Clinics in Surgery

Research Article
Published: 07 Aug, 2017

Detection of Anal Dysplasia by Chromoendoscopy with Narrow Band Imaging and Acetic Acid (NBIA) in 182 Patients

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Abstract

Anal squamous intraepithelial lesion (SIL) precedes the development of anal squamous cell carcinoma (SCC). Detection of SIL is facilitated by chromoendoscopy with narrow band imaging and acetic acid (NBIA). Between 2011 and 2017, 182 patients with abnormal anal cytology underwent NBIA to identify and ablate SIL. The majority of patients were HIV positive men. Other associated diagnoses included urogynecologic dysplasia, inflammatory bowel disease and organ transplantation. The histopathologic diagnosis of SIL/SCC was found in 65% of cases overall (52% for cytology showing atypical cells, 81% for cytology showing low-grade SIL and 73% for cytology showing high-grade SIL). Illustrative examples showing the endoscopic appearance of LSIL, HSIL, and SCC are shown. The procedure can be done in any facility where endoscopy is practiced.

Keywords: Squamous intraepithelial neoplasia; Chromoendoscopy; Narrow band imaging; Human papillomavirus; Human immunodeficiency virus; Organ transplantation; Inflammatory bowel disease

Introduction

Anal squamous cell carcinoma (SCC) and its precursor lesion, anal squamous intraepithelial lesion (SIL) are human papillomavirus-related neoplasms [1]. Risk factors include immunosuppression, human immunodeficiency virus (HIV) infection, urogynecologic dysplasia, inflammatory bowel disease and solid organ transplantation [2,3]. Detection of premalignant anal lesions using an endoscope and acetic acid was described in 1989 by Scholefield et al. [4] More recently, the application of fiberoptic flexible endoscopy with narrow band imaging (NBI) using retroflexion/rectal insufflation and *en face* views with a transparent hood has been reported [5-9]. We have previously described the application of fiberoptic chromoendoscopy with NBI and acetic acid (NBIA) in 60 consecutive patients who had abnormal anal cytology [10]. We now describe the findings of NBIA done in 182 consecutive patients with abnormal anal cytology.

Methods

In 2011, we obtained approval from the Cleveland Clinic Institutional Review Board to identify and evaluate all patients within our Health System who had received the diagnosis of anal intraepithelial neoplasia. This was a non-randomized prospective study. Patients were interviewed. A history and physical examination were obtained with attention focused on risk factors for anal dysplasia, anal examination and white light anoscopy. Cytology was reported according to the Bethesda System [11]. Those with abnormal anal cytology [12,13] were offered NBIA. Informed consent for endoscopic examination of the anorectum was obtained. The procedure was performed in an endoscopy unit using a high-definition gastroscope (Olympus GHF180). Pre-procedural bowel preparation was administered. Blood pressure, pulse oximetry and EKG/heart rate were monitored during and after the procedure. Intravenous moderate sedation with Fentanyl or Meperidine plus Midazolam was administered. Topical intra-anal 2% Lidocaine gel was applied for local anesthesia. The perianal skin was examined. The gastroscope was introduced through the anus and passed up to the sigmoid colon. The anal transitional zone (ATZ) and anal canal were inspected using both *en face* and retroflexed views (Figure 1 and 2) with white light and NBI before and after treatment of the anal transitional zone and anoderm with 3% acetic acid. Evaluation of the anal canal was done by passing the gastroscope through a self-lighted beveled Anospec™ anoscope. Lesions showing acetowhite changes and/or abnormal vascular features including punctuation or mosaicism [14]

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Received Date: *01 Jun 2017*
Accepted Date: *31 Jul 2017*
Published Date: *07 Aug 2017*

Citation:
Inkster MD, Wu JS. Detection of Anal Dysplasia by Chromoendoscopy with Narrow Band Imaging and Acetic Acid (NBIA) in 182 Patients. Clin Surg. 2017; 2: 1583.

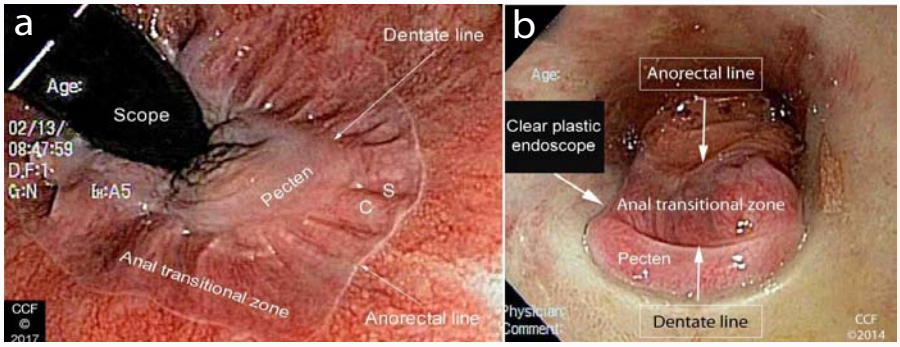

Figure 1a: Retroflexion with rectal insufflation shows the anorectal line, the ATZ, the dentate line and the pecten.
Figure 1b: *En face* view of the anal canal through a clear plastic anoscope shows the anorectal line, the ATZ, the dentate line and the pecten. The anoscope increases the diameter of the canal facilitating magnified endoscopic visualization of the ATZ and its borders.

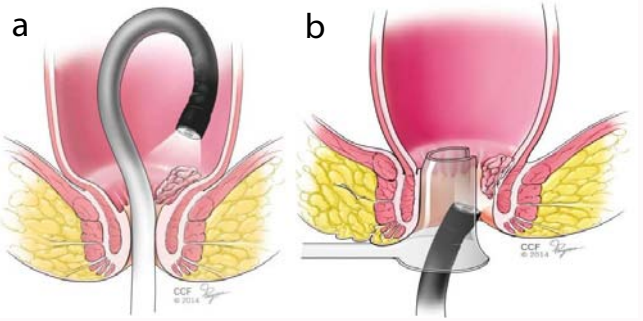

Figure 2a: Illustration of a lesion located in the ATZ seen with retroflexion and rectal insufflation.
Figure 2b: Illustration of *en face* view of an anal canal lesion seen through a lighted anoscope.

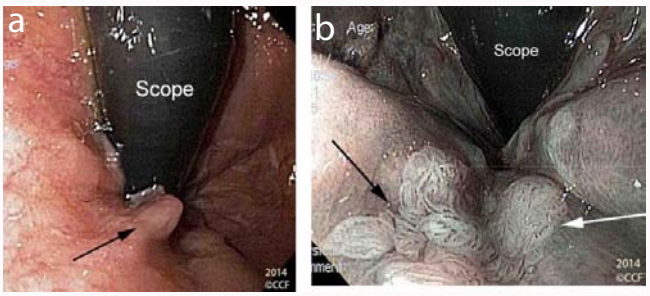

Figure 4a: White light inspection of the ATZ with retroflexion shows a raised lesion (arrow) close to the flexible endoscope.
Figure 4b: Multiple lesions (arrows) not visible with white light are seen on retroflexed view of the ATZ after treatment with acetic acid and illumination with NBI. Biopsies showed HSIL.

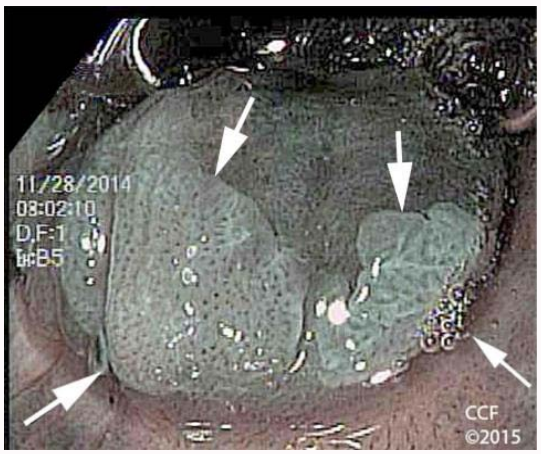

Figure 3: Anal LSIL (arrows) seen through a beveled lighted anoscope by chromoendoscopy with NBI and acetic acid (NBIA). The lesion is raised and shows diffuse punctuation.

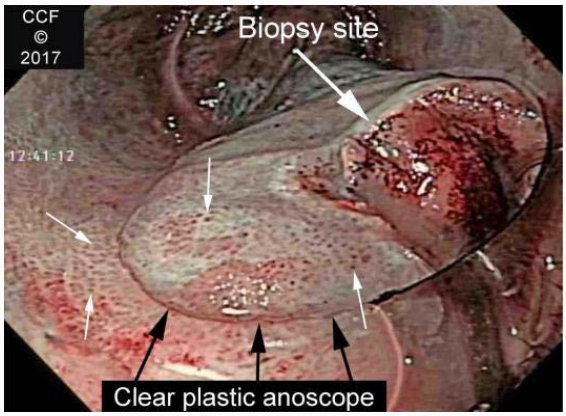

Figure 5: NBIA in a renal transplant patient. *En face* view of the anal canal with NBI after treatment with acetic acid shows diffuse punctuation (small arrows). The changes are seen directly and also through the clear plastic of the anoscope (edge marked with black arrows). The biopsy site is shown.

were biopsied and ablated. Hot biopsy forceps were preferred for small lesions. A Gold Probe™ Electrohemostasis catheter (Boston Scientific) set at 30 W soft cut was used to ablate large and irregular lesions. Photo documentation was preserved as part of the permanent electronic medical record (Provation™). Patients were recovered and discharged home. When surgery was required, NBIA was done in the operating room. Histopathology was reported according to the lower anogenital squamous terminology standardization (LAST) project for HPV-associated lesions [15]. Anal cytology readings of atypical cells of uncertain significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL) or high-grade intraepithelial lesion (HSIL) were considered abnormal. Biopsy readings of LSIL, HSIL and SCC were recorded.

Results

Between 2011 and 2017, 182 individuals were referred for management of abnormal anal cytology. Patient demographics are shown in Table 1. The majority were HIV positive men who have sex with men (MSM). Others had risk factors for anal dysplasia that included urogynecologic dysplasia, inflammatory bowel disease or organ transplantation. Detection of anal SIL or SCC by NBIA in

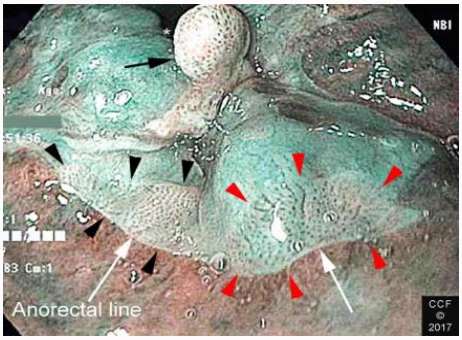

Figure 6: NBIA with rectal retroflexion shows three discrete lesions in the anterior ATZ. Biopsies of the lesions labelled with the black arrow and arrow heads showed LSIL. Biopsy of the lesion labelled with red arrowheads showed HSIL. The endoscope is identified with an asterisk. The two lesions marked with arrowheads are located in the ATZ at the anorectal line (white arrows).

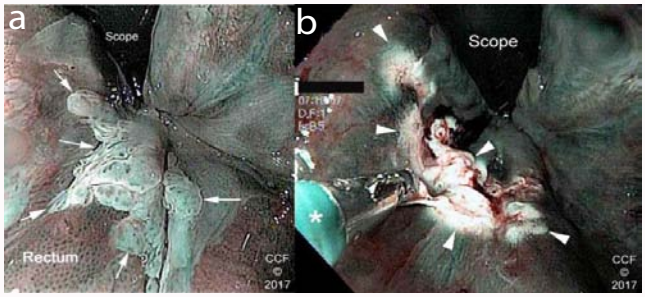

Figure 7a: The serpiginous borders of a raised acetowhite anterior ATZ lesion are identified with white arrows.
Figure 7b: The lesion (arrow heads) has been ablated with hot biopsy forceps (asterisk). Pathology showed LSIL.

these 182 patients is summarized in Table 2. The results are for the first NBIA examination performed on each patient. Biopsies showed SIL/SCC in 65% of patients overall. The pre-procedural diagnosis of ASCUS yielded a pathologic finding of SIL in 52% (35% LSIL, 17% HSIL). The pre-procedural diagnosis of LSIL yielded a pathologic diagnosis of SIL/SCC in 81% (57% SIL, 23% HSIL, SCC 1%). The pre-procedural diagnosis of HSIL showed SIL in 73% (33% LSIL, 40% HSIL). There were no post procedural admissions to hospital or emergency room visits for these patients. Illustrative examples of NBIA follow.

Example 1: *En face* view of the anal canal after treatment with acetic acid showed diffuse punctuation when illuminated with NBI (Figure 3). Biopsy of this area showed LSIL.

Example 2: Retroflexed view of the anorectum with white light shows a single discrete raised lesion (Figure 4a). Re-examination with NBI after treatment with acetic acid (NBIA) revealed a complex collection of slightly raised lesions with enhanced vascularity (Figure 4b). Biopsies of this area showed HSIL. All lesions were ablated with hot biopsy forceps.

Example 3: Chromoendoscopy (NBI/acetic acid) in a renal transplant patient, Figure 5, showed diffuse punctuation. Biopsy showed HSIL.

Example 4: An HIV positive HPV positive male with abnormal anal cytology underwent NBIA. Three discrete lesions were identified. Targeted biopsies showed both LSIL and HSIL (Figure 6).

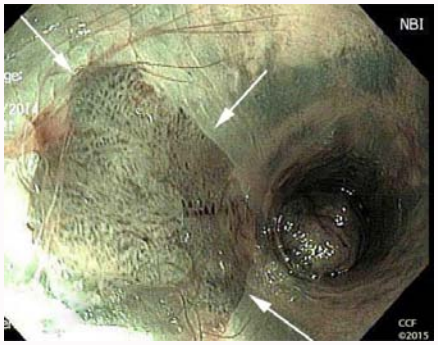

Figure 8: NBIA with *en face* view through the wall of a clear plastic anoscope shows a discrete anal canal lesion with punctuation. The lesion proved to be SCC.

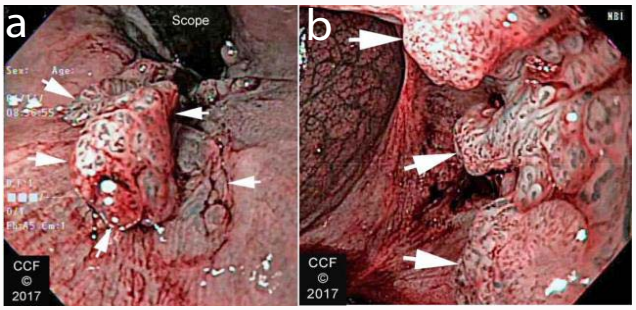

Figure 9: ATZ SCC seen with NBI with (a) retroflexed and (b) en face views. Arrows delineate the lesion. The hypervascular character of the cancer is enhanced by NBI.

Table 1: Demographics. 182 Patients referred for management of abnormal anal cytology.

M/F	147/35
Mean age (range) years	47 (21-82)
HIV positive	109
MSM	112
Anal condyloma	25
Cervical dysplasia	6
Vulvar dysplasia	6
Vaginal dysplasia	4
Penile condyloma	1
Inflammatory bowel disease	4
Renal transplant	2
Liver transplant	2
Small intestine transplant	1
Pancreas transplant	1
Bone marrow transplant	1

Example 5: An HIV positive male was found to have an anterior raised acetowhite lesion with punctuation in the ATZ (Figure 7a). The lesion was biopsied and ablated using hot biopsy forceps (Figure 7b).

Example 6: NBIA with *en face* view of the anal canal shows a flat anal lesion through the wall of the clear plastic anoscope (Figure 8). Biopsy showed HSIL. The entire lesion was excised. Final pathology showed SCC. Treatment by combined chemoradiation was initiated.

Example 7: A patient presented for assessment of anorectal

Table 2: Chromoendoscopy (NBIA) in search of anal dysplasia in 182 individuals with abnormal anal cytology Histopathology.

		SIL/SCC (%)	LSIL (%)	HSIL (%)	SCC	SIL not found
Cytology	N					
ASCUS	97	50/97 (51.5)	34/97 (35.1)	16/97 (16.5)	0 (0)	47/97 (48.5)
LSIL	70	57/70 (81.4)	40/70 (57.1)	16/70 (22.9)	1/70 (1.4)	13/70 (18.6)
HSIL	15	11/15 (73.3)	5/15 (33.3)	6/15 (40)	0 (0)	4/15 (26.7)

bleeding.[16] Flexible sigmoidoscopy with retroflexed and *en face* views of the ATZ illuminated with NBI showed an irregular, friable mass (Figures 9a and 9b). Biopsies showed SCC. Chemoradiation was initiated.

Discussion

The majority of anal cancer cases are squamous cell carcinoma [17]. Nigro credits Gabriel for suggesting that cancer of the anal region be divided into two groups according to the site of origin [18,19]. Anal margin cancer, developing in the perianal skin, is identified by direct inspection. Anal canal cancer originates in the cloacogenic zone, the tissue immediately proximal to the area of the dentate line [18]. Fenger defines this area as the anal transitional zone, "the zone interspersed between uninterrupted colorectal mucosa above and uninterrupted squamous epithelium below [20]". Between the dentate line and the skin is the pecten, described by Stroud as a stratified epithelium that "has few or no openings or sweat glands" [21]. Visualization of the ATZ, anal canal pecten and neighboring anatomic landmarks are necessary for the identification of lesions found within their boundaries. This paper describes our experience with chromoendosopic (NBIA) detection of anal dysplasia in 182 consecutive patients. The following features of this technique facilitate the detection of anal dysplasia.

- Retroflexion with rectal air insufflation provides a circumferential view of the effaced ATZ and pecten.
- Examination through a beveled self-lighted anoscope provides clear *en face* views of the ATZ and pecten.
- Chromoendoscopy with NBI and acetic acid (NBIA) facilitates identification of SIL.
- Lesions can be biopsied and ablated endoscopically using standard equipment.
- Photodocumention is preserved as part of the permanent electronic medical record.

The clinical correlation between anal cytology, chromoendoscopic findings and histopathology is not perfect. Long-term follow-up is needed to determine limitations of NBIA with regard to lesion detection and elimination.

Summary

We have described chromoendoscopy using NBI and acetic acid (NBIA) for the detection, biopsy and ablation of anal dysplasia in the ATZ and anal canal in 182 consecutive patients with abnormal anal cytology who each underwent a single examination. Overall, SIL /SCC were found in 65% of patients. Of the 97 patients with the pre-procedure cytology of ASCUS, 52% had SIL on biopsy. For the 70 patients with LSIL on cytology, SIL/SCC was found in 81%; carcinoma was detected by biopsy in 1.4%. When cytology showed HSIL, dysplasia was found on biopsy in 73%. Although the majority of patients in this report were HIV positive males, the referral of patients with urogynecologic dysplasia, inflammatory bowel disease and organ transplantation reflects an increasing awareness of the SIL in other high-risk groups. Providers who perform esophagogastroduodenoscopy and/or colonoscopy routinely should be able to perform anal chromoendoscopy to detect anal SIL since the techniques described here are already part of routine gastrointestinal endoscopic practice.

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