Perianal disease in patients with ulcerative colitis: A case-control study

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Abstract

Background: Patients with ulcerative colitis (UC) and concomitant perianal disease (PAD) are occasionally seen, but the impact of PAD on UC outcome has been scarcely assessed.

Aims: To evaluate the prevalence, clinical features and outcomes of PAD among UC patients.

Methods: Patients with an initial diagnosis of UC who ever developed PAD were identified from three IBD hospital databases. Each case was matched by age, disease extent at diagnosis, and year of diagnosis, with two UC patients who never developed PAD.

Results: Thirty-seven UC patients (5% of the whole series) developed PAD (complex in about a half of them), being more frequent among men (62%), with distal (50%) or extreme (34%) disease. Proximal spread of UC occurred in 19% of cases. No differences in demographic features, rate of proximal spread or colectomy during follow-up were found as compared to controls, but greater requirements of steroids (P=0.019) were detected in UC-PAD patients. A change in disease diagnosis occurred in 6 patients mainly because of transmural involvement in colectomy specimen, small intestinal involvement, and/or endoscopic appearance.

Conclusions: PAD may occur in up to 5% of UC patients. When complex it leads to a change in disease diagnosis in one third of cases. UC-related therapeutic requirements are not increased in these patients, except for steroids.

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1. Introduction

Perianal disease (PAD) in inflammatory bowel disease (IBD) has always been linked to Crohn’s disease (CD).1 In fact, this is one of the classical Lennard–Jones diagnostic criteria to discriminate between CD and ulcerative colitis (UC),2 as well as one of the parameters for CD Montreal’s phenotypic classification.3 Initially, PAD was considered as a direct consequence of ileal inflammation due to a supposed internal communication towards perineum in CD.4 It has been also suggested that both ileal and perianal regions were composed by a high amount of lymphoid tissue, acting synchronically and producing simultaneous activity has the greater risk for PAD occurrence because of proximity.6-8 PAD can be present in up to 26% of CD patients7,9 and it is considered that anal lesions in CD may be regarded as a herald to intestinal damage that may not be manifest until many years after the anal disease has appeared.1 Although PAD is only exceptionally considered that anal lesions in CD may be regarded as a herald to intestinal damage that may not be manifest until many years after the anal disease has appeared.1 Although PAD is only exceptionally life threatening, it often worsens the patient’s quality of life. Moreover, PAD is associated with a poorer prognosis of CD,10 predicts the phenotypical change of CD11 and, therefore, should lead to a more intensive therapeutic approach.

On the other hand, little is known about PAD among UC patients. Some authors suggested that, as far as UC implies mucosal (and not transmural) inflammation, a greater incidence of PAD among UC patients should not be expected when compared to healthy controls.12 In fact, development of PAD in UC may raise the suspicion of misdiagnosed colonic CD.6 Hence, therapeutic algorithms of PAD arising in UC patients should be the same as in general population once CD has been ruled out.13 It is not unusual to find patients with well-documented UC who develop PAD in the daily practice. However, it is not known whether it has the same consequences as in CD regarding PAD outcome itself, or disease therapeutic requirements.

Therefore, the objectives of our study were to estimate PAD prevalence in UC patients, to ascertain if there are any risk factors for PAD development in UC, and to evaluate if PAD leads to the change from UC diagnosis towards CD or unclassified colitis.

2. Patients and methods

2.1. Study population and data collection

This was a case-control study, according to the Declaration of Helsinki, and approved by the Institutional Review Board of the steering centre (Hospital Universitari Germans Trias i Pujol). UC patients were identified from the IBD databases of three Spanish referral centres. Cases were those patients with an initial diagnosis of UC with pre-existing or who developed PAD. PAD was considered only if the patient has fistulæ or abscess (and not isolate skin tags, fissure or haemorrhoids) and was classified as complex or simple based on Parks’ classification.14 Patients with UC who developed PAD after ileal pouch anal anastomosis were excluded. For each case, two controls with UC but not PAD matched by age at diagnosis (±3 years), year of diagnosis (±3 years), and UC initial extent were included.

Demographic, epidemiological and clinical features (including medical and surgical treatment, as well as PAD characteristics, and when applicable, criteria and approach for change of diagnosis from UC to CD/unclassified colitis) were collected from diagnosis until October 2008, loss of follow-up, or patient’s death. All diagnostic procedures performed in each case to rule out CD were recorded. Diagnosis of UC/CD/unclassified colitis was based on conventional Lennard–Jones criteria.2

2.2. Study outcomes

To evaluate the impact of PAD development on UC outcomes, therapeutic requirements in terms of introduction of immunomodulators-thiopurines or methotrexate-, biological therapy-infliximab or adalimumab-, hospitalisation, and colectomy were specifically addressed.

2.3. Statistical analysis

Descriptive statistics are expressed as percentage for discrete data and median with interquartile range (IQR) for continuous data. Both univariate (Chi-square test and Mann–Whitney test) and logistic regression analyses were performed to assess the associations between possible risk factors and the occurrence of each study outcome. P-values lesser than 0.05 were considered significant.

Kaplan Meier survival curves were compared by means of the Log Rank test. All statistical tests were two-tailed and were performed using the SPSS 18.0 package for Windows (Inc. Chicago IL, USA).

3. Results

Thirty-seven cases out of 758 UC patients (5%) were found to have ever developed PAD. This subset of patients were more frequently men (62%) and seldom with exclusively rectal disease (16%). PAD developed before the diagnosis of UC in 9 patients (24%), within the first month of UC diagnosis in 4 (11%), and more than 1 year after UC diagnosis in the remaining 24 (65%) patients.

In the nine cases with PAD arising before UC, this was simple in 2 (22%), complex in 2 (22%) and unknown in 5 (55.5%). Among those 28 patients who developed PAD once UC had been diagnosed, this was simple in 8 (29%), complex in 14 (50%) and unknown in 6 cases (21%). Five of these 28 patients (18%) where already on immunomodulators at the time PAD occurred, but none had ever received anti-TNF treatment before developing PAD.

After development of PAD, small bowel evaluation in order to rule out CD (small bowel follow through, ileoscopy and/or abdominal scintigraphy), was performed in 93% of those patients with complex PAD but in none with simple PAD. Baseline characteristics of cases and controls are listed on Table 1.

Monotherapy with thiopurines was started because of PAD in 8 patients, monotherapy with anti-TNF agents in 1 patient, and combination therapy in 2 patients. Local surgery was performed in 17 patients, half of them in combination with specific medical therapy. Only one patient required colectomy because of PAD during follow-up. When comparing to controls, greater and earlier requirements of immunomodulators (P=0.002) and biological therapy (P=0.019) were found in PAD patients. When those patients in whom PAD was the main cause for immunomodulators were excluded, these differences disappeared. A significantly greater proportion of PAD patients required steroid therapy (P=0.019) (Fig. 1); similarly, a marked but non-significant trend towards a higher rate of hospital admissions and colectomy was found among PAD patients (Table 2).

No differences in baseline characteristics, proximal spread of the disease, infliximab requirements, hospitalisation, or colectomy were found when analyzed in the subgroup of patients who developed PAD when they were already on immunomodulators.

Finally, change in disease diagnosis was made in 6 cases (5 to CD, 1 to unclassified colitis) because of transmural involvement in colectomy specimens (n=2), small intestinal involvement (n=2) and/or endoscopic appearance (n=4). In 5 of these 6 cases (83%) PAD was diagnosed after initial UC diagnosis and in 4 out of these 5 cases PAD was complex. This means that diagnosis was changed in 36% of patients with complex PAD after UC diagnosis.
4. Discussion

The association of PAD and UC was initially reported nearly five decades ago, as "anorectal complications" in up to 20–25% of patients with chronic UC. However, most case reports and reviews include a wide range of anorectal conditions (i.e. hemorrhoids, skin tags, anal strictures). In addition, most references of PAD in UC were published before the implementation of the Lennard–Jones criteria for the diagnosis of IBD and the widespread use of endoscopy for the diagnosis of these diseases. To our knowledge, no study has evaluated the incidence of PAD associated with UC in a large cohort to date. Applying Lennard–Jones criteria and limiting the definition of PAD to the occurrence of perianal abscesses and/or fistulae, we observed an incidence of 5% when taking into account those patients with an initial diagnosis of UC, and 4% when only analysing those patients who maintained the diagnosis of UC (despite PAD) after a diagnostic reassessment.

In the present series, UC-PAD patients had greater and earlier requirements for steroids, immunomodulators, and biological therapy, mainly due to the PAD itself. These results are in accordance with those of Beaugerie and colleagues who, in a study assessing predictors of disabling CD, found that PAD at diagnosis was independently associated with repeated courses of corticosteroids, corticosteroid dependence, hospitalisations for disease flares, immunosuppressive medications, surgical resection and/or the presence of chronic disabling symptoms. When the analysis was restricted to the 31 cases that kept their initial UC diagnosis until the end of follow-up, PAD-UC patients still had increased requirements for steroid therapy, as compared to controls (87% and 63.5%, respectively P = 0.028), suggesting that PAD may occur mainly in UC patients with more active disease.

Most patients in whom the initial UC diagnosis changed to CD or unclassified colitis had complex PAD. In fact, in more than one third of patients with UC and complex PAD the initial diagnosis was changed, whereas this did not occur in any patient with simple PAD. For this reason, an extensive work-up to rule out CD is strongly warranted in patients with UC developing complex PAD.

Our study presents several obvious limitations and potential biases. First, its retrospective design did not allow a complete data collection regarding the type of PAD (simple or complex) in about one third of cases. Second, diagnostic work-up to exclude CD was not performed uniformly in all patients and by means of some techniques with low sensitivity and specificity. Third, the number of UC-PAD patients was relatively small, although they were identified among a large UC cohort.

In conclusion, around 5% of patients with UC may develop PAD, and up to 70% of them might not meet diagnostic criteria of CD, despite diagnostic reassessment. UC patients developing PAD seem to be more often treated with steroids suggesting that this condition mainly occurs in patients with more severe or persistent rectal inflammation. Nevertheless, disease prognosis in terms of colectomy remains the same as in patients without PAD.

Conflict of interest statement

The authors declare not to have any conflict of interest.
References