

Prevalence of skin lesions in a sample of Brazilian patients with inflammatory bowel disease

Taciana Malosti da Silveira¹ , Milena Kroyzanovski¹ , Katia Sheylla Malta Purim² , Odery Ramos Júnior^{1,3} ,
Thelma Skare¹ , Renato Nisihara^{1,2,3*} 

SUMMARY

OBJECTIVE: Inflammatory bowel diseases may have extra intestinal manifestations such as those affecting the skin. This study aimed to study skin manifestations in a cohort of Brazilian patients with inflammatory bowel diseases.

METHODS: Epidemiological and clinical data were obtained through a cross-sectional study of 70 inflammatory bowel diseases patients and a control group comprising 50 healthy individuals. All patients were subjected to dermatological examination and photography of skin lesions.

RESULTS: Out of the 70 inflammatory bowel diseases patients, 50 had ulcerative colitis and 20 had Crohn's disease. Skin lesions occurred in 95.7% of the inflammatory bowel diseases patients and in 88% of individuals in the control group ($p=0.001$). Alopecia ($p<0.0001$), xerosis ($p=0.03$), striae ($p=0.02$), and acne ($p=0.04$) were more common in inflammatory bowel diseases patients than in the control group. Alopecia was more frequent in females ($p=0.01$) than in males. Two male patients, one with ulcerative colitis and the other with Crohn's disease, had pyoderma gangrenosum. Erythema nodosum was not observed in both groups.

CONCLUSION: There was a high prevalence of skin lesions in the Brazilian inflammatory bowel diseases patients. Additionally, alopecia, xerosis, striae, and acne were more common in patients with inflammatory bowel diseases than in those in the control group.

KEYWORDS: Inflammatory bowel disease. Pyoderma gangrenosum. Alopecia. Skin care.

INTRODUCTION

Inflammatory bowel diseases (IBD) are autoimmune diseases affecting the intestinal mucosa and caused by a complex interaction of genetic and environmental factors¹. In Brazil, IBD is more frequent in females than in males and occurs more frequently during the third to fifth decade of life². IBD is subdivided into Crohn's disease (CD) and ulcerative colitis (UC); location and depth of the affected intestinal wall are some of the differences between them. UC affects the mucosa and submucosa of the gastrointestinal tract and characteristically initiates in the rectum spreading proximally. CD involves the whole thickness of the intestinal wall, from the mucosa to the serosa, and may appear in any part of the gastrointestinal tract¹.

In addition to gastrointestinal tract involvement, IBD may affect several other systems, leading to high morbidity and poor quality of life^{1,3}. Skin involvement is among the extraintestinal manifestations of IBD and appears in more than 10% of affected individuals⁴.

The skin involvement associated with IBD may be specific, having the same histological characteristics as those of the

intestinal disease. The skin lesions share similar pathophysiologic mechanisms with intestinal involvement or may appear as lesions that are secondary either to the treatment or the malabsorption⁵. Specific lesions, including perianal fistula and perianal abscess, are more common in CD. Erythema nodosum (EN), pyoderma gangrenosum, and Sweet's syndrome are found in the group of reactive lesions. Skin manifestations secondary to malnutrition or malabsorption occur due to a shortage of vitamins and microminerals. For example, angular stomatitis is due to deficiencies of vitamin B12 and iron, phrynodema is due to vitamin A deficiency, scurvy is due to a deficit of vitamin C, and seborrheic dermatitis is due to vitamin E and zinc deficiency. Hair loss and skin rashes or allergic reactions may be secondary to the immune-suppressive treatment. Psoriasis and infections of the skin are associated with anti-TNF- α use^{2,5,6}. Moreover, there are other skin manifestations that are more common in IBD patients than in the general population. They are usually associated with a special expression of the HLA gene and a chronic inflammatory state. Psoriasis,

¹Mackenzie Evangelical School of Medicine – Curitiba (PR), Brazil.

²Universidade Positivo, Departamento de Medicina – Curitiba (PR), Brazil.

³Universidade Federal do Paraná, Departamento de Medicina Interna – Curitiba (PR), Brazil.

*Corresponding author: renatonisihara@gmail.com; renatonisihara@fempar.edu.br

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on May 02, 2023. Accepted on May 27, 2023.

skin vasculitis, autoimmune bullous dermatoses, vitiligo, multiform erythema, phlebitis, lichen planus, urticaria, secondary amyloidosis, and squamous cell carcinoma are some of them⁵.

This study aimed to investigate the prevalence of skin manifestations and to identify possible epidemiologic factors associated with their occurrence.

METHODS

Ethical issues

This study was approved by the local Committee of Ethics in Research, under permit number 4.252.1444 and adhered to the principles of the Declaration of Helsinki. All participants signed consent forms.

Sample and study design

This study was a cross-sectional study conducted from October 2020 to March 2022 at a single Gastroenterology Outpatient Clinic that cares for IBD patients from the Brazilian Public Health System.

Patients diagnosed with IBD according to the European Crohn's and Colitis Organization and the European Society of Gastrointestinal and Abdominal Radiology guidelines⁷ and older than 18 years of age were included in the study. This is a convenience sample that included all patients that came for a regular consultation during the above period and were invited to participate according to their appointment order and willingness to participate in the study. The control group consisted of their companions who were declared healthy.

Data were obtained from direct questioning or through chart review and included: epidemiological data (age, sex, years of formal education, and phototype according to the Fitzpatrick scale⁸) and clinical data (IBD type, disease duration, comorbidities, and treatment).

Dermatological examinations, consisting of full inspection and palpation of the patient's skin, were performed. These examinations were performed by two researchers trained and supervised by a dermatologist. Each lesion was appropriately annotated and photographed for documentation or further examination in case of diagnostic doubt.

Statistical analysis

The data were saved in Excel and analyzed using the software Graph Pad Prism 5.0. The continuous variables were expressed as mean \pm standard deviation or median and interquartile range (IQR). The experimental and control groups were compared using Mann-Whitney or independent samples t-tests. Categorical variables were expressed in percentages and compared between the two groups with the chi-square test or Fisher's exact test. Logistic regression was used to study the independence of the

use of treatment drugs and the presence of acne. p-Values less than 5% were considered statistically significant.

RESULTS

Description of studied sample

The studied sample included 70 IBD patients, of whom 45 (64.2%) were females, with a mean age of 44.7 ± 14.7 years. CD were diagnosed in 50 (71.4%) and 20 (28.6%) with UC. About treatment, aminosalicylates were used by 68.2%, azathioprine by 34.2%, biological drugs by 24.2%, glucocorticoids by 10%, methotrexate by 1.4%, and no medications by 7.1% of patients.

As a control group, we invited 50 individuals. Patients and controls were paired, and there are no differences for gender ($p=0.84$), age ($p=0.08$), years of formal education ($p=0.27$), and Fitzpatrick phototype ($p=0.57$).

Skin findings

Table 1 shows the comparison of the main skin lesions in patients with IBD and a matched control group. The following lesions were found in patients with IBD: dermatofibroma, eczema, dyshidrosis, actinic keratosis, drug lichenoid eruptions, striated lichen, scleroatrophic lichen, hidradenitis, dysplastic nevus, depapillated tongue, keloidal folliculitis, pityriasis versicolor, plantar wart, tinea corporis, chronic pigmented purpura, urticaria, erythema pernio, rosacea, hyperhidrosis, striated melanonychia, varicose ulcer, venous lake, eczematoid, and drug granulomatous reaction. These lesions were excluded from Table 1 due to their low prevalence of 1.4% (only one case of each lesion was found among the 70 patients with IBD).

The comparison of the most prevalent lesions according to the IBD type is shown in Table 2. The only observed difference was in the striae that were more common in CD patients than in UC patients. In addition, the distribution of the most common dermatological lesions according to gender shows that alopecia is more frequent in females.

Table 3 shows the comparison of main skin lesions according to the use of prednisone, azathioprine, and anti-TNF- α ; acne was more commonly seen in those using anti-TNF- α and azathioprine. When a logistic regression was done using acne as the dependent variable and azathioprine, prednisone, and anti-TNF- α as independent variables, only anti-TNF- α kept its independence (odds ratio [OR] 9.4; 95% confidence interval [CI] 1.5–58.5).

Skin lesions that have a well-established pathophysiology were grouped into three categories: reactive skin manifestations, cutaneous manifestations secondary to malnutrition or malabsorption, and skin manifestations secondary to treatment.

Table 1. Comparison of main skin lesions in inflammatory bowel disease patients and controls.

	IBD n=70	Controls n=50	p-value
Alopecia	29 (41.4%)	1 (2%)	<0.0001*
Xerosis	19 (27.1%)	5 (10%)	0.03**
Onychomycosis	13 (18.6%)	12 (24%)	0.50
<i>Tinea pedis</i>	12 (17.1%)	11 (22%)	0.80
Striae	8 (11.4%)	0 (0%)	0.02 ^s
Acne	7 (10%)	0 (0%)	0.04 ^{ss}
Pilar keratosis	7 (10%)	3 (6%)	Ns
Contact dermatitis	6 (8.6%)	2 (4%)	Ns
Folliculitis	5 (7.1%)	1 (2%)	Ns
Weak nails syndrome	5 (7.1%)	0 (0%)	0.07
Seborrheic dermatitis	5 (7.1%)	2 (4%)	Ns
Seborrheic keratosis	4 (5.7%)	8 (16%)	Ns
Common wart	4 (5.7%)	4 (8%)	Ns
Plantar keratoderma	3 (4.3%)	3 (6%)	Ns
Hypertrichosis	3 (4.3%)	0 (0%)	Ns
Pioderma gangrenoso	2 (2.9%)	0 (0%)	Ns
Aphtha	2 (2.9%)	0 (0%)	Ns
Amiloidosis	2 (2.9%)	1 (2%)	Ns
Paronychia	2 (2.9%)	1 (2%)	Ns
Sebaceous cyst	2 (2.9%)	2 (4%)	Ns
Telogen effluvium	2 (2.9%)	0 (0%)	Ns
Onycholysis	2 (2.9%)	0 (0%)	Ns
Fibroma	2 (2.9%)	0 (0%)	Ns
Herpes lesion	2 (2.9%)	1 (2%)	Ns
Hidrocystoma	2 (2.9%)	0 (0%)	Ns

*OR=34.6; 95%CI=4.5–265.7. **OR=3.3; 95%CI=1.1–9.7. ^sOR=13.7; 95%CI=0.77–243. ^{ss}OR=11.2; 95%CI=0.66–214.0.

Two cases of pyoderma gangrenosum were recorded in male patients, one in UC and another in CD ($p=0.50$). Abnormalities in skin and nails were more frequent in IBD patients (42/70; 60%) than controls (2/50; 4%) with $p<0.0001$. Skin lesions secondary to treatment, such as xerosis and eczema, were more frequent in IBD patients (27/70; 38.5%) than in controls (9/50; 18%), $p=0.02$. Cases of skin infections, liquenoid eruptions, and granulomatous reactions were similar in both groups (all $p=ns$).

DISCUSSION

Our findings indicated a higher prevalence of dermatoses in patients with IBD than in the control population. The main skin findings in patients with IBD were alopecia, xerosis, striae, and acne.

When grouped according to the underlying pathophysiological process, those associated with malnutrition and secondary to the used treatment were prominent. Striae and acne are well-known undesirable effects of glucocorticoid treatment⁹, although this association could not be demonstrated in this study. This may have happened because of the low number of individuals using glucocorticoid in this sample and by the cross-sectional design of the study, which did not consider the previous use of this medication. Striae were found to be more common in those with CD than in those with UC. It is possible that this has happened because UC patients may benefit from topical use of this medication, decreasing its systemic use¹⁰.

In the present study, acne was associated with anti-TNF- α therapy and azathioprine use, but only anti-TNF- α was independently associated with this skin lesion. This association has also been found by others¹¹. Curiously, this medication has beneficial results in acne manifestations from SAPHO syndrome¹².

Table 2. Dermatological lesions according to inflammatory bowel disease subtype and gender.

	Crohn's disease (n=20)	Ulcerative colitis (n=50)	p-value
Alopecia	10 (50%)	19 (38%)	0.8
Xerosis	6 (30%)	13 (26%)	0.65
Acne	4 (20%)	3 (6%)	0.18
Striae	5 (25%)	3 (6%)	0.03 ^a
Onychomycosis	4 (20%)	9 (18%)	0.98
<i>Tinea pedis</i>	5 (25%)	7 (14%)	0.30
	Females (n=45)	Males (n=25)	
Alopecia	24 (53.3%)	5 (20%)	0.01 ^b
Xerosis	12 (26.6%)	7 (28%)	0.9
Acne	3 (6.6%)	4 (16%)	0.40
Striae	4 (8.8%)	4 (16%)	0.44
Onychomycosis	6 (13.3%)	7 (28%)	0.19
<i>Tinea pedis</i>	5 (11.1%)	7 (28%)	0.38

^aOR=5.2; 95%CI=1.1–24.4. ^bOR=4.5; 95%CI=1.4–14.3). n: number.

Table 3. Skin lesions in inflammatory bowel disease patients according to the use of prednisone and anti-TNF- α .

	With prednisone (n=7)	Without prednisone (n=63)	p-value
Alopecia	3 (42.8%)	26 (41.2%)	1.00
Xerosis	1 (14.2%)	18 (28.5%)	0.66
Acne	2 (28.5%)	5 (7.9%)	0.14
Striae	1 (14.2%)	7 (11.1%)	1.00
Onychomycosis	0	13 (20.6%)	0.33
<i>Tinea pedis</i>	0	12 (19.0%)	0.34
	With anti-TNF- α (n=14)	Without anti-TNF- α (n=56)	
Alopecia	6 (42.8%)	23 (41.0%)	0.90
Xerosis	3 (21.4%)	16 (28.5%)	0.74
Acne	4 (28.5%)	3 (5.3%)	0.02*
Striae	3 (21.4%)	5 (8.9%)	0.19
Onychomycosis	2 (14.2%)	11 (19.6%)	1.00
<i>Tinea pedis</i>	2 (14.2%)	10 (17.8%)	1.00
	With azathioprine (n=24)	Without azathioprine (n=46)	
Alopecia	10 (41.6%)	19 (41.3%)	0.97
Xerosis	7 (29.1%)	12 (26.0%)	0.78
Acne	5 (20.8%)	2 (4.3%)	0.04**
Striae	4 (16.6%)	4 (8.6%)	0.43
Onychomycosis	3 (12.5%)	10 (21.7%)	0.51
<i>Tinea pedis</i>	5 (20.8%)	7 (15.2%)	0.73

*OR=7.06; 95%CI=1.3-36.5. **OR=5.7; 95%CI=1.03-32.5. n: number.

No descriptions of the association of acne with azathioprine use have been found in the literature.

Another important dermatological manifestation was alopecia, which was more common in females (82.7% of IBD patients). The occurrence of alopecia in IBD has been reported in a previous study¹³, but in this study, it is possible to highlight that its prevalence is higher in females than in males. Immunosuppression and/or use of aminosalicylates, nutritional deficiencies of vitamin B12, iron, and zinc may have also contributed to this finding^{13,14}. Unfortunately, micronutrients were not measured in this study, precluding any conclusion on their etiology. Hair is important to a patient's corporal image, and alopecia may have a negative impact on an individual's quality of life, influencing social relationships and self-esteem. These harmful effects are usually more prevalent and important in females¹⁵.

The occurrence of xerosis cutis could have been caused by many factors. Use of drugs such as anti-TNF-alpha may play a role, although it was not possible to prove this association in the present study. Cleynen et al.¹⁶ found xerosis cutis occurred in 10.6% of their IBD patients who used anti-TNF-alpha for a median time of 1.0 year. Nutritional aspects could also

contribute to this finding, as xerosis has been a common finding in the skin of patients with anorexia nervosa¹⁷ and in those undergoing bariatric surgery¹⁸. Skin dryness causes pruritus, which favors abrasions and increases the risk of skin infections¹⁷.

Finally, reactive skin lesions were found in two patients (2.8% of the sample), both of whom had pyoderma gangrenosum. Pyoderma gangrenosum is an autoinflammatory, chronic, and ulcerating condition that may have harmful effects that usually appears in those with severe bowel disease¹⁹. Pyoderma gangrenosum is regarded as a skin lesion associated with UC and more common in females^{4,20}, but in this study, one of the patients had CD, and both were males. In patients with CD, pyoderma gangrenosum prevalence has been estimated to be 0.7%²¹.

None of the patients in the present study had EN, although it is considered the most common form of reactive lesion in IBD²¹.

This study is limited by the small number of patients recruited and its cross-sectional design. However, it is important in that it is the first to report the prevalence of skin lesions in Brazilian patients with IBD.

In conclusion, in this study, there was a high prevalence of skin lesions in the Brazilian IBD patients. Additionally, alopecia,

xerosis, striae, and acne were more common in IBD patients than in the control group.

AUTHORS' CONTRIBUTIONS

TMS: Conceptualization, Data curation, Investigation, Writing – original draft. **MK:** Conceptualization, Data curation,

Investigation, Writing – original draft. **KSMP:** Conceptualization, Data curation, Investigation, Writing – original draft. **ORJ:** Conceptualization, Data curation, Investigation, Writing – original draft. **TS:** Conceptualization, Methodology, Formal Analysis Writing – original draft. **RN:** Project administration, Supervision, Formal Analysis, Writing – original draft, Writing – review & editing.

REFERENCES

- Pagani K, Lukac D, Bhukhan A, McGee JS. Cutaneous manifestations of inflammatory bowel disease: a basic overview. *Am J Clin Dermatol.* 2022;23(4):481-97. <https://doi.org/10.1007/s40257-022-00689-w>
- Quaresma AB, Damiao AOMC, Coy CSR, Magro DO, Hino AAF, Valverde DA, et al. Temporal trends in the epidemiology of inflammatory bowel diseases in the public healthcare system in Brazil: a large population-based study. *Lancet Reg Health Am.* 2022;13:100298. <https://doi.org/10.1016/j.lana.2022.100298>
- Lichtenstein GR, Shahabi A, Seabury SA, Lakdawalla DN, Espinosa OD, Green S, et al. Increased lifetime risk of intestinal complications and extraintestinal manifestations in Crohn's disease and ulcerative colitis. *Gastroenterol Hepatol.* 2022;18(1):32-43. PMID: 35505770
- Antonelli E, Bassotti G, Tramontana M, Hansel K, Stingeni L, Ardizzone S, et al. Dermatological manifestations in inflammatory bowel diseases. *J Clin Med.* 2021;10(2):364. <https://doi.org/10.3390/jcm10020364>
- Keyal U, Liu Y, Bhatta AK. Dermatologic manifestations of inflammatory bowel disease: a review. *Discov Med.* 2018;25(139):225-33. PMID: 29906405
- Chun JY, Kang B, Lee YM, Lee SY, Kim MJ, Choe YH. Adverse events associated with azathioprine treatment in Korean pediatric inflammatory bowel disease patients. *Pediatr Gastroenterol Hepatol Nutr.* 2013;16(3):171-7. <https://doi.org/10.5223/pghn.2013.16.3.171>
- Maaser C, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V; European Crohn's and Colitis Organization [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR guideline for diagnostic assessment in IBD Part 1: initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis.* 2019; 13(2): 144-64. <https://doi.org/10.1093/ecco-jcc/jjy113>.
- Gupta V, Sharma VK. Skin typing: fitzpatrick grading and others. *Clin Dermatol.* 2019;37(5):430-6. <https://doi.org/10.1016/j.clindermatol.2019.07.010>
- Longui CA. Glucocorticoid therapy: minimizing side effects. *J Pediatr.* 2007;83(5 Suppl):S163-77. <https://doi.org/10.2223/JPED.1713>
- Bruscoli S, Febo M, Riccardi C, Migliorati G. Glucocorticoid therapy in inflammatory bowel disease: mechanisms and clinical practice. *Front Immunol.* 2021;12:691480. <https://doi.org/10.3389/fimmu.2021.691480>
- Khatana UF, Qamar A, Ashfaq MB. Infliximab-associated acneiform eruption in a patient with inflammatory bowel disease. *Cureus.* 2021;13(9):e18213. <https://doi.org/10.7759/cureus.18213>
- Garcovich S, Amelia R, Magarelli N, Valenza V, Amerio P. Long-term treatment of severe SAPHO syndrome with adalimumab: case report and a review of the literature. *Am J Clin Dermatol.* 2012;13(1):55-9. <https://doi.org/10.2165/11593250-000000000-00000>
- Shah R, Abraham B, Hou J, Sellin J. Frequency and associated factors of hair loss among patients with inflammatory bowel disease. *World J Gastroenterol.* 2015;21(1):229-32. <https://doi.org/10.3748/wjg.v21.i1.229>
- Shohdy KS, Rashad W, Elmeligui A. Alopecia universalis associated with ulcerative colitis and the role of azathioprine. *Middle East J Dig Dis.* 2018;10(1):50-4. <https://doi.org/10.15171/mejdd.2017.91>
- Quirino, LM. Health-related quality of life of men and women with androgenetic alopecia undergoing low-level light therapy. Brazil: Universidade Federal de Uberlândia; 2022. Available from: <https://repositorio-dev.ufu.br/handle/123456789/29537>
- Cleyen I, Moerkercke W, Billiet T, Vandecandelaere P, Vande Castele N, Breynaert C, et al. Characteristics of skin lesions associated with anti-tumor necrosis factor therapy in patients with inflammatory bowel disease: a cohort study. *Ann Intern Med.* 2016;164(1):10-22. <https://doi.org/10.7326/M15-0729>
- Strumia R, Varotti E, Manzato E, Gualandi M. Skin signs in anorexia nervosa. *Dermatology.* 2001;203(4):314-7. <https://doi.org/10.1159/000051779>
- Tavarela Veloso F. Review article: skin complications associated with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2004;20:50-3. <https://doi.org/10.1111/j.1365-2036.2004.02055.x>
- Hasan NA, Freije A, Abualseel A, Al-Saati H, Perna S. Effect of bariatric surgery on weight loss, nutritional deficiencies, postoperative complications and adherence to dietary and lifestyle recommendations: a retrospective cohort study from Bahrain. *Sultan Qaboos Univ Med J.* 2020;20(3):e344-51. <https://doi.org/10.18295/squmj.2020.20.03.015>
- Harbord M, Annese V, Vavricka SR, Allez M, Barreiro-de Acosta M, Boberg KM, et al. The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis.* 2016;10(3):239-54. <https://doi.org/10.1093/ecco-jcc/jjv213>
- Thrash B, Patel M, Shah KR, Boland CR, Menter A. Cutaneous manifestations of gastrointestinal disease: part II. *J Am Acad Dermatol.* 2013;68(2):211.e11-33. <https://doi.org/10.1016/j.jaad.2012.10.036>

