Review Article

Anal Intraepithelial Neoplasia: Precursor of Anal Squamous Cell Carcinoma

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Abstract
Anal squamous cell carcinoma (SCC) is rare, but it has been commonly detected as an invasive cancer. The standard treatment for anal SCC was surgical resection. However, recent medical advances have enabled the standard treatment to be chemoradiotherapy. Anal intraepithelial neoplasia (AIN) is a premalignant lesion of SCC. The screening test for AIN and human papilloma virus vaccine are important for the following high-risk patients: patients positive for human immunodeficiency virus and men who have sexual intercourse with men. Although cytology can be easily applied for a screening test, the false-negative rate for AIN is high. Instead, high-resolution anoscopy (HRA) has been gaining attention as a promising screening method for high-risk patients. Investigations comparing characteristic findings of HRA with the histology of AIN have demonstrated that HRA is a highly specific test for AIN.

Magnifying or image-enhanced endoscopies are also routinely used for colonoscopy, as they allow detailed observations at higher magnifications than those of HRA. Hence, these endoscopic modalities can be applied for assessing AIN. Ablation therapies or topical medications are available as the local treatment for AIN. Although endoscopic submucosal dissection is considered to be feasible to remove AIN, it has a technical difficulty to approach endoscopically invisible areas. Hence, this technique may be useful to resect AIN localized in the endoscopically visible areas, when the localization is confirmed via targeted biopsy.

Keywords
anal intraepithelial neoplasia, squamous cell carcinoma, clinical management

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Introduction

In the anal canal, the interanal space has been considered as a tubular area from the puborectal muscle attachment to the anal verge. Therefore, anal canal carcinoma includes the following pathological types: (a) rectal adenocarcinoma arising from the mucosa of the rectal part of the anal canal, (b) squamous cell carcinoma (SCC) from the epithelium of the anal canal, (c) anal adenocarcinoma from the anal glands, and (d) hemorrhoidal carcinoma from their conduits. Malignant tumors originating from the anal canal account for only 1%-2% of all colorectal cancers[1]. The most common pathological type of anal canal malignant tumors is adenocarcinoma (78.3%), followed by SCC (18%) according to the report on the registration system of the Japanese Society for the Cancer of the Colon and Rectum. Conversely, SCC has been determined as the most common type of anal canal cancer, accounting for 80%-85% of all anal canal cancers in Western countries[1-3]. For squamous cell carcinoma (SCC), the risk factors for its precursor lesions have been clarified,

and clinical management has already been reported mainly in Western countries. Thus, in this article, we will focus on intraepithelial neoplasia, which are considered to be precursor lesions of SCC.

Currently, the standard treatment for SCC of the anal canal is radiation chemotherapy[4,5], as few lesions may be detected at the stage of intraepithelial carcinoma or anal intraepithelial neoplasia (AIN). Recent endoscopic advances have been enabling endoscopic therapeutic approaches for intraepithelial carcinoma and AIN, which are considered to have a very low risk of metastasis. Several case reports of its endoscopic resection have been published[6-8]. However, data as regards the feasibility of its endoscopic resection has remained to be lacking. Therefore, endoscopic resection can be considered if the lesions have no or very low metastatic risk. This work discusses the clinical features of AIN and the future possibilities for its diagnosis and treatment.

Risk Factors and Prevention of AIN

The crucial risk factors for AIN include human papilloma virus (HPV), certain sexual behaviors, and human immunodeficiency virus (HIV)[9-12]. Its association with HPV is of particularly high importance. Approximately 80%-90% of SCCs in the anal canal have been associated with HPV[13-15]. SCC can develop via persistent infection and precursor lesions of HPV. More than 100 different types of HPV have been discovered in humans, and several types can infect the skin and the mucous membranes. While anal SCC is caused by HPV-16 or HPV-18[13,15], anal condyloma, which is a variant of LSILs, has been associated with HPV-6 and HPV-11[9].

In Japan, a recombinant adsorbed quadrivalent HPV-like particle vaccine (yeast origin) was approved for preventing HPV-associated diseases in August 2011. It is indicated for the prevention of cervical cancer and its precursor lesions, vulvar intraepithelial tumors, vaginal intraepithelial tumors, and condyloma acuminatum in women aged 9 years and older. In light of the significance of prophylaxis in males, vaccination in males was later approved in December 2020. The new indication also includes anal squamous cell carcinoma and its precursor lesions. A large, randomized, double-blinded study assessed the efficacy of the quadrivalent HPV vaccine for male patients with AIN who have sexual intercourse with men and revealed that the vaccine was able to reduce the incidence of genital warts in young men[16]. This study also demonstrated that the efficacy of the vaccine for preventing AIN was 50.3% (95% confidence interval [CI], 25.7-67.2) in the intention-to-treat population; furthermore, in the per-protocol efficacy population, its efficacy for preventing AIN was 77.5% (95% CI, 39.6-93.3).

Statements regarding safety for HPV vaccines have been issued by the World Health Organization, Centers for Disease Control and Prevention, European Medicines Agency, and French National Agency for Medicines and Health Products Safety[17-19]. The European Medicines Agency statement addresses that the current evidence does not support the association between HPV vaccines and causes complex regional pain syndrome or postural orthostatic tachycardia syndrome. The Agence Nationale de Sécurité du Médicament (ANSM) statement has cited a study (which examined approximately 2.2 million individuals) that showed the risk of Guillain-Barré syndrome attributable to the vaccination was 1-2 cases per 100,000 vaccinations[20].

HPV vaccination efforts can vary among countries. In some countries, vaccination completion rates exceed 80% because of a high awareness of cervical cancer prevention. However, Japanese data in 2018 reported that the vaccination rate is only 0.8%, which is extremely lower than the rate in Western countries. HPV vaccination plays an important role in preventing cervical cancer. Given that an age-adjusted incidence of anal cancer in Japan has been increasing since 1990[21], the implementation of HPV vaccines is an issue that needs to be addressed from the perspective of anal SCC prevention. In October 2020, the Ministry of Health, Labour and Welfare asked local governments to ensure that those eligible for routine HPV vaccination are informed through individual notifications about cervical cancer and the vaccine. Furthermore, the "active recommendation for vaccination," which had been suspended since June 2013, was practically resumed. Along with monitoring of the safety of the HPV vaccine, its widespread use is expected.

Screening and Diagnosis for AIN

Screening has been recommended for early detection of AIN and prevention of anal SCC. An anal Pap smear should be performed for patients identified to be at high-risk for AIN such as immunocompromised individuals or men having sex with men (MSM)[22-24]. If atypical cells are detected in the Pap smear, high-resolution anoscopy (HRA) with magnifying observation of the anal canal and tissue biopsy are recommended. HRA uses a colposcope or operating microscope with acetic acid and Lugol's solution and is known to provide a high-power view of the squamocolumnar junction of the lower rectum and anus[25-27]. Using the vital stain method, abnormal epithelial or vascular findings can be distinct from normal tissues during examination.

Characteristics of LSILs and HSILs are listed in Table 1[28]. Considering these findings, vessel findings seem to be crucial for the detection and characterization of AIN. Magnifying endoscopy is a novel method of observing vessel findings because of its optical properties. Magnification power of endoscopy is higher than that of HRA, and its focus is adjustable according to the observation conditions. When

Table 1. Morphological Features of LSIL, HSIL, and Squamous Cell Carcinoma as Observed Using High-resolution Anoscopy.

	LSIL	HSIL	Cancer
Color	Acetowhite, shiny, barely visible, or distinct	Flat acetowhite, matted tone, gray	Thick acetowhite, red, or cannot be assessed because of friability
Contour	Flat, thin, raised or thickened, warty papillae, micropapillae	Flat, thickened, eroded, atypical papillae, ulcerations	Thickened, raised, eroded, friable ulcerations, growths
Vessels	Warty, looped capillary, punctation, striated, fine increased vascularity, fine mosaic pattern (rare)	Coarse mosaic, coarse punctuation, atypical vessels, variable dilations, friable	Very coarse, atypical or abnormal vessels with bizarre shapes, wide variability in dilations, friable
Epithelial changes		Lacy metaplasia, atypical clustered glands, honeycombing	

HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

endoscopy identifies abnormal findings, target biopsy can be performed as well. Image-enhanced endoscopy, such as narrowband imaging (NBI) and blue laser/light imaging, can visualize not only microvessels of the tumor surface by using wavelengths strongly absorbed by hemoglobin but also its surface patterns using a structure enhancement function[29,30]. Given that endoscopy has such advantages to evaluate vessel and surface patterns of the tumor in detail, it may have a better diagnostic performance compared with HRA and can be used to assess AIN as well. Although endoscopy may have some limitations to observe narrow areas such as the anal canal, the squamocolumnar junction can be sufficiently observed via insufflation and retroflexion technique. Furthermore, tip attachment makes an observation of the anal canal possible.

Image-enhanced endoscopy can be used to evaluate vascular patterns more precisely in comparison to HRA. The NBI findings of AIN are similar to magnified endoscopic patterns of superficial esophageal cancer (Figure 1)[31]. Indeed, several case reports revealed that AIN can share the following findings, which are observed in esophageal carcinoma: microvessels with dilatation, tortuosity, caliber changes, and uneven shapes. Hence, it may be feasible to apply the endoscopic classification of the Japan Esophageal Society in order to determine the extent and depth of AIN[32,33]. Future studies with larger sample size are warranted to understand its diagnostic accuracy for AIN.

Pathological Definition of AIN

AIN is a premalignant lesion of SCC. The lesion commonly appears at the anal transition zone (ATZ), where the rectal columnar epithelium meets the anal squamous epithelium. This lesion has been considered to be associated with HPV. The Lower Anogenital Squamous Terminology Standardization (LAST) project for HPV-associated lesions has provided guidelines for unified nomenclature[34]. The latest guidelines have accurately reflected the biology of HPV-related lesions and provided a two-tiered approach to low-grade intraepithelial lesions (LSILs) and high-grade intraepithelial lesions (HSILs). For many years, HPV-associated dysplasia of the anogenital tract, including the anus, was classified by three-tiered nomenclature (i.e., AIN1-3). However, the LAST published in 2012 recommended a two-tiered nomenclature, designated as LSIL or HSIL. In the anal canal, LSIL corresponds to anal intraepithelial neoplasia (AIN-1) or anal condyloma, while HSIL corresponds to AIN-2 and AIN-3 (Table 2).

Histologically, LSIL shows cytological atypia limited to the lower third of the epithelium and associated with koilocytosis, which is characterized by nuclear atypia and perinuclear halos. HSIL often exhibits involvement of at least two-thirds or more of the epithelial layer by markedly atypical cells. HSILs involve the entire epithelium or the lower two-thirds and are typified by a loss of maturation, nuclear hyperchromasia, and membrane irregularity, as well as an increase in the nucleus-to-cytoplasm ratio. HSILs typically show strong and diffuse nuclear and cytoplasmic p16 expression by immunohistochemical staining (Figure 2)[35,36].

Local Treatments of AIN

In terms of local treatment for AIN, fulguration with electrocautery during HRA or anoscopy has been reported as a treatment option. Chang et al. reported that 8 HIV-negative patients did not develop recurrent lesions, whereas 23 of 29 HIV-positive patients had persistent or recurrent high-grade squamous intraepithelial lesions after the procedure[37]. Goldstone et al. assessed clinical outcomes of infrared coagulation for AIN, an outpatient procedure, and showed that 40 patients (53%) developed postoperative recurrence[37]. In this study, local recurrence was retreated with coagulation therapy. The probability of successfully treating an individual lesion after the first infrared coagulation procedure was 81% and 93% when local recurrence was retreated. HIV-positive patients were found to be twice as likely to have persistent lesions and 1.7-times more likely to develop local recurrence[38]. These studies reported no serious adverse
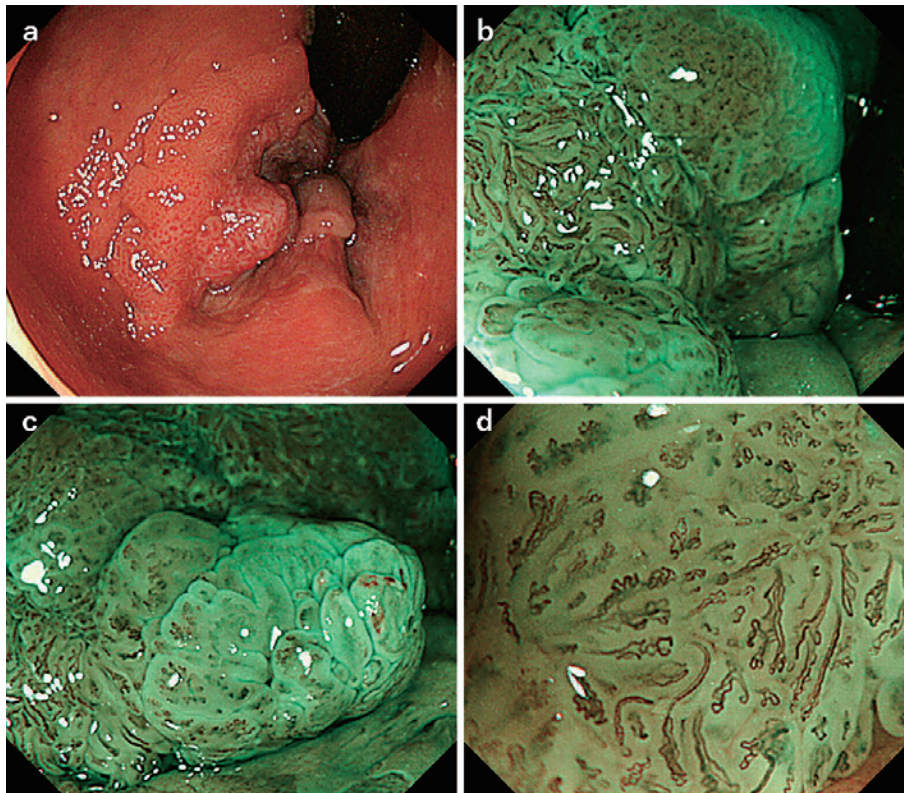
Figure 1. Anal intraepithelial neoplasia in the anal transition zone. Recognized as a flat elevated lesion with nodular elevation with mild reddish color with white-light observation (a). Irregular microvessel patterns similar to superficial esophageal carcinoma are recognized using narrowband imaging (b-d).

Table 2. The Two-tiered Nomenclature for Anal Intraepithelial Lesions.

| LSIL		HSIL	
Condyloma	AIN grade I	AIN grade II	AIN grade III
Very mild to mild dysplasia		Moderate dysplasia	Severe dysplasia/ carcinoma *in situ*

AIN, anal intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

events such as anal stenosis requiring surgical anastomosis.

Topical therapy is an alternative treatment option. The known topical agents include trichloroacetic acid (TCA), imiquimod, and 5-fluorouracil (5FU)[39-41]. TCA demonstrated the most favorable outcomes to resolve AINs to normal or LSIL pathology. Cranston et al. reported that 77 (78.6%) of 98 HSILs treated with TCA resolved to normal epithelium or LSIL during follow-up[39]. Once HRA identifies lesions, TCA can be applied during the examination, and specific serious adverse events have not been reported. Imiquimod and 5FU have also been reported as effective topical agents with clearance rates ranging from 40% to

60%; however, pain and anal burning were occasionally reported in patients using imiquimod and perianal irritation in patients using 5FU.

Given the effectiveness and safety of ablation therapies or topical medications for AIN, it is understandable that these are selected for the local treatment of AIN. However, from the standpoint of gastrointestinal endoscopists, especially considering the basic concept of endoscopic submucosal dissection for gastrointestinal tumors, the incidence of postoperative local recurrence of AIN is deemed to be relatively high. In case of gastrointestinal tumors, it is important to achieve a reliable cure using *en bloc* resection of the lesion and accurately determine the negative margins of resected lesions. With regard to AIN, case reports have shown that endoscopic findings of every single lesion may be heterogeneous, suggesting the need for *en bloc* resection and accurate histopathological evaluation of the lesion, as the endoscopic intervention of gastrointestinal tumors[8]. Several Japanese studies have demonstrated the effectiveness of endoscopic submucosal dissection as a local excision for AIN and noninvasive SCC, which are considered to have a very low risk of metastasis[6-8]. In our own experience, the tumors can spread to endoscopically invisible areas[8]. Therefore, it may be difficult to accurately determine the extent of
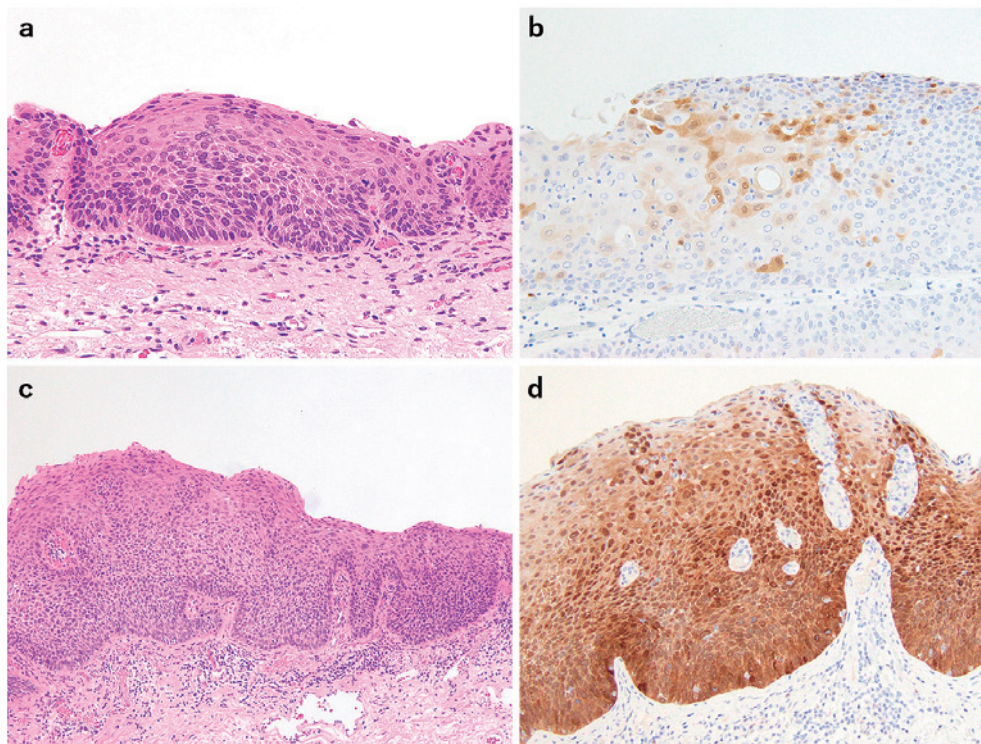
Figure 2. Microscopic images of low- (a, b) and high- (c, d) grade squamous intraepithelial lesions. Low-grade dysplasia shows atypical squamous cells with enlarged nuclei confined to the lower layer (a). The p16 staining shows scattered positive cells with weak to moderate staining (b). Atypical squamous cells occupy the entire epithelial layers (c). Diffuse, strong positive expression of p16 (d).

lesions and achieve R0 resection despite wide resection, which can often cause adverse events such as post-treatment pain and stenosis. From our perspectives, endoscopic submucosal dissection may be useful to resect AIN localized in endoscopically visible areas including the anal transitional zone or lower rectum (Figure 3).

In terms of treatment for SCC, chemoradiation therapy is recommended as the first-line treatment. However, some early and late adverse events (e.g., skin dermatitis, proctitis, hematologic toxic effects, incontinence, fecal urgency, etc.) are adverse events that cannot be ignored. As for endoscopic or surgical local excision, complications were noted, such as pain and bleeding in the short term and stenosis in the long term. However, the long-term and systemic complications are relatively less severe than those of chemoradiotherapy. Therefore, endoscopic local resection may be applicable for intraepithelial cancers that are considered to have no metastatic risk, and a clinical research plan to expand treatment options is thus expected.

Conclusions

AIN is a precursor lesion of anal SCC. Although it is considered a rare lesion, it can be detected during colono-

scopy screening because of the improved capabilities of endoscopic equipment. Magnifying or image-enhanced endoscopies such as NBI and blue laser/light imaging may be useful for AIN detection and diagnosis. However, there is no evidence to determine the optimal diagnostic and therapeutic strategy. Therefore, appropriate guidelines for AIN must be needed to understand which local treatments can be applied or which examination is the best to determine the extent of the lesion, when the localization is confirmed via target biopsy.
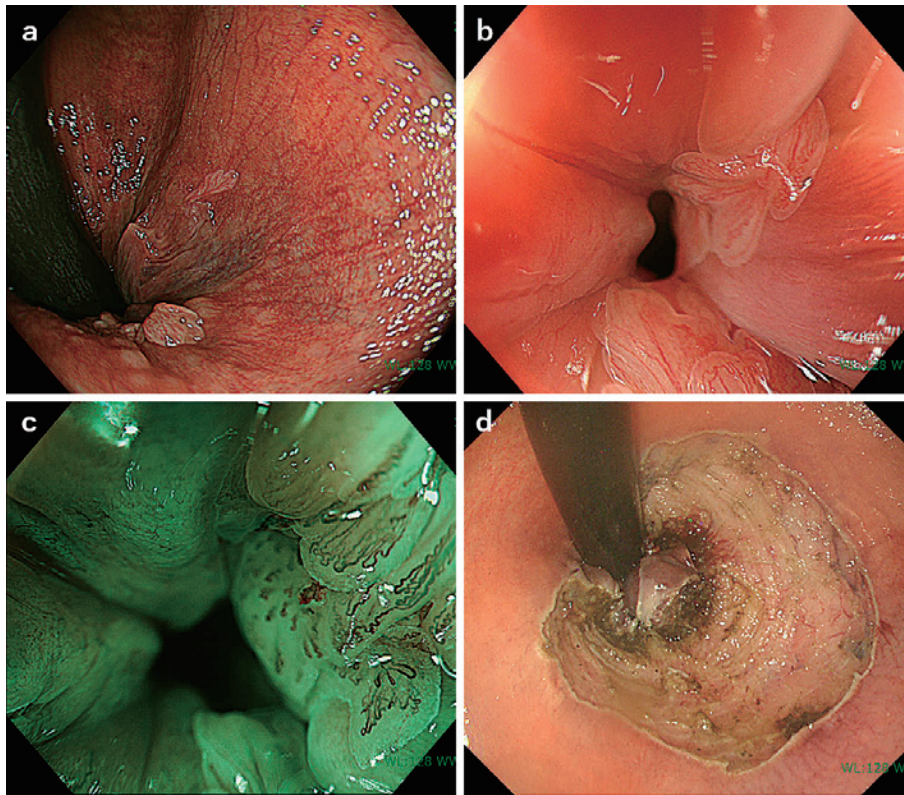
Figure 3. Intraepithelial neoplasia located between the anal canal and anal transition zone (ATZ) resected using the endoscopic submucosal dissection technique. Small or tiny lesions are scattered discontinuously in the anal canal and ATZ (a). Magnifying narrowband observations showed irregular vessel pattern similar to superficial esophageal carcinoma (b, c). Considering the localization of the lesion in the anal canal, a certain area visible as definite lesion was continuously resected by endoscopic submucosal dissection (d).

script, and project administration.

Approval by Institutional Review Board (IRB)

No approval from any IRB was required because this review article was based on previously published papers.

Disclaimer

Yutaka Saito is one of the Associate Editors of Journal of the Anus, Rectum and Colon and on the journal's Editorial Board. He was not involved in the editorial evaluation or decision to accept this article for publication at all.

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