

# Prevalence of Anal Intraepithelial Lesions in Patients with Inflammatory Bowel Disease

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J Coloproctol 2021;41(3):222–227.

## Abstract

### Keywords

- ▶ inflammatory bowel disease (IBD)
- ▶ anal cancer
- ▶ anal intraepithelial neoplasia
- ▶ human papillomavirus (HPV)
- ▶ Crohn's disease
- ▶ ulcerative colitis

**Introduction** Anal intraepithelial neoplasia (AIN) is a premalignant lesion of the anal canal associated with HPV, with a higher prevalence in immunosuppressed individuals. Patients with inflammatory bowel disease (IBD) are at potential risk for their development, due to the use of immunosuppressants and certain characteristics of the disease.

**Method** This is a prospective, cross-sectional, and interventional study that included 53 patients with IBD treated at a tertiary outpatient clinic, who underwent anal smear for cytology in order to assess the prevalence of AIN and associated risk factors.

**Results** Forty-eight samples were negative for dysplasia and 2 were positive (4%). Both positive samples occurred in women, with Crohn's disease (CD), who were immunosuppressed and had a history of receptive anal intercourse.

**Discussion** The prevalence of anal dysplasia in IBD patients in this study is similar to that described in low-risk populations. Literature data are scarce and conflicting and there is no evidence to recommend screening with routine anal cytology in patients with IBD. Female gender, history of receptive anal intercourse, immunosuppression and CD seem to be risk factors.

## Introduction

Anal intraepithelial neoplasia (AIN), or squamous intraepithelial lesion (SIL), is a premalignant lesion, precursor of anal squamous cell carcinoma (SCC), with a strong association with oncogenic strains of human papillomavirus (HPV), specifically the subtypes 16 and 18 and with risk factors and behaviors associated with the acquisition of this virus, such as HIV infection, smoking, receptive anal intercourse and a history of cervical intraepithelial neoplasia (CIN).<sup>1</sup> It is known that the prevalence of AIN, as well as its progression to

anal canal carcinoma, is greater in immunosuppressed patients, probably due to the occurrence of less viral clearance in this group. It is possible to detect the precursor lesions of anal cancer mainly through anal cytology and high resolution anoscopy.<sup>2</sup>

Anal smears for cytology, stained by the Papanicolaou method, have similar efficacy to that of collections of cervical-uterine smears.<sup>3</sup> Given the success of early cervical cancer screening and diagnosis programs, it seems reasonable to also institute anal SCC prevention programs, considering the similarity between these two malignancies.

received  
 August 31, 2020  
 accepted  
 January 15, 2021

DOI <https://doi.org/10.1055/s-0041-1730425>  
 ISSN 2237-9363.

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There are still no controlled and randomized studies that demonstrate the value of anal SCC screening programs in the general population. Routine collection of material for anal cytology is currently restricted to men who have sex with men (MSM) infected by the human immunodeficiency virus (HIV).<sup>4,5</sup> Recipients of solid organ transplants, carriers of HIV, and patients using immunosuppressive medications are also considered high-risk.

Patients with inflammatory bowel disease (IBD) are at potential risk for developing AIN.<sup>4,6</sup> In the treatment of these diseases, relative immunosuppression is routinely induced, using immunomodulators (azathioprine, methotrexate, and 6-mercaptopurine) and immunobiologicals, such as anti-tumor necrosis factor (TNF) agents (infliximab, adalimumab, and certolizumab pegol). These drugs alter cellular immunity and are associated with increased rates of viral, bacterial, and fungal infections, with a higher risk in those using combination therapy.<sup>7</sup> The use of immunosuppressants can lead to a higher rate of diseases associated with human papillomavirus (HPV), including genital warts, dysplasia, and anogenital cancer. Other studies have already demonstrated a 3 to 5-fold increase in changes in the cervical-uterine cytology of women with IBD in relation to the general population.<sup>8,9</sup> With the expansion of the indications for immunobiological therapies, there is doubt as to which care should be added to patients with IBD and whether there is a greater risk of dysplasia and anal cancer in this population.

In a study by Kane et al., it has been demonstrated that the use of immunosuppressants for more than 6 months resulted in a higher risk of cervical dysplasia in women with IBD, proposing that these women be included in different screening programs for cervical neoplasia.<sup>10</sup>

The hypothesis that IBD may increase the risk of anal dysplasia stems not only from immunosuppression, which alters cellular immunity, but also from mechanisms intrinsic to IBD that can compromise immunity against viral infections. In 2005, Wehkamp et al. have shown a reduction in human defensins in patients with Crohn's disease (CD).<sup>11</sup> Defensins are proteins found in cells of the immune system that assist in immunity against viral infections. Human alpha-defensins 1, 2, 3, and 5 have been shown to inhibit HPV in the skin and mucous membranes,<sup>12</sup> which may explain a higher risk of HPV infection in patients with IBD.

Another concern is whether immunosuppression can promote malignant transformation in patients with intraepithelial lesions. The malignancy rate is estimated at 6% in the general population, compared to 13 to 50% in immunosuppressed individuals.<sup>13,14</sup>

The present study was designed to investigate the prevalence of changes in anal cytology in patients with IBD, also seeking to identify risk factors associated with the development of lesions.

## Method

This is a prospective, cross-sectional and interventional study that included patients with ulcerative colitis (UC)

and CD treated at a tertiary outpatient clinic, a reference in the treatment of these diseases by the Sistema Único de Saúde (Unified Health System).

We included 53 patients over 18 years old, with an established diagnosis of IBD, regardless of the treatment used. Immunosuppressed patients were excluded for reasons other than the treatment of IBD, such as HIV carriers, recipients of solid organ transplants and those who used immunosuppressive medications to treat other diseases (cancer, systemic lupus erythematosus, etc.). Patients with a previous history of anal cancer, pregnant women, and patients with a history of HPV vaccination were also excluded.

In this study, patients who used Azathioprine or Methotrexate for more than 3 months, infliximab for at least 3 doses, and adalimumab or certolizumab for at least 6 weeks (3 doses) were considered immunosuppressed. Patients considered non-immunosuppressed were those treated with mesalazine and those who were untreated.

The research was approved by the ethics and research committee under CAE 09694419.5.0000.0096. All patients were instructed on the characteristics of the research and signed an informed consent form. Data collection took place between April and December 2019.

A questionnaire was applied with information about the disease, medical and social history, inferring about risk factors for HPV infection. Data from medical records and laboratory tests were also reviewed. In patients with perianal disease, the perianal disease activity index (PDAI) anal disease activity questionnaire was used.<sup>15</sup>

All patients underwent anal smear collection on an outpatient basis, on the day of their routine consultation, using a standard brush, which was introduced approximately 4 cm into the anal canal, followed by 5 rotations. Then, the brushes were rubbed on glass slides with zigzag movements until they covered the entire blade. The slides were then deposited in plastic containers with 70% alcohol for fixation and sent to cytopathology. This technique was standardized by Nadal et al. in 2009.<sup>16</sup> In the laboratory, the slides were stained by the Papanicolaou method, with the dyes hematoxylin, orange G, and EA 36.

The slides were evaluated by two experienced cytopathologists. In discordant cases (3/53 cases), there was a review by a third professional with expertise. The results were evaluated according to the Bethesda classification 2001<sup>17</sup> of cervical cytology, being classified as 1) negative for intraepithelial injury or malignancy 2) atypia of squamous cells of undetermined significance (ASC-US), 3) low-grade intraepithelial injury (LSIL), which corresponds to low-grade intraepithelial neoplasia (AIN 1, in which mild dysplasia is observed) and 4) high-grade intraepithelial lesion (HSIL), which corresponds to high-grade intraepithelial neoplasia (AIN 2 and 3, in which moderate and severe dysplasia are observed, respectively).

In the statistical analysis, the results of quantitative variables were described by means, standard deviation, medians, minimum values, maximum values (quantitative variables). For categorical variables, frequencies and

percentages were presented. The data were analyzed with the IBM SPSS Statistics v.20.0. (IBM Corp., Armonk, NY, USA) computer software.

## Results

A total of 53 samples were collected in the period of 8 months. Three were excluded due to material considered unsatisfactory (2 due to faecal residue preventing proper evaluation and in one case due to intense histological inflammation making diagnosis of dysplasia difficult).

The general descriptive statistics are shown in **►Table 1**. The average age was  $46.9 \pm 14.5$  years, varying between 18 and 74 years old. Thirty were female (60%) and 20 were male (40%).

Of the 50 included, 45 (90%) had CD and 5 (10%) had UC. The mean duration of the inflammatory disease was  $10 \pm 6.7$  years, ranging from 1 to 25 years, with a median of 11. (**►Table 1**).

There were 48 samples negative for dysplasia and 2 positive. One presented LSIL/AIN 1 and the other with atypia of squamous ASC-US. The positivity of this sample was 4% (2/50). (**►Table 2**).

In the total sample of 50, 44 patients (88%) were immunosuppressed due to treatment. Thirty-three (33/44) patients used immunobiological therapy—6 used adalimumab, 23 used infliximab, and 4 used certolizumab pegol (**TABLE 1**)—17 used a combination therapy with methotrexate or azathioprine, and 16 used monotherapy. Of the 11 in monotherapy with immunomodulator, 10 used azathioprine and 1 methotrexate. The two patients with abnormal anal cytology were immunosuppressed.

Six patients in the study did not use immunosuppressants (4 patients with UC using mesalazine and 2 with CD without treatment for more than 3 months at the time of collection). In this group, all anal cytologies were negative.

In total, 11 patients declared a history of receptive anal intercourse, 1 man and 9 women. The two patients with positive anal cytology were in this group and were immunosuppressed. The positivity of cytology in the group of immunosuppressed patients with a history of anal intercourse was 22.2% (2 positive in a group of 9 patients).

Four patients reported a previous history of genital warts, all of whom were female and immunosuppressed. One of them had anal cytology with LSIL. Six patients reported a history of changes in cervical-uterine cytology, which did not correlate with positivity of anal cytology.

The leukocyte count was evaluated and a total count below 4,000 was considered leukopenia. Three (3/50) patients had leukopenia, none of whom had changes in anal cytology. The average leukocyte count was 6,820, ranging from 2,910 to 15,230 (**►Table 1**).

Of the 45 patients with CD, 66% (30) had perianal involvement, 7 with anal canal stenosis, 2 with anal fissures and 26 with fistulas. The average PDAI score was 3, considered an inactive disease. The two patients with a positive cytology sample had perianal disease, with PDAI of 0 in the patient with LSIL, and 12 in the patient with ASC-US.

Cytological inflammation was graded on cytology slides, which ranged from 0 (without inflammation) to 3 (severe inflammation). Thirty-eight patients (76%) had cytological grade of inflammation 0, 2 patients (4%) had grade 1, 9 patients (18%) had grade 2, and 1 patient (2%) was graded as 3. (**►Table 1**)

In the analysis of positive samples (**►Table 2**), LSIL was identified in a female patient, 35 years old, with CD with 9 years of evolution, ileocolonic and perianal fistulizing pattern, using infliximab alone. This patient had negative serology for hepatitis B, C, and HIV. The perianal disease was without clinical activity, with a PDAI score of 0. The patient reported a history of receptive anal intercourse and a previous history of genital warts treated with cauterization. The leukocyte and lymphocyte counts were normal. In cytology, inflammation was graded at 0, confirming anal disease without activity.

The ASC-US result occurred in a 59-year-old female patient with CD with 13 years of evolution, colonic and perianal involvement, using infliximab and azathioprine (combined therapy). This patient had negative serology for hepatitis B, C, and HIV. The PDAI score was 12, indicating active anal disease. She reported receptive anal intercourse and denied changes in cervicovaginal cytology as well as a history of anogenital warts. Normal leukocyte and lymphocyte count. Cytological inflammation was graded as moderate (grade 2).

## Discussion

The prevalence of anal dysplasia in patients with IBD in the present study was 4% in the general sample and 4.5% in immunosuppressed patients, similar to that described in low-risk populations, which according to the literature varies from 3.9 at 10%,<sup>18-20</sup> and lower than that reported in high-risk populations (19.6–28%),<sup>21,22</sup> as patients with genital dysplasia and recipients of solid organ transplants.

There are few studies on anal intraepithelial lesions in patients with IBD. In 2017, McGowan et al. found a high prevalence of changes in anal cytology (45.7%) and HPV identification (89.1%) in a group of 45 patients with IBD who did not use immunobiological agents,<sup>6</sup> which contrasts with the prevalence found in present study (4%). In 2015, Welton et al. performed a cohort with 270 individuals, comparing patients with IBD and healthy controls, found a higher prevalence of ASC-US in patients with inflammatory diseases (8.8%) compared to healthy controls (2.6%). There was no higher prevalence of changes in immunosuppressed individuals.<sup>23</sup> This latest study found an association of changes in cytology in females with disease duration greater than 10 years, and a higher prevalence in CD compared to UC. In the present study, positive cases also occurred in women with long-standing CD.

Literature data regarding patients with UC and CD are scarce and conflicting, and there is no evidence to recommend screening with routine anal cytology, even in those using immunosuppression. Studies on anal HPV and dysplasia in the general population are also scarce, as the focus has been on groups considered to be at high risk for anal cancer,

**Table 1** General descriptive statistics

Variable	Classification	n	Result*
Age (years)		50	46.9 ± 14.5 (18 - 74)
Gender	Female	50	30 (60%)
	Male		20 (40%)
Disease	CD (Crohn's disease)	50	45 (90%)
	UC (Ulcerative colitis)		5 (10%)
Time with the disease (years)		50	10.9 ± 6.8 (1-25)
Location pattern (Crohn's disease)	Colonic + perianal	45	14 (31.1%)
	Ileal + colonic + perianal		12 (26.7%)
	Ileal		6 (13.3%)
	Ileal + colonic		5 (11.1%)
	Ileal + perianal		4 (8.9%)
	Colonic		4 (8.0%)
Location pattern (Ulcerative colitis)	Proctitis	5	2 (40%)
	Pancolitis		1 (20%)
	Left colitis		1 (20%)
	Proctosigmoiditis		1 (20%)
Immunosuppressed	No	50	6 (12%)
	Yes		44 (88%)
Leukocytes		50	6,820 (2,910-15,230)
Azathioprine	No	50	28 (56%)
	Yes		22 (44%)
Methotrexate	No	50	43 (86%)
	Yes		7 (14%)
Use of immunobiologicals	No	50	17 (34%)
	Yes		33 (66%)
Anti-TNF agent	Infliximab	33	23 (69.7%)
	Adalimumab		6 (18.2%)
	Certolizumab		4 (12.1%)
Combined therapy	No	50	33 (66%)
	Yes		17 (34%)
Perianal disease	No	50	20 (40%)
	Yes		30 (60%)
Type of perianal disease	Fistulas	30	21 (70%)

(Continued)

**Table 1** (Continued)

Variable	Classification	n	Result*
	Fistulas + stenosis		5 (16.7%)
	Fissures		2 (6.7%)
	Stenosis		2 (6.7%)
Anal surgery	No	50	27 (54%)
	Yes		23 (46%)
PDAI (score)		30	3 (0-13)
Receptive anal intercourse	No	50	39 (78%)
	Yes		11 (22%)
Changes in cervicovaginal cytology (restricted to women)	No	30	24 (80%)
	Yes		6 (20%)
History of genital warts	No	50	46 (92%)
	Yes		4 (8%)
Cytological inflammation	0	50	38 (76%)
	1		2 (4%)
	2		9 (18%)
	3		1 (2%)
Anal cytology	Negative	50	48 (96%)
	Positive (1 LSIL e 1 ASC-US)		2 (4%)

Abbreviations: ASC-US, atypia of squamous cells of undetermined significance; LSIL, low-grade intraepithelial lesion.

\*Quantitative variables described as mean ± standard deviation (minimum - maximum) or median (minimum - maximum); Categorical variables described by frequency (percentage).

which makes the correlation difficult. The present study did not find a higher prevalence of AIN in patients with IBD compared to studies in other low-risk groups.<sup>19,20</sup>

Despite the low identification of lesions (only 1 case of LSIL and 1 case of ASC-US), both patients with positivity were female, had a history of receptive anal intercourse, were immunosuppressed, and used anti-TNF agents (► **Table 2**). The positivity of cytology among immunosuppressed patients with a history of anal intercourse was 22.2% (2/9) vs. 4% (2/50) in the total sample of patients with inflammatory diseases and 4.5% in the immunosuppressed (2/44). This finding suggests that immunosuppressed individuals with receptive anal intercourse may be at increased risk of pre-neoplastic lesions of the anal canal and perhaps should be screened with periodic anal cytology.

In the present study, there was no significant difference between the prevalence of anal intraepithelial lesions in immunosuppressed patients (4.5%) and in the general

**Table 2** Characteristics of cases with positive results in anal cytology

Characteristic	Case 1	Case 2
Anal cytology	LSIL	ASC-US
Age (years)	35	59
Gender	Female	Female
Type of disease	CD	CD
Time with the disease (years)	9	13
Location pattern	Ileal + colonic + perianal	Colonic + perianal
Immunosuppressed	Yes	Yes
Azathioprine	No	Yes
Immunobiological	Yes	Yes
Anti-TNF agent	Infliximab	Infliximab
Combined therapy	No	Yes
Leukocytes	6,650	9,000
Perianal disease	Yes	Yes
Type	Fistulas	Fistulas + stenosis
PDAI	0	12
Previous anal surgery	Yes	Yes
Receptive anal intercourse	Yes	Yes
Changes in cervico-vaginal cytology	No	No
Genital warts	Yes	No
Cytological inflammation	0	2

**Abbreviation:** ASC-US, atypia of squamous cells of undetermined significance; CD, Crohn's disease; LSIL, low-grade intraepithelial lesion; PDAI, perianal disease activity index; TNF, tumor necrosis factor.

sample (4%). Likewise, Welton et al. demonstrated a higher prevalence of anal dysplasia in patients with IBD, but with no difference between immunosuppressed and non-immunosuppressed patients.<sup>23</sup>

The presence and level of cytological inflammation can make the diagnosis of dysplasia difficult.<sup>24</sup> The patient with ASC-US had moderate inflammation, which may have influenced the result. The patient with LSIL did not present cytological inflammation.

A limitation of the present study was the use of anal cytology alone for the diagnosis of dysplasia. Despite being the standard mode of screening, its sensitivity may be low, around 11.9%,<sup>21</sup> consequently underestimating the prevalence of AIN. High-resolution anoscopy is the gold standard for diagnosing anal dysplasia.

A study bias was that the questionnaire used to obtain the medical and social history of patients was applied by the researchers, which may have generated a reporting bias,

especially regarding the history of receptive anal intercourse, underestimating this data, which is a well-established risk factor for AIN.<sup>19–21</sup>

## Conclusion

The present study demonstrated a prevalence of 4% of AIN in patients with IBD, similar to that described in low-risk populations in the literature.

There is no evidence to support routine screening for AIN in IBD patients.

Female gender, history of receptive anal intercourse, immunosuppression, and long-standing CD were present in both cases of positive anal cytology, suggesting that patients with these characteristics could benefit from routine screening.

More studies are needed, especially controlled ones, to determine the indications and ways of tracking anal dysplasia in patients with IBDs.

## Conflict of Interests

The authors declare that there is no conflict of interests.

## Acknowledgment

The authors are especially grateful to Margarida Souza dos Santos for her assistance in revising cytopathology slides.

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