (PAIN) regions.[4] Anal squamous intraepithelial lesions (ASIL) include two anatomic groups of pathologies—PAIN and AIN. The former involves keratinized integumentary tissue outside the anus, while the latter refers to nonkeratinized epithelium within the anal canal extending 8 cm into the rectum. ►**Table 1** summarizes the relevant pathologic terms, their abbreviations, anatomic locations, and their clinical relevance.

Virology

Forty subtypes of HPV known to infect human anogenital regions are stratified according to their oncogenic propensity (►**Table 2**). HPV genotypes 6 and 11 are of low risk. They produce the majority of LG-SIL.[5] Persistent high-risk HPV infection is associated with HG-SIL.[6] Genotypes 16 and 18 are among the most common precursors of SCC. In one series, genotype 16 was found in 81% of SCC. Genotype 18 was found in 4%.[7]

Pathophysiology

HPV is transmitted through direct contact with infected mucosa or skin. It invades the cells of the basal layer of the

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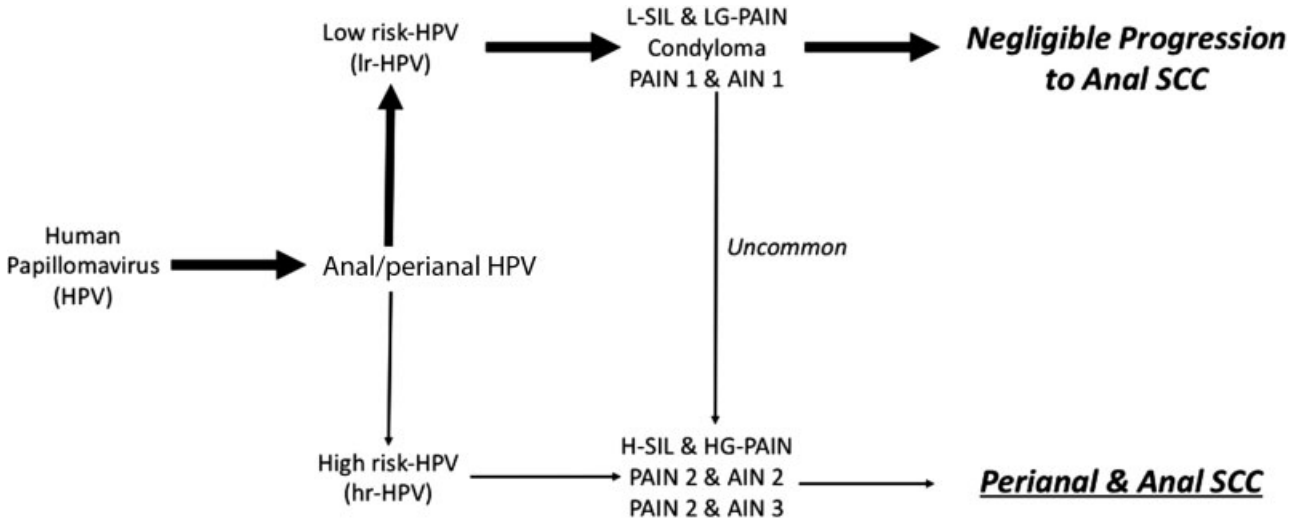

Fig. 1 An overview of the natural history of human papilloma virus (HPV) infection. Note that condyloma and intraepithelial neoplasia 1 (perianal intraepithelial neoplasia [PAIN1] and anus intraepithelial neoplasia [AIN 1]) are considered low oncogenic risk (low-grade squamous intraepithelial lesion [LG-SIL]) and are the more common outcome (thick arrows). Abbreviation: SCC, squamous cell carcinoma.

Table 1 LG-SIL are the more common outcome (thick arrows)

Abbreviation	Pathology		Anatomic location	ASIL relevance/equivalence
ASIL	Anal squamous intraepithelial lesion		Anal canal and perianal	
SIL	Squamous intraepithelial lesion		Ubiquitous	
LG-SIL	Low-grade squamous intraepithelial lesion		Ubiquitous	Not precancerous
HG-SIL	High-grade squamous intraepithelial lesion		Ubiquitous	Pre-cancerous
-IN	Intraepithelial neoplasia		Ubiquitous	
PAIN	Perianal intraepithelial neoplasia		Perianal	
LG-PAIN	Low-grade perianal intraepithelial neoplasia		Perianal	Perianal LG-SIL
HG-PAIN	High-grade perianal intraepithelial neoplasia		Perianal	Perianal HG-SIL
AIN 1	Anal intraepithelial neoplasia 1	Reflects Intradermal Depth: 3 > 2 > 1	Anal Canal	Anal canal LG-SIL
AIN 2	Anal intraepithelial neoplasia 2		Anal Canal	Anal canal LG-SIL versus HG-SIL[c]
AIN 3	Anal intraepithelial neoplasia 3		Anal Canal	Anal canal HG-SIL
HPV	Human papilloma virus		Ubiquitous[a]	
lr-HPV	Low-risk human papilloma virus		Ubiquitous	Progresses to LG-SIL
Hr-HPV	High-risk human papilloma virus		Ubiquitous	Progresses to HG-SIL
LGT -IN	Lower genital tract intraepithelial neoplasia		Cervix, vagina, vulva	Increases risk for AIN in females
SCC	Squamous cell carcinoma		Ubiquitous[b]	
HGD	High-grade dysplasia[d]			HG-SIL
Cis	Carcinoma in situ[d]			HG-SIL
	Bowenoid papulosis[d]		Perianal	HG-SIL
	Bowen's disease[d]		Perianal	HG-SIL

[a]HPV infection rarely involves oro- and nasopharyngeal regions.
[b]SCC can involve all dermal as well as foregut and hindgut derived tissues in addition to anogenital zones.
[c]Immunohistochemical evaluation of p16 is required for AIN 2 to be denominated as H-SIL.
[d]HGD, Cis, Bowenoid papulosis, and Bowen's disease are historical terms categorized currently as H-SIL.

Table 2 Stratification of HPV subtypes according to oncogenic risk. The nanovalent HPV vaccine is effective against those annotated in bold

Risk	HPV subtypes
High (Hr- HPV)	**16**,**18**,**31**,**33**,35,39,**45**,51,**52**,56,**58**,59,68
Probably high	26,53,66,73,82
Low (lr-HPV)	**6**,**11**,40,42,43,44,54,61,70,72,81, CP6108

Abbreviation: HPV, human papilloma virus.

epidermis through microabrasions. At the anogenital level, infection occurs almost exclusively during sexual intercourse, but could eventually be transmitted by sharing sex toys or similar items. Regular and proper condom use does not achieve complete protection against infection. HPV can be transmitted by contact with unprotected areas such as the vulva or the scrotum.[8,9] Most patients do not use a condom from the beginning to the end of their sexual contacts. Microlesions in the anus are aggravated by scraping, excessive hygiene, and depilation or during defecation. Normal immune responses usually destroy the HPV virus. It persists and integrates within the host deoxyribonucleic acid (DNA) when cellular immunity fails.[10] The integrated virus is present in more than 80 to 90% of SIL and SCC.[11] Both the anal and cervical canals develop from the cloacal membrane. The fusion of endodermal and ectodermal tissues results in their respective squamocolumnar junctions. Normal metaplastic changes and abnormal dysplastic changes associated with HPV infection can occur in both areas.[4]

Current Nomenclature of Squamous Neoplastic Conditions

The American College of Pathologists in conjunction with the American Society of Colposcopy and Cervical Pathology endorsed a unified nomenclature in 2012—Lower Anogenital Squamous Terminology (LAST).[4] This classification divides anogenital HPV infections into LG-SIL (usually self-limited) and HG-SIL that have a greater potential to progress to SCC. LG-SIL includes -IN 1 and condyloma which are not considered pre-neoplastic. These low-grade lesions can progress to HG-SIL. -IN 2 and -IN 3 are both HG-SIL (►**Table 3**).

Historical Terms in Perianal Disease

High-grade dysplasia and carcinoma in situ are commonly used terms that are equivalent to HG-SIL.[12] There are several terms applied to perianal lesions. Bowen's disease is the classic example. It is a diffuse form of PAIN-2 or 3 sometimes recognizable on physical diagnosis. It also falls into the category of HG-SIL with the LAST project denominations (►**Fig. 2**). Bowenoid papulosis is also a PAIN 2 or 3 (HG-SIL).

Kreuter classified four forms of PAIN. They are listed in ►**Table 4**.[13] Three variants are demonstrated in ►**Fig. 3**.

Risk Factors for Progression of ASIL to SCC

The two population sectors at highest risk of progression from intraepithelial neoplasia to invasive anal SCC are human immunodeficiency virus positive (HIV [+]) MSM (Male who have Sex with Men) and immunocompromised individuals—particularly transplanted patients requiring chronic immunosuppression.[14]

A variety of immunocompromised conditions predispose individuals to developing anal cancer. The standardized incidence ratio for anal squamous disease is listed in ►**Table 5**.[15,16]

Condylomas in immunocompromised patients present as voluminous, rapidly growing, exophytic lesions with a poorer response to treatment and a higher rate of recurrence.[17] Solid organ transplant patients are at greater risk of SIL and SCC secondary to immunosuppressive therapy.[18] The risk of anal SCC in this group is 4.54 times higher than the general population.[19]

Patients with inflammatory bowel disease can develop ASIL, SCC, and anal adenocarcinomas. Carcinogenesis in this setting is influenced by local and systemic chronic inflammation, immunosuppression by drugs and HPV infection. The cutaneous and mucosal lesions associated with the epithelization of the fistulous tracts may facilitate HPV entry into keratinocytes. The literature concerning the development of SCC in Crohn's perianal fistula disease is limited.[20] However, appropriate vigilance for ASIL and SCC may be warranted.[21,22]

HIV (+) MSM have higher rates of perianal infection by multiple HPV genotypes. Historically, the progression of HG-PAIN to SCC was only 5%.[18] More recent work reported progression to SCC in 18.4% of in 550 HIV (+) individuals with HG-SIL.[23] Other factors operant in the progression of ASIL to SCC include HPV infection, high-risk sexual

Table 3 The original World Health Organization (WHO) classification was replaced by the cytology-based Bethesda terminology. The LAST Project nomenclature is the current unifying standard

WHO	Bethesda	LAST project
Low-grade dysplasia/-IN 1	L-SIL	L-SIL (condyloma, -IN 1)
Moderate-grade dysplasia/-IN 2	H-SIL	H-SIL (-IN 2)
High-grade dysplasia/-IN 3	H-SIL	H-SIL (-IN 3)
Carcinoma in situ		H-SIL

Abbreviations: H-SIL, high-grade squamous intraepithelial lesion; IN, intraepithelial neoplasia; L-SIL, low-grade squamous intraepithelial lesion.

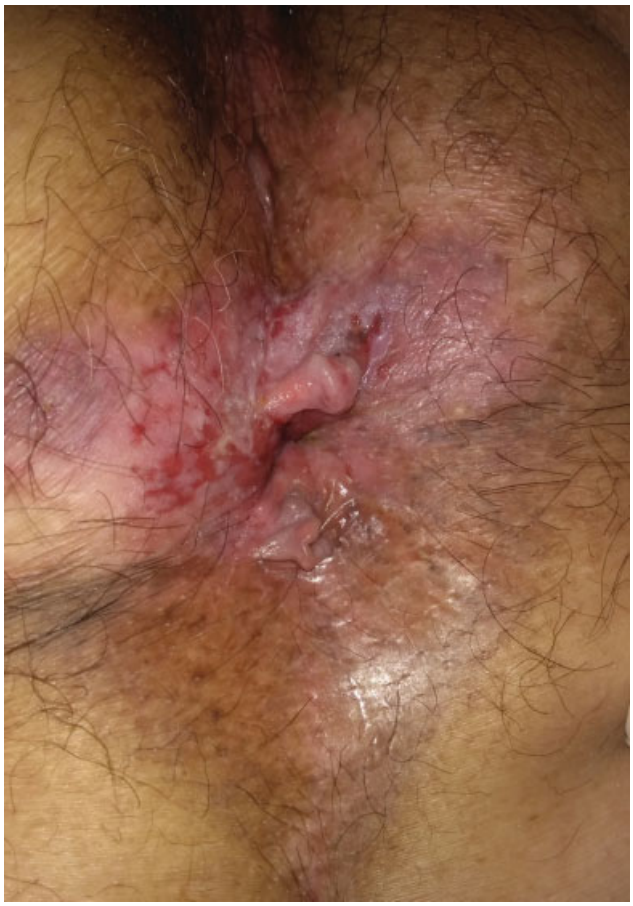

Fig. 2 Bowen's disease circumferentially present at the anal verge. Ulceration suggests invasion (Photo—L. Svidler López and L. La Rosa).

behavior,[24] and HIV infection particularly if associated with CD4 levels below 200 cps/mL.[25] Unprotected anal intercourse, past history of H-SIL or SCC of the lower genital tract (LGT), anal condylomas, other STDs, smoking, and drug abuse are additional risk factors.

HG-SIL is statistically much less frequent in heterosexual women and men. H-SIL and SCC can be found in condylomas of HIV (+) patients. HG-SIL or SCC were found in 47.1% of HIV (+) MSM who had only condyloma on clinical evaluation. HIV (-) MSM were found to have multiple foci of HG-SIL in their condylomas in 41.1%.[5,26]

HIV infection is a risk factor for the development of ASIL in women. HIV (+) females with a history of LGT intraepithelial neoplasia pose a greater risk of developing AIN and PAIN.[27,28] Multicentricity of the HPV infection contributes to this observation. The anal mucosa also acts as a viral reservoir favoring reinfections in the LGT.[29,30] These observations underscore the importance of concomitant genital, perianal, and endoanal examination.

Two studies in predominantly immunocompetent women found a prevalence of AIN of 12 to 27% when accompanied with a diagnosis of –IN of the LGT.[31,32] Women with HG-CIN had the highest risk of developing AIN. Immunosuppression, vulvar –IN, and anal intercourse are associated with AIN in the setting (sensitivity of 47% and a specificity of 86.2%).[32]

It is important to consider that lesions persistent over time (chronic) are associated with an increased risk of SCC even if they originate from low-risk HPV infections.[33]

Clinical Evaluation

Patients presenting with condyloma endorse a variety of nonspecific symptoms. Many are asymptomatic but concerned about the perianal growths. Pruritus is a common complaint. Pain and bleeding may be present with larger lesions. Very large lesions may become markedly malodorous. Appropriate clinical interrogatories include sexual practices, prophylactic habits, and a history of other STD as well as all the other elements of a complete medical history. A focused examination of all anogenital zones is required including proctoscopy by qualified providers. The clinical spectrum of HPV is dramatic from isolated diminutive wart-like growths to voluminous conglomerations as illustrated in ►**Fig. 4**.

Clinical inspection is generally sufficient to diagnose perianal condyloma. Biopsy is not required but may be helpful when the diagnosis is in doubt. Lack of response to medical treatment, rapid increase in size of lesions, or suspicion of malignancy is also valid indication for excisional biopsy.

Inspection and palpation are important components in physical diagnosis. Changes in color, presence of masses, painful induration, or ulceration should be noted. Many centers throughout the world use high-resolution anoscopy (HRA) as an adjunct to inspection and rectal examination. HRA is useful in the early detection of endo- and perianal HG-SIL. It can guide selective biopsies and in the early diagnosis of microinvasive SCC (►**Fig. 5**).

HRA magnification is a complimentary technique for a precise clinical examination—especially when the diagnosis

Table 4 Kreuter's descriptions of four forms of PAIN

Perianal intraepithelial neoplasia (PAIN) signs		
Class	**Denomination**	**Characteristics**
I	Bowenoid papulosis	A form of H-SIL is characterized by slightly raised and well-defined brown or violaceous papules
II	Erythroplastic	Presents many erythematous plaques similar to Queyrat's erythroplasia
III	Leukoplastic	Flat, well-delimited and punctate lesions
IV	Verrucous	Characterized by one or more exophytic lesions with a hyperkeratotic surface

Abbreviation: H-SIL, high-grade squamous intraepithelial lesion; PAIN, perianal intraepithelial neoplasia.

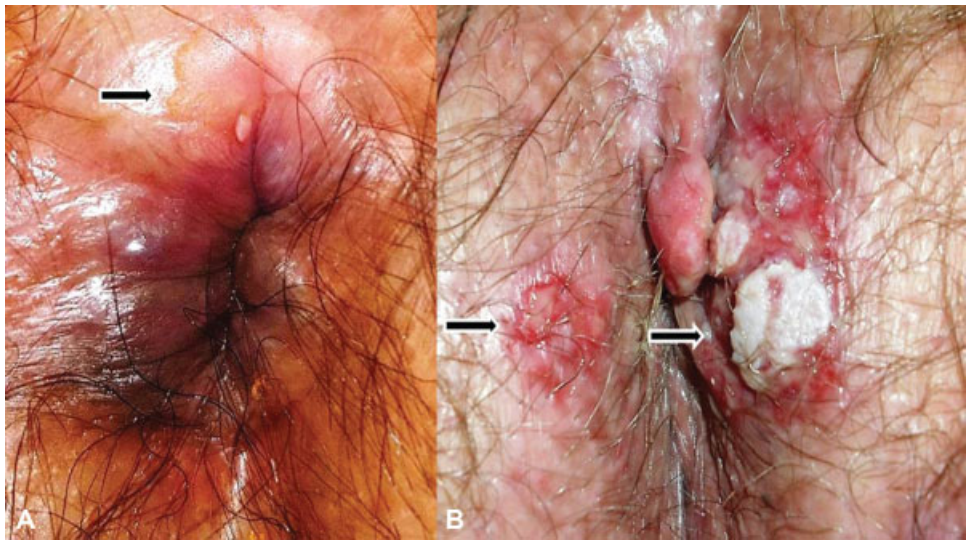

Fig. 3 (**A**) Perianal intraepithelial neoplasia 3 (PAIN 3) leukoplastic variant; (**B**) PAIN 3 erythroplastic/verrucous variants (Photo—L. Svidler López and L. La Rosa).

is in doubt in high-risk individuals. Perianal HRA helps discriminate between subtle, frequently diffuse, and lesions that are difficult to distinguish from benign skin alterations.

The procedure requires topical application of 5% acetic acid. It is important to recognize that not all acetowhite areas are PAIN. LG-SIL can be flat or slightly raised, acetowhite or warty, and may have unique vascular patterns referred as *warty vessels* in evidence. Punctate or mosaic vascular changes are rare. Their presence suggests HG-SIL. The distinction between LG-SIL and HG-SIL requires biopsy and histological confirmation. Lugol's iodine solution is not useful in the setting of keratinized epithelium. It is not used in the diagnosis of PAIN.

Differential Diagnosis

PAIN and numerous perianal dermatologic conditions may resemble one another. Flat lesions should be differentiated from dermatosis including lichen planus, psoriasis, scar leukoplakia as well as seborrheic and contact dermatitis. Anal lesions may represent systemic conditions also associated with pruritus ani. HPV condyloma can be distinguished from syphilitic lesion by the presence of secondary syphilitic lessions.[9] The differential diagnosis is difficult with verrucous herpes even with biopsies.[34] Molluscum contagiosum has a central umbilication unlike condyloma (►**Fig. 6**) More aggressive and long-standing lesions in adults can suggest immunosuppression.[35] Mibelli's porokeratosis is a group of pathologies that present with abnormal epidermal keratinization. They are usually asymptomatic but can produce pruritus. This condition presents in the anogenital region of immunocompromised patients. It can be difficult to differentiate from HPV without a histological diagnosis.[36]

Table 5 Standardized incidence rate (SIR) for anal squamous disease according to the predisposing pathology

Diagnosis	SIR
HIV+	81.1
Systemic lupus erythematosus	26.9
Solid organ transplant patients	14.4
Polyarteritis nodosa	8.8
Wegener's granulomatosis	12.4
Psoriasis	3.1
Crohn's disease	3.1

Abbreviation: HIV + , human immunodeficiency virus positive; SIR, standardized incidence ratio.

Treatment

The treatment of PAIN initially requires the exclusion of endoanal lesions that are managed differently. There is no current consensus for the management of either PAIN or endoanal disease due to the lack of controlled studies.[37] LG-PAIN does not require a-priori treatment due to its low rate of malignancy and the possibility of spontaneous regression. Perianal condylomas more often require treatment because of the symptoms or fear of infecting others. Other factors include a desire to return to normal sexual activities quickly, for aesthetic and/or emotional reasons. It is unclear if HG-PAIN requires treatment also because of a relatively low risk of malignant transformation. The inconclusive status of the dysplasia–carcinoma sequence is an additional mitigating factor into the decision to treat. Many centers worldwide recommend treatment because of the inability to predict which patients will develop cancer. Available treatments can eliminate ASIL but not the virus itself. Radical resection with clear microscopic margins does not prevent recurrence. ►**Fig. 7** represents a case in point. HPV may still be present in surrounding in apparently normal tissues. Tissue-preserving techniques are preferred over wide excision to prevent stenosis and incontinence.[38]

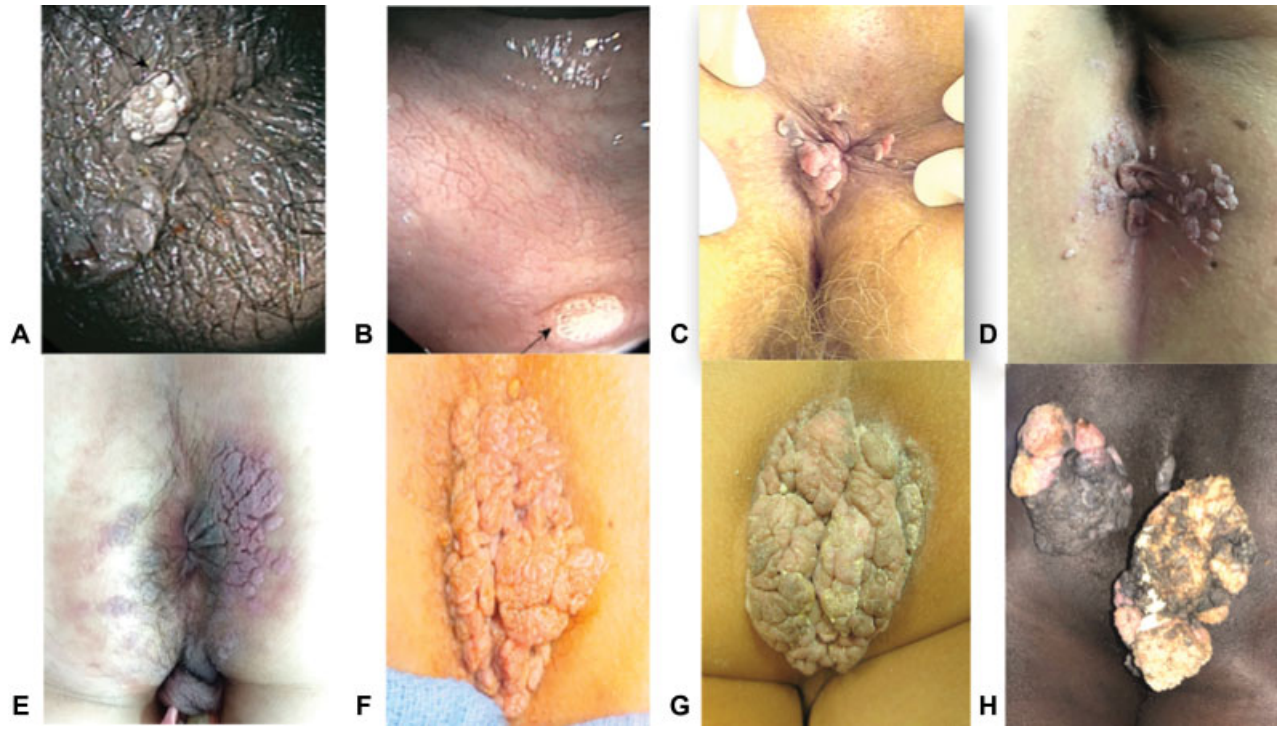

Fig. 4 The clinical presentations of anorectal condyloma are pleomorphic. Isolated external (**A**) or internal (**B**) lesions are in evidence. Lesions may be small and nonconfluent (**C, D**) or form large plaque-like conglomerates (**E, F**). Giant condyloma can surround the anal orifice (**G**) or present as multiple lobulated lesions (**H**) (Photos—L. Svidler López, L. La Rosa, A. Ortega)

Some topical treatments can be self-applied. Others required medically trained personnel for administration. Independently, there is a high recurrence locally in the perianal skin.[38] Therapeutic options are mitigated by the number and characteristics of the lesions as well as location, physician's experience, patient preferences, and costs.

All SIL can be treated similarly regardless of their degree of dysplasia. Self-administered therapies include imiquimod, fluorouracil (5-FU), sinecatechin, and cidofovir creams. These have the advantage of suitability for outpatient use as well for multifocal disease.[39,40] Topical treatments given by the physician include 90% trichloroacetic acid (TCA), podophyllin/podophyllotoxin, and intralesional interferon. Additional options include cryotherapy, infrared coagulation, electrocautery, and resectional surgery.[37]

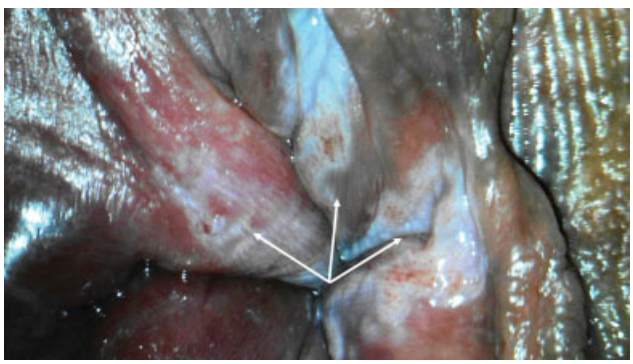

Fig. 5 Perianal intraepithelial neoplasia 3 lesion under 10 × magnification on high-resolution anoscopy demonstrates aceto-white, flat, demarcated lesions with radial extensions in three trajectories. (Photo—L. Svidler López and L. La Rosa).

Ninety percent TCA represents a reasonable first-line treatment given its ease of use, low cost, and safety. It is especially useful for small perianal lesions. TCA has a 70% response rate and is generally well-tolerated. TCA can produce a complete response or decrease the classification to

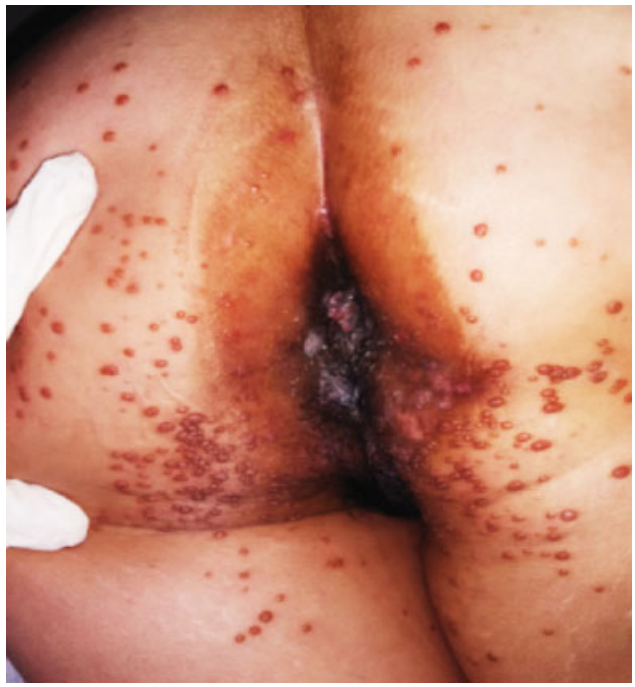

Fig. 6 Molluscum contagiosum is an uncommon sexually transmitted disease but important in the differential diagnosis of human papilloma virus infection (Photo—L. Svidler López and L. La Rosa).

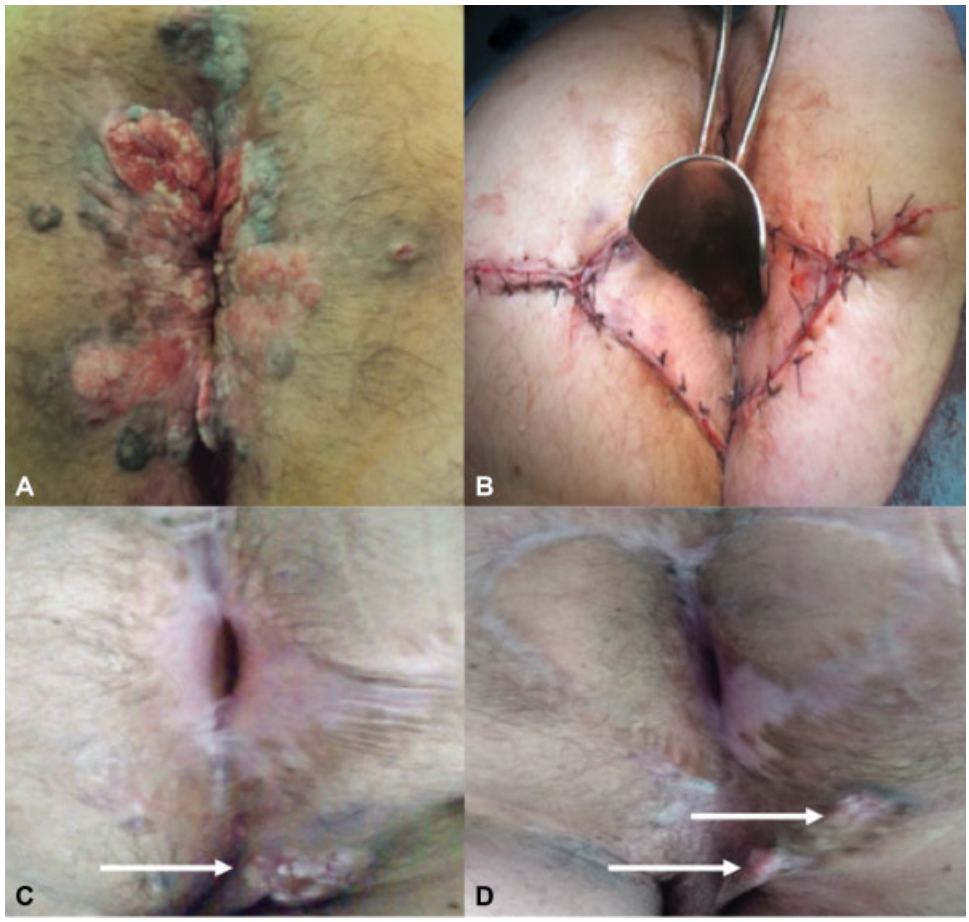

Fig. 7 (A) Circumferential high-grade perianal intraepithelial neoplasia with microinvasive foci was treated by wide local excision and (**B**) reconstructed with V-Y flaps. (**C**) Invasive squamous cell carcinoma (SCC) outside the flapped area was excised at 40 months later and (**D**) two SCC recurrences are evident 58 months later despite clear margins in all previous excisions. Progression to SCC is indicated with arrows. (Photos—L. Svidler López and L. La Rosa).

AIN 1 in HIV-positive MSM (73%). AIN 2 to 3 responded similarly in 71%. Younger HIV (+) individuals with two or fewer lesions respond best to TCA[41] (►**Fig. 8**).

Imiquimod is an effective immunomodulatory drug as topical treatment in HIV (+) and HIV (-) individuals. Treatment of perianal SIL with imiquimod decreases viral DNA load and reduces the number of genotypes at the end of therapy.[42] It is particularly useful against multifocal or circumferential lesions because it treats obvious lesions and surrounding skin simultaneously. It can be used at 5% strength on alternate days or 3.75% strength on successive days. It produces a partial or complete response of 66% after 16 to 32 weeks. Imiquimod is generally well tolerated but may cause local irritation[43] (►**Fig. 9**).

5-FU cream is useful for diffuse lesions. It decreases viral load locally. The partial or complete response rate is close to 60%. 5-FU has a 50% recurrence rate at 6 months of follow-up.[44] Local irritation is operant in both compliance and recurrence rates.

Podophyllin is a resin extracted from the root of the plant *Podophyllum sp*. Berberidaceae (mandrake). It contains numerous compounds including *Podophyllotoxin* that produce necrosis of HPV lesions. Most of studies concerning podophyllin/podophyllotoxin applications date back to the 1990s. More recent studies do not include it as a therapeutic option. Some groups report satisfactory results using 25% podophyllin in vaseline.[45] Podophyllin is particularly useful for decreasing the size of bulky perianal lesions in the authors' experience[45,46] (►**Fig. 10**). They recommend once a week application during 4 to 6 weeks. It can produce pain and itching and should be avoided to use during pregnancy.

Cidofovir 1% cream is an analog of cytidine. It has activity against HPV. It achieves a complete response in 19%. Forty-six percent had a greater than 50% volume reduction in lesions in the setting of HG-PAIN in HIV (+) hosts. The majority of patients had moderate local skin irritation.[39] Its efficacy was also demonstrated in anogenital condyloma with a partial or complete response of 70 to 90%.[47] Topical therapies do not usually resolve lesions completely. They may often better serve as adjunctive treatment following ablative procedures when there is less volume of disease and better tolerance can be anticipated.

HRA can help guide ablative options including cryotherapy, electrocautery, infrared coagulation, and CO_2 laser. It lessens the impact on anal physiology and sexual dysfunction in anoreceptive individuals. Infrared coagulation has been used in the ambulatory setting for the treatment of flat lesion. It is well tolerated in the treatment of HG-SIL[48] (►**Fig. 11**).

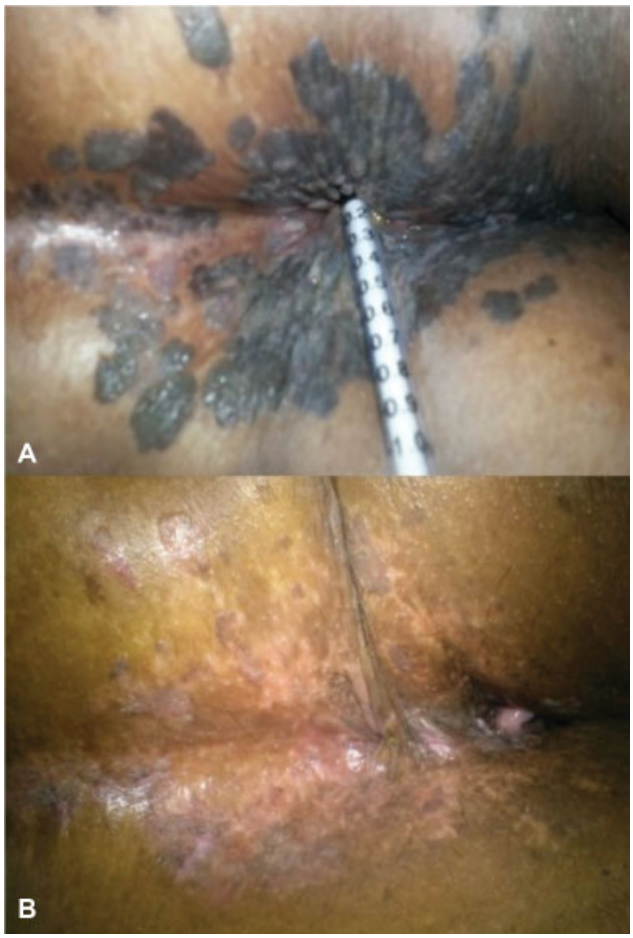

Fig. 8 (**A**) Bowenoid papulosis in human immunodeficiency virus positive patient with a (**B**) complete response to trichloroacetic acid 90% and imiquimod (Photo—L. Svidler López and L. La Rosa).

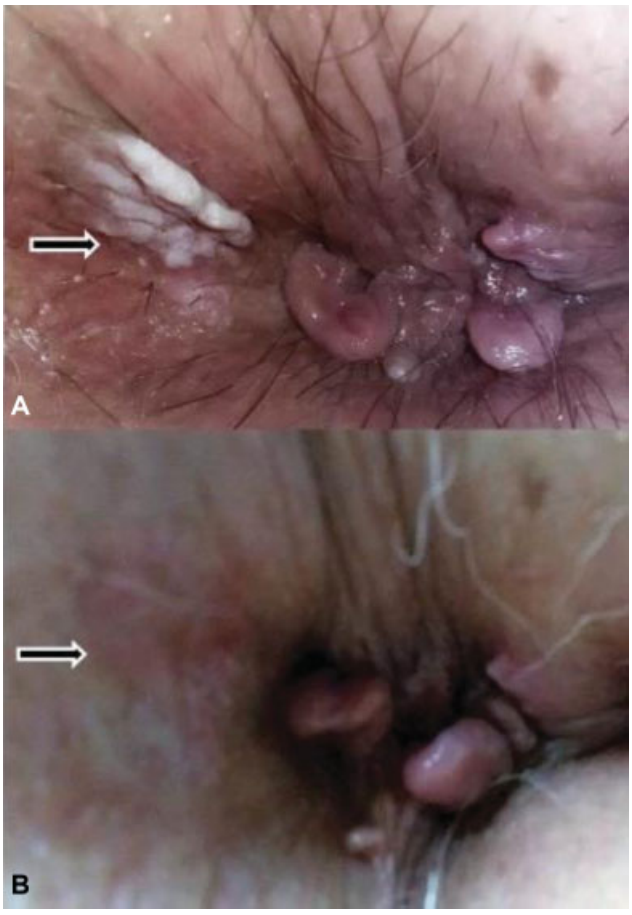

Fig. 9 (**A**) Perianal intraepithelial neoplasia 3 verrucous variant with a (**B**) complete response to imiquimod (Photo—L. Svidler López and L. La Rosa).

Meta-analysis of cryotherapy, infrared coagulation, imiquimod, and podophyllin revealed similar results.[49] Cryotherapy has more immediate adverse side effects including erythema, local irritation, and pain. Electrocautery has better clearance rates.[38] It achieved a 60% overall response rate in HG-AIN and HG-PAIN in HIV (+) MSM. There was a 33% partial or complete response in PAIN.[50]

Johnstone et al evaluated various HRA-directed ablative methods for the treatment of HG-PAIN in 70 HIV (+) MSM.[38] HIV (+) individuals have a 3.72 higher relative risk of HG-PAIN than HIV (-) subjects. Kaplan–Meyer curves predicted a recurrence rate of 38, 59, and 68% at 1, 3, and 5 years, respectively, in HIV (+) individuals. These results are lower for perianal than anal canal disease. Ablation with CO_2 laser, electrocautery, or infrared coagulation resulted in no cases of stenosis or incontinence.[51]

Surveillance

There are no universal guidelines for the follow-up of patients with the various stages and locations of HPV infection.[52,53] There are several factors that should be taken into consideration. HPV infection is usually multicentric and involves normal appearing tissues. The natural history of PAIN is not well established. It has been suggested that, in HIV (+) patients, the presence of PAIN represents a more advanced stage of disease patients and it is a marker for HG-PAIN recurrence.[51] There is agreement that there are more vulnerable groups including high-risk patients with HG-SIL or persistent lesions for more than 3 years. These individuals should be closely monitored.

Johnstone et al suggest evaluation at 6 to 12 weeks after the end of treatment with an anal digital examination and conventional anoscopy.[38] Abnormal findings are studied with the aid of HRA. Anal cytology and HRA are performed at 6 months. In the absence of HG-SIL patients continue on follow uo every 3 to 6 months for 2 years and then on a yearly basis. Considering that the post-treatment approach commonly used for SCC is carried out every 3 to 6 months for the first 2 years, it would not be justified to make it stricter for PAIN. The aim of a selected strategy should be to detect early progressive or recurrent disease as well as invasion.[36,37]

Early Detection (Screening)

Some authors propose anal screening in at-risk populations based on the similarities with cervical cancer and the impact of cervical cancer screening. The aim in the hindgut region is screening for ASIL. It entails cytology, proctologic examination,

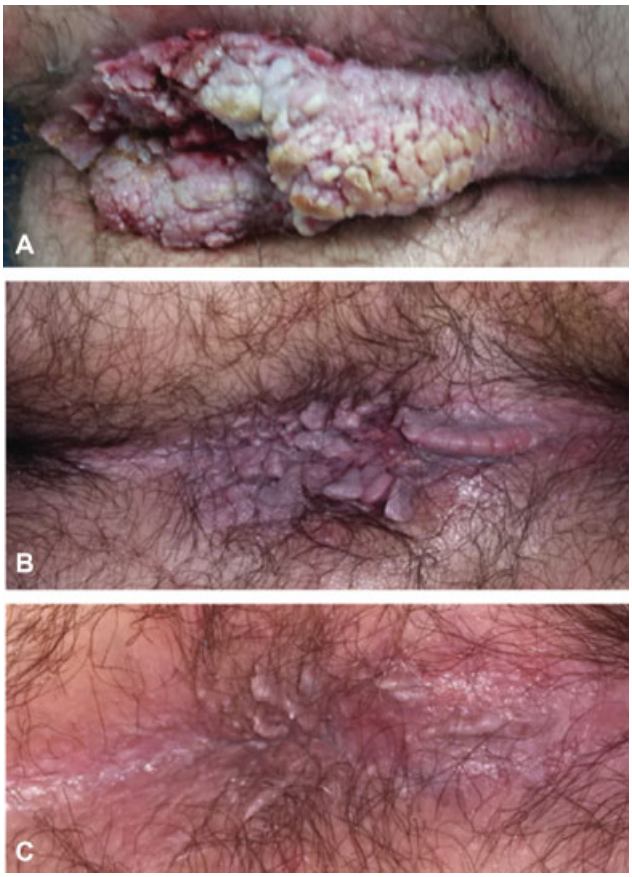

Fig. 10 (**A**) An advanced circumferential presentation of human papilloma virus infection (**B**) treated with topical podophyllin demonstrating (**C**) complete resolution. Podophyllin is useful in cytoreduction of bulky human immunodeficiency virus infection. (Photos—L. Svidler López and L. La Rosa).

and HRA.[22,38] The progression from HG-PAIN to SCC at the anal margin is reported at 18.4%. This observation underscores the need for perianal HG-SIL screening in high-risk patients.[23]

The Study for the Prevention of Anal Cancer[54] and Anal Cancer HSIL Outcomes Research[55] studies are currently underway. These studies will provide evidence regarding the natural evolution and response to treatment of HG-SIL in HIV (+) and MSM, respectively. The results should valuable information to define screening, treatment, and follow-up protocols.

Editorial Comment

Any lesion(s) within the anal canal should be considered potentially as an AIN. Those outside the anal canal over skin are PAIN. Lesions straddling the skin, anoderm, and mucosa are best considered AIN for all intents and purposes. Overlap between these zones is common. Isolated endoanal involvement of HPV is reported between 12.6 and 18%.[53,56] Exclusive perianal involvement is reported at 32.3 to 55.1%. Combined endoanal and surrounding anogenital involvement is common at 44.9 to 69%.[53,57] These figures are important in considering treatment options that also overlap considerably. They also underscore the importance of proctologic examination in all cases (►**Fig. 12**).

Perhaps the single most important unanswered question is whether regimented follow-up evaluation actually decreases the incidence of SCC, morbidity, and mortality in at-risk individuals. In the absence of definitive data, discretion is the better part of valor. HPV infection affects normal appearing tissues. Recidivism is the norm. All individuals with HPV infections should be followed closely indefinitely.

There are no optimal therapies for HPV or the lesions that result from this infection. Wide-local excision does not prevent recurrence or progression to SCC. Tissue preserving techniques are better options. Therefore, mapping biopsies around the anus is probably an anachronistic concept. Selective use of HRA seems more reasonable. Sustained vigilance is the only practical approach to this complex problem.

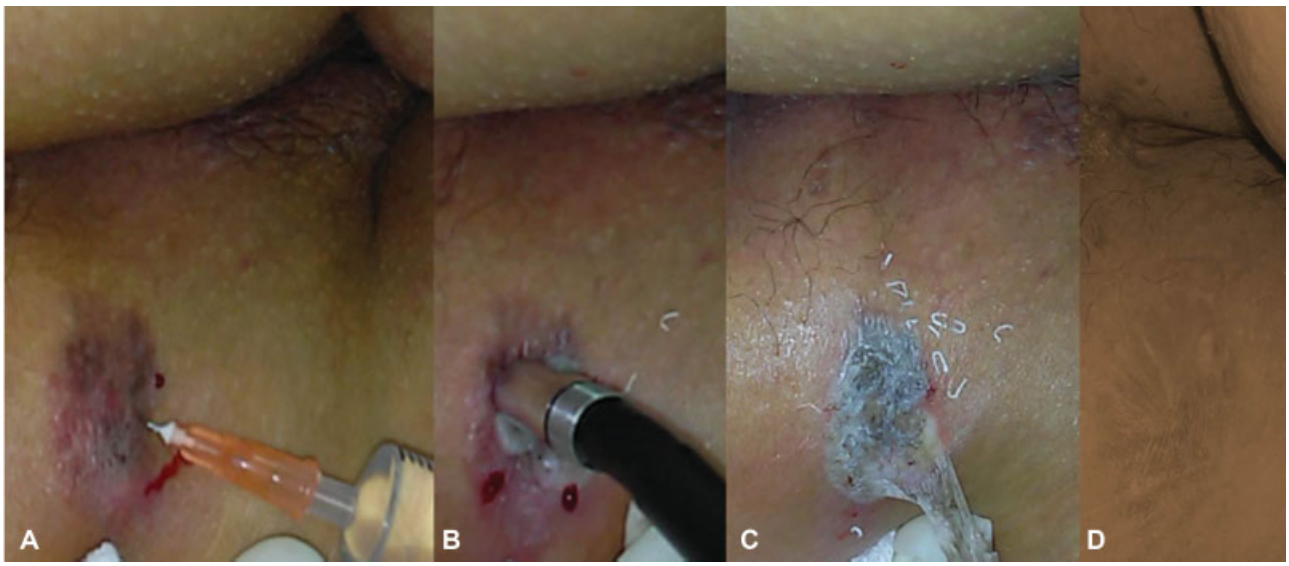

Fig. 11 (**A**) A perianal intraepithelial neoplasia lesion can be treated under local anesthesia (**B**) infrared coagulation application and (**C**) debridement of necrotized epidermis with (**D**) complete response evident on follow-up at 1 year. (Photos—L. Sviedler and L. La Rosa)

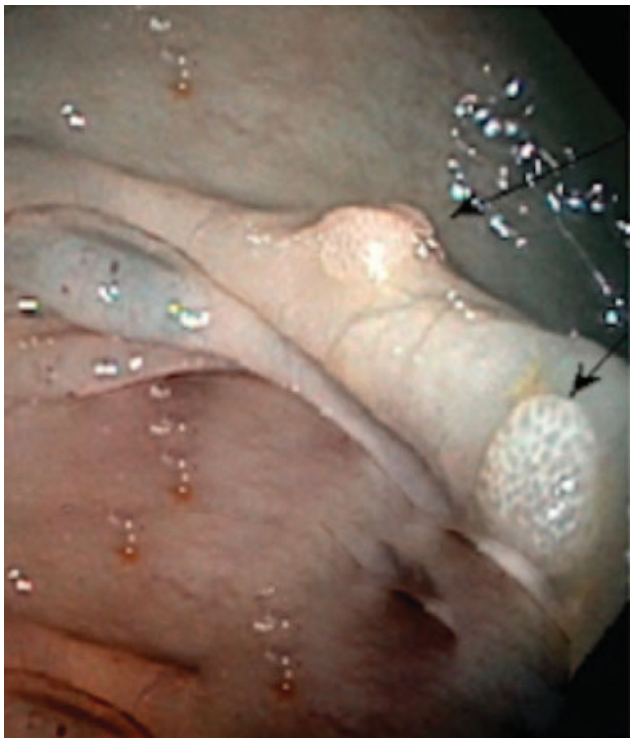

Fig. 12 Two condylomata (arrows) are evident on the *third* rectal valve of Houston. This case highlights the importance of proctologic evaluation of all human papilloma virus cases. Most rectal condylomata are found within 8 cm from the dentate line. These were detected at 15 cm. (Photo—A. Ortega).

Conflict of Interest
None.

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