High-grade anal intraepithelial neoplasia treated with endoscopic submucosal dissection: a case report

J. Santos-Antunes[1], E. Dias[1], R. Coelho[1], M. Marques[1], P.A. Canão[2], J. Magalhães[2], G. Macedo[1]

(1) Gastroenterology Department, Centro Hospitalar de São João, Porto, Portugal; (2) Pathology Department, Centro Hospitalar de São João, Porto, Portugal.

Abstract

Anal intraepithelial neoplasia is a premalignant lesion for anal squamous cell carcinoma. Current treatment options, consisting of topical therapy and local ablative procedures with electrocautery or radiofrequency ablation, are effective although recurrence rates are high. Experience with endoscopic submucosal dissection for anal lesions is limited, with only a few cases of anal intraepithelial neoplasia and early anal squamous cell carcinoma. We present a 65-year-old woman with high-grade anal intraepithelial neoplasia successfully removed by endoscopic submucosal dissection with no complications or signs of recurrence after 5 months, suggesting that this technique could be a safe and effective approach for management of anal premalignant lesions. (Acta gastroenterol. belg., **2022,** 85, **108-110**).

Keywords: anal intraepithelial neoplasia, anal squamous cell cancer, endoscopic submucosal resection.

Introduction

Anal squamous cell carcinoma (ASCC) is a relatively rare malignancy, accounting for approximately 1% of all gastrointestinal cancers (1). Anal intraepithelial neoplasia (AIN) is a premalignant lesion for ASCC. It is more commonly found in high-risk patients, including human immunodeficiency virus (HIV)-positive patients, post-organ transplantation patients and men who have sex with men (MSM) and its development is driven by human papillomavirus (HPV) infection, especially with high-risk serotypes (16 and 18) (2).

Conventional treatment is based on topical and local ablative approaches. However, recurrence rates are high. Endoscopic submucosal dissection (ESD) is a minimally invasive treatment for early malignant and premalignant lesions of the gastrointestinal tract, including esophagus, stomach and colorectum. However, there is limited experience with this technique for anal lesions; to date, there is only one case of AIN (3) and six cases of early ASCC (4-9) treated with ESD. Here we report one case of AIN successfully resected with ESD.

Case Report

A 65-year-old woman performed a screening colonoscopy. Retroflexed view of rectum with white light imaging revealed a white, flat lesion in distal rectum in contact with dentate line (Figure 1A). No signs of dysplasia including course punctuation, striation or mosaicism were visualized. High-resolution anuscopy after application of acetic acid showed the edge of the lesion clearly, demarcating a white, flat lesion with a diameter of approximately 20 mm at the distal rectum extending into the anal canal (Figure 1B). Biopsies were performed and histopathological examination revealed squamous epithelium with high-grade dysplasia, representing AIN-2 associated with signs of HPV infection. Immunohistochemistry staining was strongly positive for p16, and nucleic acid hybridization was positive for HPV type 16. ESD was performed and the lesion was removed *en bloc*. The procedure started at the distal part of the lesion and took approximately 45 minutes. At the end, a specimen with 45x40 mm was obtained and margins appeared endoscopically free (Figure 2A,B). No complications occurred and the patient was discharged on the day following the procedure. Pathological examination of the specimen revealed the presence of AIN-2/AIN-3 (Figure 2C) with maximal extension of 23 mm of width. There was strong positivity for p16 (Figure 2D). Follow-up flexible rectosigmoidoscopy performed after 5 months revealed a regular scar at distal rectum with no signs of recurrence.

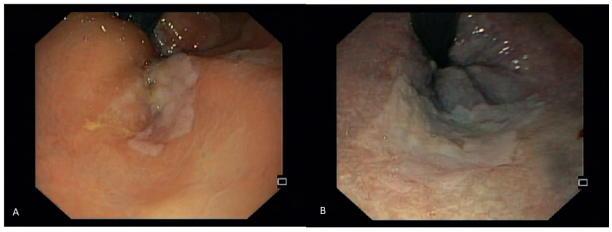

Figure 1. — A. Retroflexed view of the rectum with white light imaging reveals a white flat lesion with ill-defined border at distal rectum in contact with dentate line. B. After application of acetic acid the lesion is more clearly demarcated. A white flat lesion with a diameter of approximately 20 mm at distal rectum extending into anal canal is now clearly visible.

Correspondence to: João Santos-Antunes, Gastrenterology Department, Centro Hospitalar de São João, Alameda Professor Hernâni Monteiro, 4200-319, Porto, Portugal.
Email: joao.claudio.antunes@gmail.com

Submission date: 20/09/2020
Acceptance date: 03/01/2021

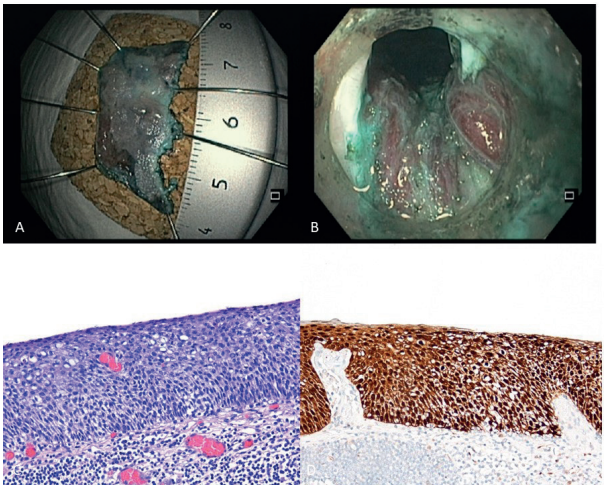

Figure 2. — The resected specimen obtained after endoscopic submucosal resection is shown. A. ESD ulcer at the end of the procedure. C. Histologically, the lesion is characterized by near full-thickness immaturity, irregular polarity and mitotic figures (HE, 200x). D. Strong and diffuse nuclear and cytoplasmic p16 positivity (p16, 200x).

Discussion

AIN is a dysplastic growth of squamous epithelial cells in the transition zone of the anal canal and is a clinically important premalignant lesion with high rate of progression to ASCC if left untreated (10). Its development is driven by HPV infection, especially with high-risk subtypes 16 and 18, which are estimated to be responsible for 80-90% cases of ASCC. HPV-related squamous epithelial dysplasia is currently classified into low-grade or high-grade squamous intraepithelial lesion (LSIL or HSIL, respectively). In anal canal, LSIL correlates with AIN-1 and HSIL correlates with AIN-2 and AIN-3. Although ASCC is relatively rare, incidence rates have been steadily increasing, especially among certain high-risk populations which are predisposed to HPV infection, including HIV-positive patients, high-risk sexual behavior (MSM, receptive anal intercourse or history of multiple sexual partners), post-organ transplantation patients or history of HPV-mediated genital cancers. (2,11)

Diagnosis is made from cytology or biopsy. If cytology is positive for LSIL or HSIL, then patients should be referred for formal biopsy, usually performed via high-resolution anoscopy following application of acetic acid which will cause dysplastic cells to be more visible compared with surrounding tissue. Screening is controversial. Low-risk individuals are not routinely screened given the low incidence of AIN and anal cancer. For high-risk individuals, however, infectious disease societies recommend yearly surveillance for HIV-positive patients (especially those who are MSM or have a history of cervical cancer) and every 3-6 months for those with low- or high-grade AIN. The optimal screening tool is debated. Cytology has a high false-negative rate, however high-resolution anoscopy has higher costs and less availability. A quadrivalent vaccine for HPV types 6, 11, 16 and 18 may represent an effective primary prevention tool. Currently, management strategies include surveillance and interventional strategies. These include topical therapy (trichloroacetic acid, 5-fluorouracil or imiquimod) or local ablative therapy with electrocautery or radiofrequency ablation. Topical therapy is generally well tolerated and has reasonable efficacy, although a substantial portion of patients will not respond and others will recur. Local ablative procedures are also reasonably well tolerated, however, recurrence rates are also significant (especially among HIV-positive patients) leading to repetitive treatment sessions and need for long-term surveillance. Surgical excision is no longer recommended for AIN, since it is associated with significant morbidity (risk of stenosis or fecal incontinence) and patients can still have recurrences. (2,11)

ESD is a minimally invasive approach that has demonstrated safety and effectiveness in the treatment

Table 1 — **Previous case reports of ESD for premalignant and early malignant lesions of the anal canal**

Age	Sex	Form	Size	Color	Type of lesion	Stage	HPV	No recurrence	Reference
65	F	Flat	20 mm	Whitish	AIN	Tis	+	5 mo	Our case
39	F	Flat	10 mm	Reddish	AIN	Tis	+	16 mo	(3)
66	M	Slightly elevated	25 mm	Whitish	SCC	Tis	+	5 mo	(4)
66	F	Slightly elevated	15 mm	Whitish	SCC	Tis	+	12 mo	(5)
71	M	Slightly elevated	25 mm	Whitish	SCC	Tis	+	19 mo	(5)
70	F	Slightly elevated	10 mm	Whitish	SCC	T1a	Not available	23 mo	(6)
89	F	Slightly elevated	15 mm	Whitish	SCC	Tis	Not available	15 mo	(7)
66	M	Elevated	12 mm	Whitish	SCC	Tis	Not available	23 mo	(7)
82	F	Slightly depressed	30 mm	Whitish	SCC	T1b	Not available	-	(8)
60	F	Flat	20 mm	Brownish	SCC	Tis	Not available	3 mo	(9)

of premalignant and early malignant lesions in gastrointestinal tract. *En-bloc* resection, histopathological evaluation of curative resection status and low recurrence rates have established ESD as first-line for resection of early malignant and premalignant lesions in esophagus, stomach, colon and rectum. ESD has revealed to be feasible and safe for resection of recurrent colorectal lesions after endoscopic mucosal resection when fibrosis make repeat mucosal resection difficult while surgery is considered overtreatment (12). However, there is limited experience with this technique for the management of anal lesions; these could be amenable for resection via ESD, particularly if they can be adequately visualized in retroflexion and partially involve distal rectum. There is one case of AIN in a 39-year-old female resected *en-bloc* by ESD with little morbidity and no recurrence within a 16-month follow-up period (3). In addition, there are some cases of early ASCC resected by ESD with no recurrence during follow-up periods ranging from 3 to 23 months (4-9). These cases are summarized in Table 1. Our case supports the idea that ESD could also represent a safe and effective treatment for AIN (and early ASCC) with little morbidity and lower recurrence rates than conventional treatment. However, experience with ESD in the treatment of anal premalignant lesions is limited and larger studies are necessary to establish conclusive evidence for the role of this technique in the treatment of AIN.

Disclosures

The authors have no potential financial, professional or personal conflicts relevant to the manuscript. This work did not have any funding. Informed patient consent was obtained.

References

1. NELSON R.A., LEVINE A.M., BERNSTEIN L., SMITH D.D., LAI L.L. Changing patterns of anal canal carcinoma in the United States. *J Clin Onc*. 2013; **31**(12): 1569-75.
2. SIDDHARTHAN R.V., LANCIAULT C., TSIKITIS V.L. Anal intraepithelial neoplasia: diagnosis, screening, and treatment. *Ann Gastroenterol.* 2019; **32**(3): 257-63.
3. WAGNER A., NEUREITER D., HOLZINGER J., KIESSLICH T., KLIESER E., BERR F. Endoscopic submucosal dissection (ESD) for anal high-grade intraepithelial neoplasia: a case report. *Z Gastroenterol.* 2018; **56**(5): 495-8.
4. UOZUMI T., SUMIYOSHI T., KONDO H., MINAGAWA T., FUJII R., YOSIDA M., *et al.* Endoscopic submucosal dissection for early squamous cell carcinoma in the anal canal and Lugol chromoendoscopy for assessment of the lateral margin. *Endosc Int Open*. 2018; **6**(9): E1130-e3.
5. TAMARU Y., OKA S., TANAKA S., NINOMIYA Y., ASAYAMA N., SHIGITA K., *et al.* Early squamous cell carcinoma of the anal canal resected by endoscopic submucosal dissection. *Case Rep Gastroenterol.* 2015; **9**(1): 120-5.
6. CHOU Y.P., SAITO Y., MATSUDA T., NAKAJIMA T., MASHIMO Y., MORIYA Y., *et al.* Novel diagnostic methods for early-stage squamous cell carcinoma of the anal canal successfully resected by endoscopic submucosal dissection. *Endoscopy*. 2009; **41** Suppl 2: E283-5.
7. ITO T., MORITA S., SHIMENON., UEHARA K., IMAI Y., INOKUMA T. The prospect of endoscopic submucosal dissection for early anal canal squamous cell carcinoma. *Clin J Gastroenterol.* 2016; **9**(6): 384-8.
8. IWATATE M., SANO W., SANO Y. Superficial anal canal squamous cell carcinoma diagnosed using narrow-band imaging and treated by endoscopic submucosal dissection. *Digest Endosc.* 2015; **27**(5): 627-9.
9. TSUJI S., DOYAMA H., YAMADA S., TOMINAGA K., OTA R., YOSHIKAWA A., *et al.* Endoscopic submucosal dissection of a squamous cell carcinoma in situ in the anal canal diagnosed by magnifying endoscopy with narrow-band imaging. *Clin J Gastroenterol.* 2014; **7**(3): 233-7.
10. WATSON A.J., SMITH B.B., WHITEHEAD M.R., SYKES P.H., FRIZELLE F.A. Malignant progression of anal intra-epithelial neoplasia. *ANZ J Surg.* 2006; **76**(8): 715-7.
11. ROBERTS J.R., SIEKAS L.L., KAZ A.M. Anal intraepithelial neoplasia: A review of diagnosis and management. *World J Gastrointes Oncol.* 2017; **9**(2): 50-61.
12. SUZUKI T., KITAGAWA Y., NANKINZAN R., HARA T., YAMAGUCHI T. Feasibility of endoscopic submucosal dissection for recurrent colorectal tumors after endoscopic mucosal resection. *Acta Gastroenterol Belg.* 2019 Jul-Sep; **82**(3): 375-378.