

## Endoscopic Diagnosis and Treatment of Anorectal Condyloma Acuminatum with High-Grade Intraepithelial Neoplasia.

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### Abstract

Anal Intraepithelial Neoplasia (AIN) and Condyloma Acuminatum (CA) are common sexually transmitted diseases caused by Human Papilloma Virus (HPV) infection. Although AIN and CA do not necessarily show the malignant transformation, they are precursors of invasive anal cancer. There are various therapies for AIN and CA, including surgery, immunotherapy, topical treatment, and endoscopic resection. Some studies have reported that treatment by Endoscopic Submucosal Dissection (ESD) may be associated with a lower frequency of recurrence, based on which it is believed that ESD may be the most suitable treatment option for AIN and CA. Herein, we describe a case of high-grade AIN with CA treated by ESD and also describe the difficulty that we had in establishing the diagnosis, even by magnifying endoscopy with Narrow-Band Imaging (NBI). A 72-year-old man presented with a positive fecal occult blood test and underwent a screening colonoscopy.

Colonoscopy showed a long, flat elevated lesion measuring 30 mm in diameter, extending from the anal canal to the lower rectum. The lesion was composed with two different components; which were elevated whitish component and flat discolored component. The margin of this lesion could be confirmed using indigo carmine dye, and magnifying colonoscopy with NBI revealed loop-like and meandering micro vessels resembling the intraepithelial papillary capillary loops. Although the pathological diagnosis by biopsy was low-grade AIN, we diagnosed AIN with CA based on the detection of the two components. Therefore, we performed diagnostic ESD for en-bloc resection of this lesion, and the pathological diagnosis was CA and high-grade AIN, confirming our suspicion. However, the histopathology also revealed AIN on the oral aspect, which we had endoscopically diagnosed as being free of tumor, and the horizontal margin was positive. Even by a retrospective review, it was difficult to determine the extent of the tumor margin accurately. Thus, it is necessary to bear in mind the difficulty in determination of the area of tumor extension into the intestinal mucosa, even by magnifying colonoscopy with NBI.

### Introduction

Condyloma Acuminatum (CA) is a common, sexually transmitted disease caused by Human Papillomavirus (HPV) infection, which can cause anorectal lesions in patients with receptive anal intercourse [1]. Anorectal CA is endoscopically identified as whitish, clearly demarcated warts or condyles. Meanwhile, Anal Intraepithelial Neoplasia (AIN) can also occur in the anorectum in patients with HPV infection [2]. AIN is identified

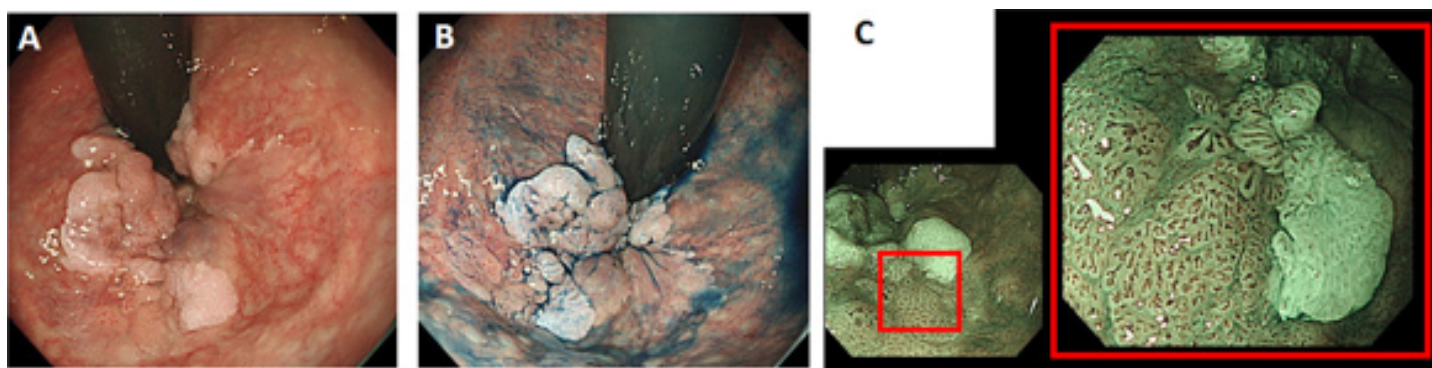
by conventional endoscopy as a slightly elevated flat discolored lesion, and as a brownish area on magnifying colonoscopy with Narrow-Band Imaging (NBI). Importantly, AIN is usually regarded as a precursor of anorectal Squamous Cell Carcinoma (SCC), while CA is potentially treated as a benign lesion [3]. In the gynecologic field, the uterine cervix, which is the most common site of occurrence of Cervical Intraepithelial Neoplasia (CIN), is anatomically separated from the vulva, which is the most common site of occurrence of CA, suggesting that the two are probably

caused by different genotypes of HPV [4,5]. In contrast, CA and AIN can simultaneously occur in the anorectum, because the shift zone of the anal region and the original squamous epithelium domain are common [6].

Although Trans-Anal Resection (TAR) is available as a therapeutic option for anorectal CA with intestinal neoplasia, poor visualization of the operative field may contribute to local recurrence because of the difficulty in identifying the margins of the tumor spreading to the dentate line [7,8]. As compared to surgical treatment, endoscopic resection, in particular, Endoscopic Submucosal Dissection (ESD) has been reported to be more useful to achieve en-bloc resection [9]. Herein, we present a case of anorectal CA accompanied by AIN that was treated by ESD. Unfortunately, the surgical margin was found to be positive, even though the ESD procedure had been accomplished as intended. Since the present case was instructive, we retrospectively reviewed the endoscopic and pathological findings in order to determine why the endoscopic examination could not precisely delineate the tumor margin.

## Case Report

A 72-year-old man underwent screening colonoscopy as part of further workup for a positive fecal occult blood test. His medical history included Human Immunodeficiency Virus (HIV) diagnosed 13 years ago, Kaposi sarcoma, and chronic hepatitis B. He had a male partner and had receptive anal intercourse. The patient's physical and laboratory examinations were standard. Colonoscopy revealed a flat elevated whitish lesion extending from the anal canal to the lower rectum, that measured 30 mm in diameter (Figure 1A). Indigo carmine dye staining allowed clear visualization of a discolored area on the oral side of the lesion (Figure 1B). Magnifying endoscopy with NBI revealed loop-like and meandering microvessels resembling the Intraepithelial Papillary Capillary Loops (IPCL) observed in early-stage squamous esophageal carcinoma (Figure 1C). Since the lesion contained a dysplastic area on histopathology, we performed ESD to achieve en-bloc resection of the lesion.



**Figure 1:** Endoscopic findings of the anorectal lesion.

**A:** A flat elevated whitish lesions extending from the anal canal to the lower rectum; the lesion measured 30 mm in diameter.

**B:** Indigo carmine dye staining clearly showing the margin of the tumor.

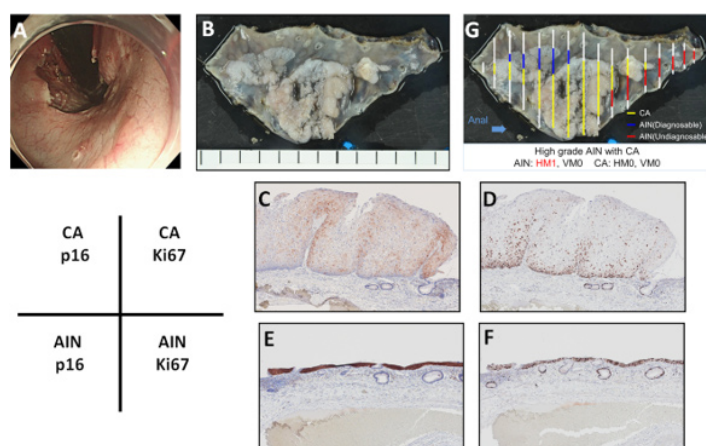
**C:** Magnifying endoscopy with narrow-band imaging revealed loop-like and meandering micro vessels resembling the intraepithelial papillary capillary loops.

The ESD procedure was performed using an upper gastrointestinal endoscopy with a single channel that was 3.2 mm in diameter (GIF-Q260J; Olympus Optical Co., Tokyo, Japan), under conscious sedation with flunitrazepam and buprenorphine. Both the circumferential incision and submucosal dissection were performed using a dual knife (KD650Q; Olympus Optical Co.) with local injection of sodium hyaluronate solution (Figure 2A). The procedure time was 50 minutes and there were no adverse events during the perioperative period. The diameter of the resected tumor was 60 mm (Figure 2B). As for the histopathological findings of the flat elevated whitish lesion, an atypical squamous

epithelium with koilocytosis was observed, with the proliferating cells forming papillary structures. Immunohistochemistry (IHC) for p16 was slightly positive, and IHC for Ki-67 was positive, mainly in the half of the lesion that was close to the basal layer (Figure 2C and D).

Based on these findings, the lesion was diagnosed as CA. On the other hand, in the slightly elevated discolored component of the lesion, proliferation of atypical epithelium with monotonously enlarged nuclei through the squamous epithelial layer was observed, forming a flat lesion. IHC for p16 showed diffuse strong

positivity, and IHC for Ki-67 was positive through the epithelial layer (Figure 2E and F). Based on these findings, this flat lesion was diagnosed as high-grade AIN. In the oral aspect of the lesion, some columnar epithelium with intracytoplasmic mucin was observed on the surface of the high-grade AIN, suggesting that this area represented an extension of the AIN into the intestinal mucosa, resulting in the positive horizontal margin (Figure 2G). The demarcation of the AIN on the oral aspect was misdiagnosed despite our performing magnifying endoscopy with NBI.



**Figure 2:** The resected specimen and the results of histopathological analyses.

**A:** Post-ESD ulcer floor. The lesion was completely resected as intended.

**B:** Resected specimen.

**C:** In the flat elevated whitish lesion, immunohistochemical staining was slightly positive for p16.

**D:** In the flat elevated whitish lesion, Ki-67 staining was positive mainly in the epithelial layer.

**E:** In the slightly elevated discolored lesion, p16 immunohistochemistry showed diffuse strongly positive staining.

**F:** In the slightly elevated discolored lesion, Ki-67 stain was positive through the epithelial layer.

**G:** Resected specimen. The red line was AIN, which was difficult to diagnose by NBI, indicating that the horizontal margin was positive.

## Discussion

Although no standardized therapeutic strategies have been conclusively established for anorectal CA, accompanied by AIN, endoscopic resection is reported as a safe and effective treatment option [10]. ESD allows a high rate of en-bloc resection with a negative tumor margin to be achieved, which can reduce the risk of local recurrence [9]. The reason depends on the efficacy of

magnifying endoscopy with NBI which often allows recognition of the tumor border that is difficult to detect macroscopically. Magnifying endoscopy with NBI shows hyperplastic, loop-like and meandering microvessels resembling the intraepithelial papillary capillary loops observed in early-stage squamous esophageal carcinoma, and these endoscopic findings are reported to be useful not only for margin diagnosis but also qualitative diagnosis [11]. However, the endoscopic differentiation of the morphologic type and vascular structures between CA and AIN is difficult, and histological examination and IHC for both p16 and Ki-67 are said to be useful for a precise diagnosis of AIN [12,13]. The postsurgical rate of local recurrence is high because of the difficulty in precisely detecting the margin of the lesion, especially for lesions located in the anal canal. It is reported that ESD with NBI to diagnose the lesion margin is associated with few recurrences as compared to surgical treatment.

Wagner A et al. reported a case of CA with high-grade AIN treated by ESD [14]. They concluded that precise demarcation of the tumor is possible by magnifying colonoscopy with NBI. In contrast, we were not able to arrive at a precise diagnosis of the tumor margin by endoscopy, probably due to the following reasons. Firstly, it is challenging to recognize AIN involving both the cloacogenic zone and the columnar epithelium. The anal canal has a cloacogenic zone lined by columnar epithelium only, as well as squamous epithelium. In the cloacogenic zone, the surface microstructure, such as the glandular openings or crypt epithelium, that is characteristic of rectal epithelium, is not recognizable. Moreover, mucinous cells located at cloacogenic zone may reduce the visibility of the expanded blood vessels in the columnar epithelium. Secondly, recognition of the micro vessel pattern by magnifying colonoscopy with NBI in the anal canal may be more complicated than in early-stage squamous esophageal carcinoma. The reason depends is that the zone of anal canal is highly vulnerable to inflammation. Hence, further studies are needed to determine the characteristic micro vessel pattern on magnifying colonoscopy with NBI in the anal canal, although ESD is a more effective and safe treatment option for AIN.

## Conclusion

We should keep in mind that demarcation of the extent of AIN is sometimes difficult, even by magnifying endoscopy with NBI, in cases with extension into the intestinal mucosa. To establish a precise preoperative diagnosis and the optimal treatment for anorectal CA with intestinal neoplasia, accumulation of more cases is necessary.

## Competing Interests

The authors have no competing interests to declare.

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