Natural history and progression risk factors of ulcerative proctitis: a retrospective study from a single tertiary centre in Poland

Katarzyna Gaweł[1,2], Krzysztof Dąbkowski[1,2], Iwona Zawada[1,2], Magdalena Szczygłowska[2], Marta Zykowska[2], Wojciech Marlicz[1,2], Teresa Starzyńska[1,2]

[1]Gastroenterology Department, Pomeranian Medical University, Szczecin, Poland
[2]Pomeranian Medical University, Szczecin, Poland

Address for correspondence: Katarzyna Gaweł MD, Gastroenterology Department, Pomeranian Medical University, 1 Unii Lubelskiej St, 71-252 Szczecin, Poland, phone +48 914253211, e-mail: ka.gawel88@gmail.com

Abstract

Introduction: Ulcerative proctitis is a chronic disease, characterized by lower risk of complications and less aggressive treatment in comparison to other forms of ulcerative colitis. Therefore, the key issue is to predict the natural course of the disease and protect against proximal spread of inflammatory lesions in the future.

Aim: To identify risk factors for progression of ulcerative proctitis and investigate the natural history of the disease.

Material and methods: We performed a retrospective study and included patients with ulcerative proctitis, diagnosed between January 2010 and December 2020, who suffered from ulcerative proctitis for at least 1 year. The collected data were then subjected to statistical analysis.

Results: We identified 116 cases of ulcerative proctitis in patients aged between 19 and 84 years. Proximal extension of the disease occurred in 65 (56%) people – left sided colitis developed in 55 (85%) and pancolitis in 10 (15%) patients. We detected many progression risk factors of ulcerative proctitis, among which the most meaningful were Mayo Endoscopic Score at levels 2 and 3 at onset ($p < 0.05$), high stress level ($p < 0.05$), more than one exacerbation in the first year of the disease ($p < 0.05$), and the use of systemic glucocorticosteroids during exacerbations in mild-to-moderate activity of the disease ($p < 0.05$).

Conclusions: According to our study, early identification of progression risk factors in ulcerative proctitis is crucial for the future outcomes of the disease. The proper treatment at onset is relevant in preventing the progression of inflammatory lesions and the development of disease complications.

Introduction

Ulcerative colitis (UC) is a non-specific inflammatory bowel disease of unknown aetiology characterized by periods of exacerbation and remission. It usually affects young people aged between 20 and 40 years, with equal frequency in men and women. The pathogenesis of ulcerative colitis is still not fully understood, but it is known that immunological, environmental, and genetic factors are involved. Despite new methods of treatment, including innovative biological therapy, ulcerative colitis is still an incurable disease, requiring medication to achieve and maintain remission, often throughout life [1–3]. Ulcerative colitis has negative psychological consequences, and it adversely affects professional and social life of patients, significantly reducing its quality [4]. UC typically starts with the rectum (ulcerative proctitis – UP), being diagnosed at this stage in 25–50% of patients [5]. The natural history of ulcerative proctitis has not been fully understood so far – in some patients the inflammatory lesions progress to the left-sided colitis or pancolitis, while in others the disease has a mild course and the extent of lesions remains limited to the rectum [6, 7]. It is said that patients with inflammatory lesions exceeding the rectum are at greater risk of developing UC complications with the need for glucocorticosteroids, immunosuppressive drugs, and biological and surgical treatment [8–10]. For this reason, it is important to be able to predict the course of ulcerative proctitis at the time of diagnosis [11]. Little research on

progression risk factors in ulcerative proctitis has been carried out, the available data are still scarce, and none of the studies have concerned the Polish population. Knowledge of the extent of inflammatory lesions in ulcerative proctitis is necessary to determine the appropriate therapeutic strategy and to estimate the risk of colectomy in the future [2, 8, 11].

Aim

The aim of the study was to identify risk factors for the progression of ulcerative proctitis and investigate the natural history of the disease, taking into account the following parameters: sex, age, body mass index (BMI), type of treatment, endoscopic activity of the disease at diagnosis, smoking, pregnancy, past infections, the patient's knowledge and awareness of the disease, the number of exacerbations per year, family history of inflammatory bowel diseases (IBD), place of residence, occupation, severity of stress, and personality disorders. Many of these factors have not been studied yet.

Material and methods

This is a retrospective study, which included 116 patients – 75 females and 41 males with ulcerative proctitis, aged between 19 and 84 years, diagnosed in the Gastroenterology Department of Pomeranian Medical University in Szczecin (Poland) from January 2010 to December 2020, who suffered from ulcerative proctitis for at least one year. The average time of follow-up from the diagnosis was 7 years and 6 months. All patients agreed to participate in the study. The study did not require consent from the Bioethics Committee.

The study consisted of the analysis of medical documentation, including endoscopic and histopathological examinations, data collected using the author's questionnaire, the Perceived Stress Scale (PSS-10), and the Polish adaptation of the Ten-Item Personality Inventory (TIPI-Pl) questionnaire. We also used the Simple Clinical Colitis Activity Index (SCCAI) to assess clinical disease activity and the Mayo Endoscopic Score to assess endoscopic activity of the disease.

The author's questionnaire comprised 54 questions divided into 3 periods of the patient's life: before the diagnosis of UP, at the time of the diagnosis of UP, and after the diagnosis of UP. The PSS-10 scale, which consists of 10 questions including subjective feelings related to various events and problems in personal life and methods of coping with them in the last month, was used to assess the intensity of perceived stress. Respondents rated their answers on a scale from 0 to 4, where 0 means never, 1 – almost never, 2 – sometimes, 3 – often, and 4 – very often. The obtained result is the sum of all points collected, which ranges from 0 to 40.

A higher result correlates with greater intensity of stress experienced [12, 13]. The TIPI-Pl was used to measure personality disorders in patients with ulcerative proctitis. This is the most popular and the shortest tool for measuring the "Big Five" personality model, which includes 5 basic personality dimensions: extraversion, agreeableness, conscientiousness, emotional stability, and openness to experience. Respondents rated their answers on a scale from 1 to 7, where 1 means strongly disagree, and 7 means strongly agree. The obtained result was the average of 2 items, and one of them was an inverted position [14].

Statistical analysis

The analysis was performed using R software (R Core Team [2022]), version 4.1.3. The obtained results are presented as values of OR parameters with a 95% confidence interval. Kaplan-Meier curves were compared using the log-rank (LR) test. The analysis of the impact of quantitative variables on PFS was performed using the Cox proportional hazards model. The analysis adopted a significance level of 0.05. Thus, all p-values below 0.05 were interpreted as significant associations.

Results

The average duration of the disease was 7.62 years (SD = 4.78) and ranged from 2 to 23 years. The average age at the time of diagnosis was 36.11 years (SD = 15.09) and ranged from 13 to 73 years. Most of the patients were females (65%) (Table I). The time from the first symptoms to the visit to the doctor was on average 2.16 months (SD = 3.69), ranging from 2 days to 24 months, and the time from the presentation to the diagnosis and the start of treatment was on average 3.35 months (SD = 5.27), ranging from 2 days to 36 months. At the time of the diagnosis almost 45% of patients had moderate and 15% of patients had severe endoscopic disease activity. Progression occurred in 65 out of 116 (56%) patients. Left-sided UC developed in 55 (85%) patients, and extensive UC in 10 (15%) patients. The progression of inflammatory lesions most often occurred during the first 5 years of the disease. We detected many factors that affect the extent of inflammatory lesions in ulcerative proctitis. They can be divided into modifiable, non-modifiable, and partially modifiable factors and are presented in Table II. Factors that reduce the risk of progression in UP were also identified and are presented in Table III.

Discussion

This is the first single-centre study for the Polish population that looked for progression risk factors of inflammatory lesions in ulcerative proctitis. Many of them have

been detected for the first time and constitute a new discovery in this topic. However, the risk factors such as presence of extraintestinal symptoms, the use of glucocorticoids and immunosuppressants, and moderate and high endoscopic inflammatory activity at onset are consistent with the results obtained in the studies carried out by Farmer, Meucci, Anzai, and Huguet *et al.* [5, 9, 15, 16]. It is worth adding that progression risk factors in UP, established in the above-mentioned studies, which include young age at diagnosis, BMI, male sex, and smoking cigarettes, were not confirmed in our research, which may be due to population differences; previous studies looked at Italian, Spanish, Belgian, Swedish, American, Korean, and Japanese populations. Our study also confirmed that the use of systemic glucocorticosteroids, both in the first flare of the disease and in exacerbations in mild-to-moderate UP, is a significant risk factor for the progression of ulcerative proctitis [5, 9, 16]. However, no such trend was observed for budesonide. Of the 65 patients who experienced progression, 42 received systemic glucocorticosteroids in the first exacerbation, but only 10 of them had endoscopic disease activity rated at level 3 on the Mayo Endoscopic Score. Our study also showed that the use of oral, not topical, mesalamine increases the risk of progression. The use of suppositories at the time of diagnosis reduces that risk by almost 60%, while the use of oral mesalamine increases the risk of progression 2.5-fold. The exact explanation of this phenomenon is not clear; however, this finding underlines the need to follow the guidelines, which recommend rectal mesalamine as a basic treatment for ulcerative proctitis [1, 2]. It is worth mentioning that the progression of inflammatory lesions in UP occurred more often in patients with endoscopic disease activity at the time of diagnosis defined on the Mayo Endoscopic Score at levels 2 and 3 and is consistent with the results confirmed by Walsh *et al.* [17]. Based on our study results, a type of patient with ulcerative proctitis, in whom progression of inflammatory lesions should be expected in the future, can be created. This is the patient who delays a visit to the doctor because of symptoms, with late treatment included and constantly active inflammation despite the use of drugs, with endoscopic disease activity assessed on the Mayo Endoscopic Score as 2 or 3 and the extent of inflammatory lesions in the rectum > 5 cm at the time of diagnosis, requiring treatment with systemic glucocorticosteroids and/or immunosuppressive and/or biological drugs, and with more than one exacerbation per year – this is partly consistent with the observations of Meucci *et al.*; other factors were detected in our study for the first time [5]. Our study also indicates the significant role of patient education in preventing progression of inflammatory lesions in

Table I. Characteristics of the study population

Chosen features	Median (range) or *n* (%)
Gender: male (%) female (%)	41 (35); 75 (65)
Age [years]	43.07 (19.0–84.0)
Symptoms at onset:	
Constipation (*n* = 25)	4 (16)
Diarrhoea (*n* = 90)	60 (67)
Abdominal pain (*n* = 60)	39 (65)
Weight loss (*n* = 31)	23 (74)
Extraintestinal symptoms (*n* = 24)	20 (83)
Endoscopic severity at onset:	
Mayo 2 (*n* = 51)	44 (86)
Mayo 3 (*n* = 17)	16 (94)
Extent of inflammatory lesions at onset:	
< 5 cm (*n* = 22)	5 (23)
> 5 cm (*n* = 94)	60 (64)
Current smoking (*n* = 12)	9 (75)
Ever smoking (*n* = 45)	24 (53)
Appendectomy (*n* = 12)	5 (42)
Number of exacerbations in the first year of the disease:	
None (*n* = 51)	6 (12)
1 (*n* = 15)	10 (7)
> 1 (*n* = 50)	49 (98)

ulcerative proctitis. Some of the results obtained in our research differ from the results of other studies. Farmer *et al.*, Langholz *et al.*, Anzai *et al.,* and Roda *et al.* found an association between early age at onset of ulcerative colitis and risk of spreading the disease, which was not confirmed in this study [6, 8, 15, 16].

The use of non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics in remissions is the next risk factor for the UP progression identified in this study. Several cohort and retrospective studies have confirmed the association of NSAIDs with UC exacerbations [18–20]. The overuse of antibiotics has become quite popular in recent years, and in ulcerative colitis excessive and irrational antibiotic therapy carries a risk of exacerbation as well as proximal extension of the inflammatory lesions [21]. Moreover, the use of antibiotics is known to carry an increased risk of *Clostridioides difficile* infection, which may also lead to the development of left-sided or extensive UC.

Our study is the first to evaluate personality disorders and stress as potential risk factors for the progression of ulcerative proctitis. It is thought that patients with inflammatory bowel diseases are more likely to de-

Table II. Progression risk factors of ulcerative proctitis

Factor	Impact on the disease extension	*P*-value
Modifiable factors		
Time from onset of symptoms to seeing a doctor	Each month of delay increases the risk of progression by 21%	< 0.05
Time from seeing the doctor to the diagnosis of the disease and the initiation of treatment	Each subsequent month of delay in starting treatment increases the risk of progression by 23%	< 0.05
The use of oral mesalamine for treatment of the first flare	Increases the risk of progression 5-fold	< 0.05
The use of systemic GCS in a treatment of the first flare in mild-to-moderate UP	Increases the risk of progression 85-fold	< 0.05
The use of oral mesalamine in maintenance therapy	Increases the risk of progression 3-fold	< 0.05
The use of systemic GCS during exacerbations in mild-to-moderate UP	Increases the risk of progression 356-fold	< 0.05
The use of combined contraceptives in remissions	Increases the risk of progression 6-fold	< 0.05
The use of NSAIDs in remissions	Increases the risk of progression 4-fold	< 0.05
The use of antibiotics in remissions	Increases the risk of progression 3-fold	< 0.05
Discontinuation of mesalamine in remissions	Increases the risk of progression 10-fold	< 0.05
Irregular maintenance mesalamine use in remissions	Increases the risk of progression 14-fold	< 0.05
High stress level on the PSS-10 scale	Increases the risk of progression 71-fold	< 0.05
Average openness to experience on the TIPI-Pl scale	Increases the risk of progression 8-fold	< 0.05
Extroversion on the TIPI-Pl scale	Increases the risk of progression 23-fold	< 0.05
Non-modifiable factors		
Diarrhoea at the diagnosis	Increases the risk of progression by 8-fold	< 0.05
Abdominal pain at the diagnosis	Increases the risk of progression 2-fold	< 0.05
Weight loss at the diagnosis	Increases the risk of progression 3-fold	< 0.05
Extraintestinal symptoms, especially joints and eye symptoms at the diagnosis	Increases the risk of progression 5-fold	< 0.05
Mayo 2 at the diagnosis	Increases the risk of progression 54-fold in comparison to Mayo 1	< 0.05
Mayo 3 at the diagnosis	Increases the risk of progression 138-fold in comparison to Mayo 1	< 0.05
Extent ≥ 5 cm in the rectum at diagnosis	Increase the risk of progression 6-fold compared to < 5 cm	< 0.05
SCCAI score at the diagnosis	Each subsequent point increases the risk of progression by 48%	< 0.05
Time until symptoms disappear during first-line treatment	Each additional month of symptoms persists increases the risk of progression by 44%	< 0.05
The appearance of extraintestinal symptoms, especially joints and eye symptoms after diagnosis	Increases the risk of progression 11-fold	< 0.05
Partially modifiable factors		
One exacerbation in the first year of the disease	Increases the risk of progression 15-fold	< 0.05
> 1 exacerbation in the first year of the disease	Increases the risk of progression 368-fold	< 0.05
Intestinal virus infections during the disease	Increases the risk of progression 11-fold	< 0.05

velop emotional disorders than the general population [22]. Sajadinejad *et al.* examined the impact of type D personality and the "Big Five" personality model on the adaptability and quality of life of patients with UC compared to healthy family members. It transpired that type D personality, defined as stress-prone, may adversely affect the quality of life in ulcerative colitis. Patients with this personality type experience more

Table III. Factors that reduce the risk of progression in ulcerative proctitis

Factor	Impact on the disease extension	*P*-value
Constipation at diagnosis	Reduces the risk of progression by 90%	< 0.05
Presence of crypt abscesses and cryptitis in histopathological examination at diagnosis	Reduces the risk of progression by 97%	< 0.05
Cryptitis in the histopathological examination at the time of diagnosis	Reduces the risk of progression by 98%	< 0.05
Providing the patient with information about the disease and treatment by the doctor	Reduces the risk of progression by 99%	< 0.05
The use of topical mesalamine in maintenance therapy	Reduces the risk of progression by 60%	< 0.05
Regular use of mesalamine for maintenance treatment	Reduces the risk of progression by 99%	< 0.05
Awareness of regular use of drugs after symptoms have resolved	Reduces the risk of progression by 97%	< 0.05
High and medium emotional stability on the TIPI-Pl scale	Reduces the risk of progression by 97%	< 0.05

anxiety, have low self-esteem, and are more likely to experience negative emotions. In relation to the "Big Five" personality model, significantly higher scores were observed in neuroticism, indicating emotional instability with overwhelming negative emotions and lower extraversion, which is characterized by assertive, talkative, and sociable people with the ability to develop interpersonal interests and social interactions [13]. In our study we analysed the "Big Five" personality model in the context of the progression of inflammatory lesions in ulcerative proctitis, and statistical significance was obtained in openness to experience, neuroticism, and extroversion. Stress, similarly to personality disorders, has never been considered as a potential risk factor of progression in ulcerative proctitis, and our study is the first in which such an analysis was performed. We showed that a high level of stress increases the risk of UP progression 71-fold compared to the average level. As many as 70 out of 116 patients reached a high level of stress, which is slightly more than 60% of all respondents, indicating that stress is a significant problem for many IBD patients.

The study has some limitations, including the retrospective nature of the study and estimation of disease clinical activity by using SCCAI, a relatively small group of patients, and a lack of randomization and control group. Nevertheless, it was possible to collect and analyse data on many potential risk factors for the progression of inflammatory lesions in UP.

Conclusions

The ability of predicting the course of ulcerative proctitis at the time of diagnosis is relevant for future outcomes. It enables better optimization of treatment, more accurate observation of patients, and prevents disease complications.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

References

1. Eder P, Łodyga M, Gawron-Kiszka M, et al. Guidelines for the management of ulcerative colitis. Recommendations of the Polish Society of Gastroenterology and the Polish National Consultant in Gastroenterology. Gastroenterology Rev 2023; 18: 1-42.
2. Raine T, Bonovas S, Burisch J, et al. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment. J Crohns Colitis 2022; 16: 2-17.
3. Chateau T, Feakins R, Marchal-Bressenot A, et al. Histological remission in ulcerative colitis: under the microscope is the cure. Am J Gastroenterol 2020; 115: 179-89.
4. Black J, Sweeney L, Yuan Y, et al. Systematic review: the role of psychological stress in inflammatory bowel disease. Aliment Pharmacol Ther 2022; 56: 1235-49.
5. Meucci G, Vecchi M, Astegiano M, et al. The natural history of ulcerative proctitis: a multicenter, retrospective study. Gruppo di Studio per le Malattie Infiammatorie Intestinali (GSMII). Am J Gastroenterol 2000; 95: 469-73.
6. Langholz E, Munkholm P, Davidsen M, et al. Changes in extent of ulcerative colitis: a study on the course and prognostic factors. Scand J Gastroenterol 1996; 31: 260-6.
7. Gajendran M, Loganathan P, Jimenez G, et al. A comprehensive review and update on ulcerative colitis. Dis Mon 2019; 65: 100851.
8. Roda G, Narula N, Pinotti R, et al. Systematic review with meta-analysis: proximal disease extension in limited ulcerative colitis. Aliment Pharmacol Ther 2017; 45: 1481-92.

9. Huguet JM, Ferrer-Barceló L, Suárez P, et al. Endoscopic progression of ulcerative proctitis to proximal disease. Can we identify predictors of progression? Scand J Gastroenterol 2018; 53: 1286-90.

10. Anzai H, Hata K, Kishikawa J, et al. Clinical pattern and progression of ulcerative proctitis in the Japanese population: a retrospective study of incidence and risk factors influencing progression. Colorectal Dis 2016; 18: 97-102.

11. Sahami S, Konté K, Buskens CJ, et al. Risk factors for proximal disease extension and colectomy in left-sided ulcerative colitis. United European Gastroenterol J 2017; 5: 554-62.

12. Juczyński Z, Ogińska-Bulik N. Tools for measuring and coping with stress. Psychological Test Laboratory, Warsaw 2009.

13. Sajadinejad MS, Molavi H, Asgari K, et al. Personality dimensions and type D personality in female patients with ulcerative colitis. J Res Med Sci 2012; 17: 898-900.

14. Sorokowska A, Słowińska A, Zbieg A, et al. Polish adaptation of Ten Item Personality Inventory test (TIPI) – TIPI-PL – standard and internet version, Wroclaw 2014.

15. Farmer RG, Easley KA, Rankin GB. Clinical patterns, natural history, and progression of ulcerative colitis. A long-term follow-up of 1116 patients. Dig Dis Sci 1993; 38: 1137-46.

16. Anzai H, Hata K, Kishikawa J, et al. Appendiceal orifice inflammation is associated with proximal extension of disease in patients with ulcerative colitis. Colorectal Dis 2016; 18: 278-82.

17. Walsh E, Chah YW, Chin SM, et al. Clinical predictors and natural history of disease extension in patients with ulcerative proctitis. Inflamm Bowel Dis 2017; 23: 2035-41.

18. Hijos-Mallada G, Sostres C, Gomollón F. NSAIDs, gastrointestinal toxicity and inflammatory bowel disease. Gastroenterol Hepatol 2022; 45: 215-22.

19. Klein A, Eliakim R. Non steroidal anti-inflammatory drugs and inflammatory bowel disease. Pharmaceuticals (Basel) 2010; 3: 1084-92.

20. Meyer AM, Ramzan NN, Heigh RI, et al. Relapse of inflammatory bowel disease associated with use of nonsteroidal anti-inflammatory drugs. Dig Dis Sci 2006; 51: 168-72.

21. Olczak-Pienkowska A, Hryniewicz Q. Monitoring of antimicrobial consumption – aim, methodology and use. Adv Microbiol 2020; 59: 305-14.

22. Sun Y, Li L, Xie R, et. al. Stress triggers flare of inflammatory bowel disease in children and adults. Front Pediatr 2019; 7: 432.