ORIGINAL ARTICLE

INFLAMMATORY BOWEL DISEASE AND ASSOCIATED SKIN MANIFESTATIONS

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Background: Inflammatory bowel disease (IBD) is a group of chronic inflammatory conditions of the gastrointestinal tract. Skin manifestations are frequently found with IBD yet they are not completely comprehended regarding how common they are and whether they reflect the seriousness of disease. Objective was to determine the prevalence, type and treatment of skin recall manifestations among a cohort of patients with CD and ulcerative colitis (UC). **Methods:** A total of 250 IBD patients (140 CD and 110 UC) were enrolled in the study. Demographics of patients, disease duration, skin morphology were enrolled. We evaluated the frequency of skin manifestations, their association with disease activity, and course in response to therapy. **Results:** Skin manifestations appeared in 31.2% of patients, and were more prevalent in CD (35%) compared to UC (26%) (p=0.04). The most common skin manifestations were erythema nodosum (11.2%), pyoderma gangrenosum (5.6%), and perianal skin tags (8%). Active disease demonstrated a significant association with skin manifestations (45% active disease vs 18% remission, p<0.001). Patients receiving anti-TNF therapy had fewer new skin manifestations (20%) when compared to patients receiving conventional therapy (36%) (p=0.03), however 5% of patients receiving biologic therapy reported developing paradoxical skin reactions. Management of skin manifestations consisted mainly of systemic corticosteroids therapy, which was effective in 80% of cases, while 10% of patients with more severe perianal disease underwent surgical intervention to treat their skin manifestations. **Conclusion:** Skin manifestations appear to be common in patients with IBD, and a significant difference was observed between patients with CD and UC. The disease activity showed a strong association with the occurrence of skin manifestations. Anti-TNF therapy is likely to be associated with less frequent new skin manifestation, however it remains substantive that patients with biologic therapy can have paradoxical skin reactions.

Keywords: Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; Skin manifestations

Citation: Ghani U, Ahmed M, Omar J, Butt AI, Nayeem A, Qayyum Z. Inflammatory bowel disease and associated skin manifestations. J Ayub Med Coll Abbottabad 2024;36(3):616–20.

DOI: 10.55519/JAMC-03-13956

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) as part of Inflammatory Bowel Disease (IBD) are deteriorating inflammatory diseases affecting the gastrointestinal tract which have a multifactorial origin including genetic predisposition and immunological responses to the environment. Apart from primarily gastrointestinal symptoms, a considerable number of patients present with extraintestinal manifestations that can involve virtually any organ of the body, including the skin. Skin signs in IBD are not innocent eyewitnesses but may be the presenting features and parts of the three important types of IBD. More recent studies have attempted to clarify the relationship between IBD and skin symptoms and have demonstrated the need for comprehensive and coordinated therapy of the gastrointestinal tract and skin condition of the patients.[1,2]

Recent studies have advanced the existing knowledge of IBD skin lesions in regard to frequency, aetiology, and relevance. Skin manifestations of IBD are quite varied and include erythema nodosum, pyoderma gangrenosum and different forms of vasculitis. Erythema nodosum, which is manifested as tender, erythematous, nodules located predominantly on the lower extremities, is one of the most frequently reported dermatological manifestations of IBD. It is associated with the presence of active disease and its severity in most instances and its course is paralleled with that of the underlying IBD.[3] In the same way, pyoderma gangrenosum is a comparatively rare but serious condition manifesting with painful ulcers that is becoming more recognized as a major extra-intestinal association with IBD, including Crohn's disease in particular.[4]

Still, other, cutaneous disorders like vasculitis and psoriasis and lichenoid drug reactions

further make up the clinical picture of patients with IBD. These manifestations may not only deteriorate the quality of patients' life but also influence the treatment process and impose the need for a polymodal approach to the management of this pathology as cited in Zhao *et al*., 2024.[5] New discoveries regarding the dermatological literature have described the immunologic processes responsible for these skin manifestations, particularly immune dysregulation and systemic inflammation.[6]

The research in the last few years has mainly concentrated on the effect of newer therapeutic agents in IBD and skin diseases related to it. That is why biologic therapies that aim at modifying certain inflammatory processes can be efficient in treating both gastrointestinal and cutaneous manifestations. These approaches include the use of JAK inhibitors and anti-TNF agents that have improved the methods of handling complicated cases that cannot be effectively handled through traditional treatment techniques.[7] In additional, only recent studies have suggested that management of skin lesions can be used as an indicator of disease activity and therapeutic response in IBD patients.[8]

Skin lesions often have a significant impact on patient's quality of life through developing psychological issues and causing discomfort. Managing skin lesions in IBD is quite complex because it may not always be treated with therapy used in the treatment of IBD. The knowledge gap concerning IBD and associated skin manifestations is due to the fact that most studies investigating IBD are based primarily on IBD's gastrointestinal symptoms with more limited attention given to cutaneous symptoms.[9,10] It is envisaged that the findings of this study will improve the diagnosis, management and clinical outcomes of IBD through advancing knowledge of the relationship between inflammation and dermatological manifestations.

MATERIAL AND METHODS

This descriptive cross-sectional study was planned to determine incidence and pattern of skin changes in IBD. The study was conducted in a period of three years from January 2021 to January 2024 in the departments of Gastroenterology, Medicine and Dermatology Mohtarma Benazir Bhutto Shaheed Medical College, Mirpur AJK. The study was started after taking ethical approval from hospital ethics committee. All the patients fulfilling inclusion exclusion criteria were briefly described about the study procedure and purpose and informed written consent was taken. Any participant recruited into the study had their consent taken before they agreed to participate in the study.

Patients diagnosed with Inflammatory Bowel Disease inclusive of Crohn's Disease as well as Ulcerative Colitis were enrolled in the study. The patients having age 25–65 years, and of both genders having clinical, endoscopic, and histopathological confirmation of the IBD were selected for the study sample. The exclusion criteria included patients with other dermatologic conditions, not related to IBD, the patients on immunosuppressive medications for conditions other than IBD and the patients who refused to participate in the study. Sample size estimation was done using WHO sample size calculator with 95% confidence level, and anticipated population proportion, rate of skin manifestations in IBD patients of 20.3%, with absolute precision level of 5%. The total sample size turned out to be 250 patients.

For the Clinical Assessment, a Closed ended question was used to obtain information on the demographic characteristic of respondent including; age, gender, duration of disease, history of IBD in the family, type of disease (Crohn's Disease or Ulcerative Colitis), disease duration, degree of IBD severity, and the treatment the patient.

All the participants were subjected to a dermatological examination by the certified dermatologist after the medical examination. Skin lesions were grouped as IBD-associated which include pyoderma gangrenosum, erythema nodosum and those that are not specific to IBD like psoriasis, eczema. Skin biopsy was done wherever required. Patients' permission was sought to take photographs of the skin lesions. The IBD activity was also evaluated using the scoring systems, that is the CDAI for Crohn's Disease and the Mayo Score for Ultraerative Colitis.

The data were entered into and analyzed through SPSS v. 25. Categorical data was summarized by frequency and percentages and quantitative data was presented with mean±SD. Chi-square test and Fisher's exact were used to analyze categorical data while continuous which data was compared using t-test depending on the distribution of data. For statistical analysis of data, A p-value of < 0.05 was used as the cut off point for statistical significance.

RESULTS

A total of 250 patients diagnosed with Inflammatory Bowel Disease (IBD) were included in the study, comprising 140 patients with Crohn's Disease (CD) and 110 with Ulcerative Colitis (UC). The median age of the cohort was 38 years (range 18-65), with a slight female predominance (54%). The mean disease duration was 6.5 years (Table 1).

Among the total IBD patients, 78 patients (31.2%) exhibited at least one skin manifestation. Of these, 49 patients (62.8%) had Crohn's Disease, while 29 (37.2%) had Ulcerative Colitis. The prevalence of skin

manifestations was significantly higher in patients with Crohn's Disease (35%) compared to Ulcerative Colitis (26%), p=0.04. The most common skin manifestations observed were erythema nodosum (EN) in 28 patients (11.2%), pyoderma gangrenosum (PG) in 14 patients (5.6%), and perianal skin tags in 20 patients (8%). Less common manifestations included aphthous ulcers (4%), psoriasis (3%), and hidradenitis suppurativa (2%). There was a statistically significant association between Crohn's Disease and perianal skin tags (p<0.01) (Table 2).

A strong correlation was noted between disease activity and the presence of skin manifestations. Patients with active disease were more likely to have skin involvement (45% in active disease vs. 18% in remission, p<0.001). Erythema nodosum and pyoderma gangrenosum were predominantly observed during active disease flares, while perianal skin tags were more commonly associated with longstanding disease (Table 3).

The study found that patients on anti-TNF therapy (infliximab or adalimumab) had a reduced frequency of new skin manifestations (20%) compared to those on conventional therapies (35%), p=0.03. However, a small subset (5%) of patients on biologic therapy developed paradoxical skin reactions, including psoriasiform rashes (Table 4).

Skin manifestations were recurrent in 25% of the patients. Management strategies varied, with systemic corticosteroids being the most commonly used treatment for erythema nodosum and pyoderma gangrenosum, resulting in partial or complete resolution in 80% of cases. Surgical intervention was required in 10% of patients with severe perianal disease (Table 5).

Table-1: Patient demographics and disease characteristics

Characteristic	Crohn's Disease (n=140)	Ulcerative Colitis (n=110)	Total (n=250)
Median Age (years)	39 (18–65)	37 (18–65)	38 (18–65)
Female (%)	55%	53%	54%
Mean Disease Duration (years)	7.0	5.8	6.5
Active Disease (%)	45%	40%	43%

Table-2: Prevalence and types of skin manifestations in IBD patients

Skin Manifestation	Crohn's Disease (n=140)	Ulcerative Colitis (n=110)	Total (n=250)	*p*-value
Erythema Nodosum (%)	16 (11.4%)	12 (10.9%)	28 (11.2%)	0.75
Pyoderma Gangrenosum (%)	9 (6.4%)	5 (4.5%)	14 (5.6%)	0.45
Perianal Skin Tags (%)	16 (11.4%)	4 (3.6%)	20 (8%)	<0.01
Aphthous Ulcers (%)	6 (4.3%)	4 (3.6%)	10 (4%)	0.68
Psoriasis (%)	5 (3.6%)	3 (2.7%)	8 (3%)	0.54
Hidradenitis Suppurativa (%)	4 (2.9%)	1 (0.9%)	5 (2%)	0.22
Any Skin Manifestation (%)	49 (35%)	29 (26%)	78 (31.2%)	0.04

Table-3: Correlation between disease activity and skin manifestations

Disease Activity	Patients with Skin Manifestations (n=78)	Patients without Skin Manifestations (n=172)	*p*-value
Active Disease	35(45%)	31 (18%)	<0.001
Remission	14(18%)	141 (82%)	

Table-4: Impact of medication on skin manifestations

Medication Type	Patients with Skin Manifestations (n=78)	*p*-value
Anti-TNF Therapy (Infliximab, Adalimumab)	16 20.51%)	0.03
Conventional Therapy	27 (34.61%)	
Paradoxical Reactions (Biologic Therapy)	4 (5%)	

Table-5: Management of Skin Manifestations

Management Strategy	Frequency (%)	Resolution Rate (%)
Systemic Corticosteroids	62 (79.49%)	80%
Surgical Intervention (for perianal disease)	8 (10.25%)	-
Recurrence of Skin Manifestations	20 (25.64%)	-

DISCUSSION

The paper aims to provide an overview of skin manifestations in inflammatory bowel disease (IBD) population, focusing on Crohn's disease (CD) and ulcerative colitis (UC) with particular reference to frequency, distribution and types. Skin involvement is a common problem of IBD patients, as identified in the present study where 30% of the participants reported clinically relevant skin issues. This calls for doctors to accept that extraintestinal manifestations for IBD are inevitable because what may be manifesting on the

skin can actually provide information on the severity and activity of the related gastrointestinal disease.[11]

Another important finding in this study is the skin manifestations showed an increased incidence of 35% in Crohn's Disease patients than in the 26% of the Ulcerative Colitis patients (p=0.04). This is in line with other investigations, as more frequent connection of CD with extraintestinal manifestations such as dermatologic disorders.[12] Perhaps one of the reasons for such variations might be the transmural involvement of CD which leads to a systemic inflammation and tissue destruction so disease manifestations are more severe extra-intestinal. UC is diagnosed in mucosa, though less intensely affected, and therefore skin symptoms may not be quite typical. Therefore, assessment of the patient with CD presenting dermatologic symptoms is recommended for clinicians as it may demonstrate active or severe disease processes.[13]

The skin manifestations most often diagnosed were EN, PG, and perianal skin tags. For example, it was established that EN was identified in 11.2% of the patients, which is the most common skin lesion in this population, compared to perianal skin tags, observed in 8% of the patients, as well as PG, diagnosed in 5.6% of the cases. This correlation between the activity of systemic inflammation and skin manifestation is supported by levels of EN and PG raised during active disease phases. Relapses are characteristic of both conditions and may be utilized as markers for increased disease activity, according to current knowledge. These figures (45% skin manifestations in active disease, 18% in remission, p<0.001) clearly indicate that controlling disease activity reduces the risk of developing extraintestinal complications. In addition, it is worthy to underscore that the association of perianal skin tags with long-standing disease is more evident in this population; though Crohn's Disease is less common compared with UC, it has more frequent and severe perianal involvement.[14,15]

The study also gives useful information on the usage of these skin conditions in therapy. Patients treated with anti-TNF therapy including infliximab and adalimumab had a significantly lower prevalence of newly developed skin lesions 20% compared with concomitant treatments 35% indicating protective effects of biologic therapy against some forms of EM. This might be because of the drug's anti-inflammatory actions that are systemic and not just limited to the gastrointestinal organs, but other organs such as the skin are well known to be affected as well when disease activity is being subdued.[16] Nevertheless, the well-known development of paradoxical skin reactions in 5% of patients on biologic therapy, like psoriasis form rashes is the indicator of the complexity of the biologic therapy. Hypersensitivity reactions can be paradoxical and are a recognized complication which may require modification or cessation of therapy.[17,18]

Skin complications in IBD in general, and especially in PG and perianal disease, are difficult to manage; systemic corticosteroids were used in this study as the main approach. The effectiveness of corticosteroids and the overall clinical outcomes with the management of EN or PG are highly satisfactory where 80% of treated patients had partial or complete response; meanwhile the 10% of patients that required surgical intervention for their perianal disease suggest that better management strategies are warranted where other interventions fail. This is true even for uncomplicated psychiatric, musculoskeletal, or neurological disease for which surgeons, psychiatrists, physiotherapists, and neurologists could be of great value depending on impact and course of the illness.[19,20]

The observed characteristics of the patients correlate with the IBD course marked by relapses, as skin lesions were identified in 25% of the patients at some point after the initial treatment. Cutaneous inflammation, presumably independently of clinical activity, may be thought to account for skin disease chronicity and relapse. Based on this finding, it may be necessary to subject patients to maintenance therapy to reach optimal remission so that no recurrent skin manifestation is likely to occur.[21] These findings also highlight the need for additional research on the long-term management of a population of IBD patients who experience recurrent skin manifestations and raise questions about the possible use of novel therapeutic approaches that may hint at the simultaneous control of extra-intestinal and intestinal aspects of the illness.[22]

Since skin manifestations of IBD significantly impacted the lives of CD patients, we assessed the impact of these skin manifestations on these patients as well. Considering the aforementioned elements, one may draw the conclusion that in order to eradicate these drawbacks, effective outcome-oriented techniques, maintenance of the state of remission, and control over disease activity and skin involvement are necessary. Although biologic therapy appears to reduce the frequency of cutaneous manifestations, they should still be carefully monitored as they may manifest as paradoxical reactions. Research on IBD skin lesions is also necessary, including how to prevent them over an extended length of time and how they affect the quality of life for those who have the disease.

A large sample size and the comparison of CD and UC are among the article's strengths, as they are helpful in providing a broad picture of prevalence

and treatment options. Through a comparison between anti-TNF therapy and conventional treatments, it highlights a strong association between disease activity and skin symptoms and provides helpful information on the practical management of these implications. However, because the current study is cross-sectional, it is unlikely to make any inferences about causality. Because it is a single-center study, its significance to the general community may also be limited. There was no information provided regarding the modality's potential for long-term management, and the study only assessed anti-TNF therapy without evaluating any other biologic treatments.

CONCLUSION

In conclusion, skin lesions are a common extraintestinal symptom of IBD, especially in CD, and they typically show an association with disease activity. Although biologic regimens have paradoxical skin side effects, they may be helpful in regulating the course of the disease and in suppressing IBD, which may help reduce these issues. Therefore, in order to obtain better outcomes, it is critical to have appropriate treatment and effective management measures that prevent the condition from relapsing. Further research is needed on this topic as well as the influence of skin lesions on quality of life and long-term care in IBD patients.

AUTHORS' CONTRIBUTION

UG, MA: Concept, Proof reading. AN, ZQ: Data collection, analysis, interpretation.

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Submitted: May 21, 2024	*Revised: -*	*Accepted: September 26, 2024*

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