Long-term Outcome of Patients with Distal Ulcerative Colitis and Inflammation of the Appendiceal Orifice

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Abstract

Background & Aims: Skip inflammation of the appendiceal orifice has been described in distal UC (UC-IAO) but long-term clinical outcomes are poorly established. Our aim was to evaluate the long-term clinical outcomes of UC-IAO as compared to classic distal UC. **Methods**: Patients with UC-IAO were identified from the local IBD database. Disease outcome and therapeutic requirements during follow-up were accurately collected, and compared with a control group of patients with distal UC without periappendiceal involvement matched by disease extent (proctitis/distal), smoking habit, and date and age at diagnosis. **Results**: Fourteen UC patients were found to have UC-IAO, most of them with initial extent of UC limited to the rectum. All patients were initially managed with mesalazine administered orally (28.5%), topically (28.5%), or in combination (43%). After a median follow-up of 78 months (interquartile range - IQR 45-123) most UC-IAO patients were successfully managed with oral and/or topical aminosalycilates. Only one of them developed proximal disease progression. As compared to controls, no differences in clinical outcomes or therapeutic requirements were found. **Conclusions**: Patients with UC-IAO tend to present a mild course, with a low probability to develop proximal progression of disease extent or to require immunosuppressive therapy or colectomy.

Key words

Ulcerative colitis – appendiceal – prognosis – outcomes – treatment.

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Introduction

Ulcerative colitis (UC) is traditionally considered a chronic inflammatory condition, characterized by the involvement of rectal mucosa with extension proximally in a continuous manner. Disease extent and severity of inflammatory activity are key factors when deciding the most appropriate therapeutic approach (drug and route of administration). Moreover, it is well known that disease extent influences both long-term prognosis and cancer risk [1-4].

In contrast to Crohn's disease, in which disease location tend to be stable over time [5, 6], up to 35% of patients with ulcerative proctitis or distal UC will present a proximal progression of their disease extent [7, 8]. Some decades ago, a variant of conventional distal forms UC with skip inflammation of the appendiceal orifice (UC-IAO) without macroscopic and microscopic mucosal lesions within the ascending and transverse colon was described [9]. Appendiceal orifice inflammation is now considered a distinct skip lesion of UC, with a prevalence ranging from 8% to 75% [10-14]. These heterogeneous results might be explained mainly by differences in the used definition for UC-IAO (endoscopic and/or histological, UC involvement limited to the left colon vs. hepatic flexure), and even in environmental and genetic factors that may play a role in the phenotypic expression of UC. Beyond the real prevalence of this phenotypic form of distal UC, it is not well established if this variant holds a different prognosis regarding disease severity, risk of proximal progression, or development of dysplasia. In fact, there are no particular therapeutic or monitoring recommendations for patients with UC-IAO, and even the Montreal classification of UC extent does not consider this subset of patients [15]. Therefore, whether these patients should follow oral, topical, or combined therapy still remains to be answered.

The aims of our study were to describe the clinical outcomes and therapeutic requirements of UC-IAO, and to compare them to those of patients with distal UC without appendiceal orifice involvement.

Material and Methods

Patients

This was a retrospective study approved by the Institutional Review Board of the Hospital Universitari Germans Trias i Pujol, Badalona. All IBD patients in our centre are registered in a local database that includes demographic, epidemiological, clinical, and therapeutic features of patients. Among the collected variables, the endoscopic or radiologic involvement of each segment of the upper gastrointestinal tract, colon, and rectum, is recorded. All patients with confirmed distal UC and macroscopic (endoscopic) description of inflammation of the appendiceal orifice (UC-IAO) who had visited our centre were identified. Patients were diagnosed with UC by the traditional Lennard-Jones criteria [16]. To be included in the study, UC extent could not exceed the splenic flexure at disease diagnosis and at the time that endoscopic involvement of the appendiceal orifice was noticed. Patients with either extensive UC at diagnosis (beyond the splenic flexure) or previous appendectomy were excluded.

For the study purposes, each UC-IAO patient was matched with 1-2 controls. Controls had distal UC without IAO. To reduce biases from potential confounding factors, they were matched with cases for year of diagnosis, smoking status, extent and age at diagnosis. All controls had at least one complete colonoscopy (evaluation to cecum).

Medical records of all cases and controls were accurately reviewed for epidemiological variables (gender, age, family history of inflammatory bowel disease, smoking status at diagnosis), UC-related clinical variables at disease diagnosis (age, date of the first colonoscopy, initial disease extent, time from UC diagnosis when UC-IAO was first stated, severity of the first UC flare), therapeutic requirements both at diagnosis and over time (oral and/or topical mesalazine, systemic or topical corticosteroids, immunomodulators, colectomy), UC-related outcomes (extraintestinal manifestations during disease course, proximal progression –as defined by a change in Montreal's UC extent classification, development of dysplasia, change in diagnosis to Crohn's disease), as well as follow-up time and the total number of colonoscopies during this period.

Statistical analysis

Results are expressed in absolute numbers (frequencies) or median (range). Comparisons between the study groups (UC-IAO and controls) were performed by the Chi-square test (for qualitative variables) and Student's *t* test (for continuous variables). All statistical analyses were performed using the statistical package SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Fourteen patients met the inclusion criteria for UC-IAO. Eleven of them (78%) were men, and UC extent at diagnosis was proctitis in the majority (78%). The median age at diagnosis was 40 years (range, 19-61 years). None of them had a family history of inflammatory bowel disease and only one patient had developed extraintestinal manifestations. At the time of diagnosis, half of the patients were life-long non-smokers, five patients previously smoked and one patient was a current smoker. Nine patients (64%) were noted to have UC-IAO at initial endoscopic examination. In five patients, IAO was observed on subsequent examinations; however, a complete colonoscopy at diagnosis was available in only two out of these five patients. Regarding the initial therapeutic approach, none of the UC-IAO patients received oral or intravenous corticosteroids, and maintenance therapy was based on topical mesalazine in 4 patients (28.5%), oral mesalazine in 4 patients (28.5%), and combined therapy in the remaining 6 patients (43%). Worth noting was that similar features concerning the control group were found as summarized in Table I, with only a greater proportion of males in the UC-IAO group (P=0.02).

Table I. Baseline characteristics of patients with inflammation of the appendiceal orifice (UC-IAO) and controls.

	UC-IAO (n=14)	UC controls (n=25)	P
Gender (M / F)	11/3	10/15	0.02
Family history of IBD	0	5	0.18
Age at UC diagnosis (years)	40 (19-61)	40 (21-69)	0.92
Smoking habit at diagnosis (yes / no / former)	7/1/5	17/1/7	0.67
UC extent at diagnosis (proctitis / distal)	11/3	21/4	0.67
Follow-up (months)	78 (12-300)	96 (17-204)	0.48
Systemic steroids at UC diagnosis	0	4	0.30
Initial mesalazine treatment (oral / topical / combination)	4/4/6	11/9/5	0.30

*Expressed in absolute numbers or median (range)

Follow-up clinical outcomes are summarized in Table II. After a median follow-up of 78 months (range 12-300), only two UC-IAO patients required a course of oral corticosteroids during follow-up, one of them meeting the criteria for steroid-dependency and requiring azathioprine.

Table II. Follow-up characteristics of patients with inflammation of the appendiceal orifice (UC-IAO) and controls.

	UC-IAO (n=14)	UC controls (n=25)	P
Follow-up (months)	78 (12-300)	96 (17-204)	0.48
Proximal spread	1	4	
Extraintestinal manifestations	1	3	0.97
Systemic steroids during follow-up	2	5	0.99
Steroid dependency	1	2	0.92
Steroid refractoriness	0	3	0.47
Requirements of rescue therapies	0	3	0.47
Colectomy	0	1	0.76

None of the UC-IAO patients required rescue therapies such as cyclosporine, infliximab, or colectomy. Colonoscopy during follow-up was available in nine UC-IAO patients (64%). Proximal disease progression was noticed in only one patient (from proctitis to extensive UC).

Median follow-up among controls was 96 months (range, 17-204). Five patients (20%) required at least one course of systemic steroids during follow-up (P=0.99), three of them requiring rescue therapies because of steroid-refractoriness (1 cyclosporine, 1 infliximab, 1 colectomy) and another one meeting criteria for steroid-dependency and requiring azathioprine. Seventeen controls (68%) had at least one colonoscopy during follow-up, and proximal progression from proctitis to distal UC was found in 4 cases (16% of controls).

No deaths, dysplasia, or cancers were registered in either group.

Discussion

Cecal appendix has been repeatedly involved in the pathogenesis and the clinical course of UC. Appendectomy is strongly correlated with a decreased risk of developing UC [17-20]. Moreover, some authors suggested that UC patients undergoing appendectomy experience an improvement in their clinical course [21]. However, it is not well known if those with distal UC and skipped cecal and/or appendiceal involvement have the same results as distal or extensive forms of UC in terms of disease severity.

Only a few studies addressed the impact of UC-IAO on clinical outcomes. Matsumoto et al reported a better short-term response to treatment in UC-IAO [11]. Although their results have not been reproduced in other studies, they reported a higher endoscopic remission rate among 23 UC-IAO patients as compared to 17 controls. Many authors reported a low rate of severe disease activity among UC-IAO patients [10, 11, 13, 14, 22]. However, the requirements of systemic steroids or immunosuppressants in the long-term had never been reported before; our data suggest that UC-IAO patients did not have an increased need for systemic steroids or even for rescue therapies as compared to patients with classic distal UC forms.

Another important issue is the risk of proximal progression in the disease extent. In addition to the worse prognosis in terms of risk of colectomy, dysplasia or mortality of extensive UC, proximal progression has also been associated to a more severe course [8]. Byeon et al, in the only prospective study in UC-IAO patients with a control group, did not find an increased risk of proximal progression in control endoscopies performed 1 to 2 years after the index examination. In accordance with these findings we did not find an increased risk of proximal progression after a median follow-up of 6 years. On the other hand, in a recently published retrospective UC-IAO series that included some patients with UC involvement beyond the splenic flexure, 38% of patients progressed to more extensive disease after a median of 9 years, most of them to pancolitis [14].

Finally, we found similar outcomes whathever was the maintenance treatment schedule (oral, topical, or combined), also as in other studies [14].

Yamagishi et al described the healing of peri-appendiceal inflammation in 48% of UC-IAO patients in whom a second endoscopic examination was performed at least one year after the index examination [22]. Byeon et al reported that the change in the IAO status is a usual event, with 43% of UC-IAO patients experiencing a healing of these skip lesions, and 29% of patients with classical distal UC developing peri-appendiceal involvement in follow-up examinations [13]. This phenomenon might explain the similar clinical outcomes found among UC-IAO and classic distal UC.

Our study has some important limitations. First, the retrospective design makes difficult to collect some relevant information, mainly related to the endoscopic features. Endoscopic examination for typical UC may often be discontinued once the upper limit of inflammation is reached. Moreover, an accurate description of peri-appendiceal involvement may be under-reported in the absence of other findings raising the suspicion of Crohn's disease. Secondly, although previous studies reported a number of cases very close to ours [10,12,14], the present study is clearly limited by its small sample size. Finally, peri-appendiceal involvement was only based on endoscopic appearance. Nevertheless, a high correlation between macroscopic and microscopic involvement was strongly demonstrated in a Belgian study [10]. Conversely, the long follow-up period and the comparison to a control group matched for potential confounding variables should strengthen our results.

Conclusion

The UC-IAO represents a phenotypic presentation of UC with similar clinical outcomes as classic distal UC. Our results do not support the use of any particular monitoring or therapeutic approach in this subset of patients as long as they have not an increased risk for proximal progression or severe disease course. There was not a uniform therapeutic approach in our patients, reflecting the scarce information about how to manage UC-IAO (as extensive or as distal forms).

Conflicts of interest

None to declare.

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