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ORIGINAL ARTICLE

Increased faecal calprotectin predicts recurrence of colonic diverticulitis

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Abstract
Background and aims Colonic diverticulitis shows a high recurrence rate, but the role of faecal markers in predicting recurrence is unknown. The aim of this study was to investigate the role of faecal calprotectin (FC) in predicting recurrence of diverticulitis.
Patients/methods A prospective cohort study was performed on 54 patients suffering from acute uncomplicated diverticulitis (AUD) diagnosed by computerized tomography (CT). After remission, patients underwent to clinical follow-up every 2 months. After remission and during the follow-up, FC was analysed. Recurrence of diverticulitis was defined as return to our observation due to left lower-quadrant pain with or without other symptoms (e.g. fever), associated with leucocytosis and/or increased C-reactive protein (CRP). Presence of diverticulitis was confirmed by means of CT.
Results/findings The mean follow-up was 20 months (range 12–24 months). Forty-eight patients were available for the final evaluation, and six patients were lost to follow-up. During follow-up, increased FC was detected in 17 (35.4 %) patients and diverticulitis recurred in eight patients (16.7 %). Diverticulitis recurred in eight (16.7 %) patients: seven (87.5 %) patients showed increased FC during the follow-up, and only one (12.5 %) patient with recurrent diverticulitis did not show increased FC. Diverticulitis recurrence was strictly related to the presence of abnormal FC test during follow-up.
Conclusions In the present prospective study, increased FC was found to be predictive of diverticulitis recurrence.

Keywords Diverticulitis · Faecal calprotectin · Follow-up · Recurrence

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Introduction

Diverticular disease (DD) of the colon is common in westernized societies, and its prevalence increases with age. Diverticulosis affects about two thirds of the elderly, and a large majority of those affected will remain entirely asymptomatic. Nonetheless, an estimated 20–25 % of patients may manifest clinical illness: the so-called DD [1].

The most important complication of DD is represented by acute diverticulitis [2]. It may be subdivided into acute uncomplicated diverticulitis (AUD), characterized by acute inflammation of diverticula but without complications, and complicated diverticulitis, characterized by acute diverticular inflammation associated to complications (abscesses, fistulas, stenoses) [3].

Some factors have been identified as predictors of diverticulitis recurrence. For example, severity of computerized tomography (CT) scan at entry [4], high white cells count (>12,000) [5] or high body mass index [6] seem to be prognostic factor for the outcome. Finally, persistence of endoscopic or histological inflammation has been recently identified as risk factors for diverticulitis recurrence [7].

The presence of active intestinal inflammation in patients with ulcerative colitis is associated with an acute phase reaction and migration of leucocytes to the gut, and this leads to

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the release of several neutrophil proteins, which may be measured in stool samples [8]. Faecal markers are non-invasive, simple, in-expensive, sensitive and specific tests to detect gastrointestinal inflammation. Calprotectin is a calcium-binding protein, representing up to 60 % of the cytosolic proteins in neutrophils [9]. Since calprotectin is primarily derived from neutrophils, its concentration is directly proportional to the concentration of neutrophils in the colonic/rectal mucosa [10]. It is resistant to bacterial degradation in the gut and is stable in the stool for up to 1 week at room temperature [11, 12].

Faecal calprotectin (FC) has been shown to have a role in monitoring disease activity in patients with inflammatory bowel disease [13–18]. FC expression was also linked to the severity of the DD [19], but its role in monitoring the disease after an attack of AUD is unknown.

The present study was designed to evaluate whether or not FC is clinically relevant for predicting relapse after an attack of AUD.

Patients and methods

From January 2011 to September 2012, 54 patients underwent diagnosis of AUD.

The diagnosis of AUD was made according to (CT) scan criteria [3, 20]: inflammation involving the colon harbouring diverticula, with thickening of bowel wall and involvement of pericolic fat but without complications (namely absence of fistulas, abscesses, stenoses).

All patients were treated with mesalazine 3.2 g/day, rifaximin 800 mg/day and metronidazole 1 g/day for 7 days. Forty-three (79.6 %) patients obtained remission, whilst 14 (20.4 %) patients required further treatment with intravenous infusion of third-generation cephalosporin to obtain remission. All patients underwent remission, defined as absence of symptoms and leucocytosis and/or increased C-reactive protein (CRP), and none of them required surgery at that time.

After the remission, patients underwent to clinical follow-up. During the follow-up, the patients were treated with mesalazine 2.4 g/day.

Clinical assessment

A medical control visit was performed every 2 months after remission.

Recurrence of diverticulitis was defined as return to our observation due abdominal pain in the left lower-quadrant pain with or without other symptoms (constipation or diarrhoea and/or fever), associated with leucocytosis and/or increased CRP. CT was again performed to confirm recurrence of diverticulitis in all patients. Moreover, the patients were invited to a control visit whenever they considered necessary.

Informed consent for the study procedures was obtained from all the participants.

Faecal calprotectin assessment

FC was analysed 2 weeks after the end of antibiotic therapy and every 2 months during follow-up. It was analysed using a quick test (CAL Detect®, Sofar SpA, Trezzano Rosa (MI), Italy). This semi-quantitative test was developed from the quantitative ELISA method regarded as the gold standard, showing similar effectiveness [21]. The result of this test was given in one to four bands of colour, the numbers indicating increasing calprotectin concentration:

1. a solitary control line (C) in the results windows indicates that the test has run correctly and calprotectin is undetectable;
2. the presence of two colour bands (C and T1) within the results windows indicates a calprotectin concentration ≤15 μg/g: absence of bowel inflammation;
3. the presence of three colour bands (C, T1 and T2) within the results windows indicates a calprotectin concentration between 15 and 60 μg/g: an inflammatory process is going on in the mucosa;
4. the presence of four colour bands (C, T1, T2 and T3) within the results windows indicates a calprotectin concentration higher than 60 μg/g: a high-grade inflammatory process is going on in the mucosa.

Statistics

The collection and analysis of data were performed by using the SPSS® Release 13.0 (SPSS, Inc., Chicago, IL). Statistical analysis was performed by Kaplan-Meier method, and groups were compared with the log rank test. Values of $p<0.05$ were considered as statistical differences.

Results

The characteristics of the study group are showed in Table 1. The mean follow-up was 20 months (range 12–24 months). Forty-eight patients were available for the final evaluation, and six patients were lost to follow-up.

After induction of the remission, FC test was normal in all patients.

FC values during follow-up are summarized in Fig. 1. During the follow-up, increased FC was detected in 17 (35.4 %) patients. In six (12.5 %) patients, it was detected

Table 1 Characteristics at baseline

Characteristics	Study group (54 patients)
Mean age (95 % CI)	64.7 (46.5–82.3)
Sex male	21 (38.9)
Previous diverticular disease	17 (31.5)
Radiological findings	
Bowel wall thickening	47 (87.0)
Soft tissue stranding	45 (83.3)
Diverticula	50 (92.6)

Values are given as number (%) of patients, unless otherwise specified

CI confidence interval

increased at each control visit: in four (8.3 %) patients, it showed concentration persistently >60 μg/g, whilst in two (4.2 %) patients, it showed concentration ranging from mild (between 15 and 60 μg/g) to high (>60 μg/g). FC was intermittently increased in 11 (22.9 %) patients: eight (16.7 %) patients showed intermittent FC concentration persistently mild (between 1 and 60 μg/g), whilst three (6.2 %) patients showed intermittent FC concentration ranging from mild (between 15 and 60 μg/g) to high (>60 μg/g). During the follow-up, diverticulitis recurred in eight patients (16.7 %): seven (14.6 %) patients showed recurrence of AUD, whilst one (2.1 %) showed recurrence of diverticulitis with abscess in the pelvis, requiring radiological drainage. Diverticulitis recurred within 1 year after the first episode in five (62.5 %) patients.

Diverticulitis recurrence was strictly related to the presence of abnormal FC test at least once during the follow-up (Fig. 2).

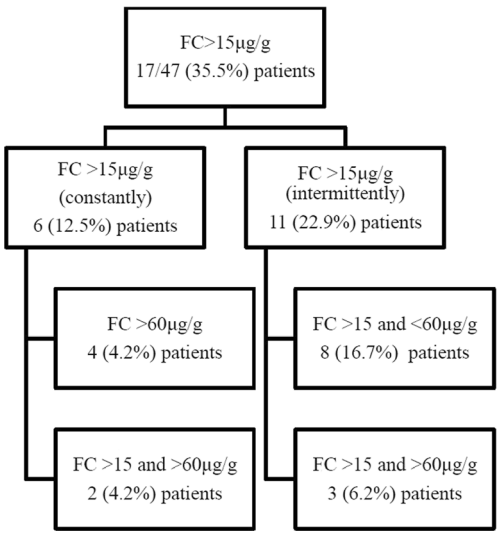

Fig. 1 Flowchart describing faecal calprotectin values during the follow-up

Discussion

Diverticulitis represents a significant economic and clinical burden to the Western Health Care Systems and its patients [22]. Recent studies took a lot of care in identifying prognostic factors for recurrence and in identifying the best treatment in maintaining remission. We currently know that CT scan severity at entry is a good prognostic factor [23]. In particular, CT scan showing inflammation confined to the colonic/pericolonic wall (Hinchey modified stages Ia–Ib) is at lower risk of diverticulitis recurrence than CT scan showing presence of retroperitoneal abscesses or peritoneal free fluids (Hinchey modified stages II–IV) [23].

We have recently found that persistence of both endoscopic and histological inflammation after an attack of AUD is predictive of diverticulitis recurrence. Therefore, the endoscopic behaviour of the AUD seems to be similar to that of inflammatory bowel disease in which persistence of endoscopic damage during the follow-up is a predictor of the course of the disease [24–26]. The persistence of histological inflammation during the follow-up is a predictor of disease recurrence too. This histological behaviour of AUD seems to be surprising similar to that occurring in inflammatory bowel disease, in which persistence of histological damage during the follow-up is a predictor of the disease recurrence [27, 28]. These results warrant the aim to use a faecal marker of intestinal inflammation in order to predict diverticulitis recurrence.

We know that FC values are related to the degree of the DD, making this test useful in distinguishing mild to severe colonic inflammation. Different FC values are consistent with the different colonic inflammatory infiltrate, detected in different degrees of DD [19]. In fact, inflammatory infiltrate in symptomatic uncomplicated DD is characterized by a prevalently lymphocyte infiltration of the mucosa, whilst AUD is characterized by a diffuse lymphocyte infiltration with numerous neutrophils [29].

We found that increased FC was detected in 35 % of patients during the follow-up after an attack of AUD. It may be detected always increased or increased in intermittent way but, significantly, it was detected in the vast majority of patients experiencing diverticulitis recurrence. Interestingly, FC in monitoring diverticulitis shows the same behaviour showed in monitoring inflammatory bowel disease. A recent review found that FC assessed by a cutoff value ranging from 15 to 50 μg/g shows sensitivity, specificity, PPV and NPV in distinguishing inflammatory bowel disease from non-inflammatory bowel disease similar to that showed in this study [30]. It means that inflammation plays a significant role in causing diverticulitis recurrence and that detection of inflammation during the follow-up is a

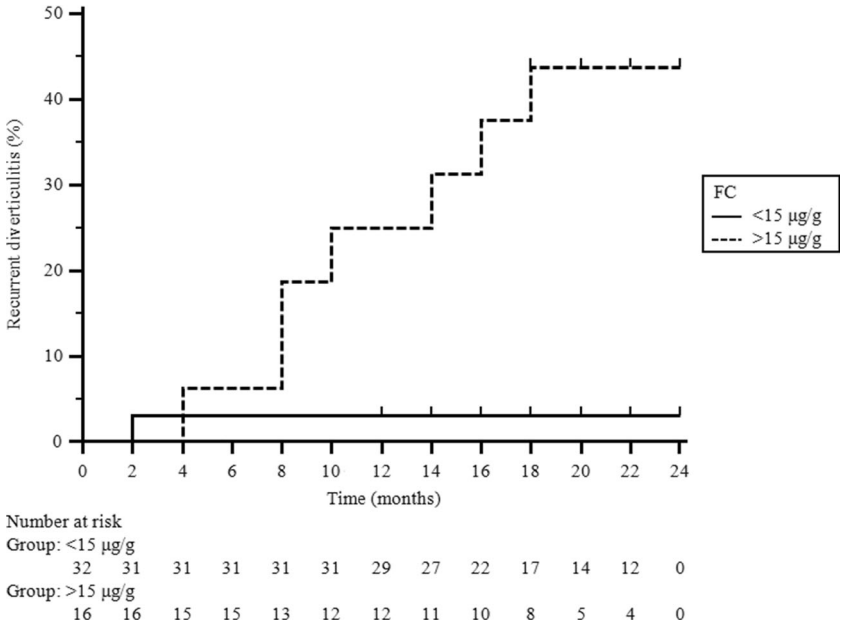

Fig. 2 Kaplan-Meier analysis of cumulative rates of recurrent acute diverticulitis by normal (<15 µg/g) and abnormal (>15 µg/g) faecal calprotectin (FC) test at least once during follow-up. $P<0.0004$, log rank test

significant risk factor for disease recurrence. It means that if a patient shows normal FC values during the follow-up after an attack of acute diverticulitis, it is highly probable that the patient will not experience diverticulitis recurrence. Therefore, the use of this simple and rapid test may be very useful for clinicians.

Of course, this diagnostic method has some limitations. The first one is related to sample collection. When the faeces sample is small or aqueous, fewer particles and material from the sample stick to the sample collection device, thus influencing the amount of test material. The second is strictly related to the method limitation. FC concentration, measured by the rapid test, was given in four levels, the highest being >60 µg/g. The rapid test, being semi-quantitative, may be not sufficient when the clinician needs a marker to monitor the disease activity. In these cases, it would be still necessary to use the ELISA method to analyse the stool samples, since this test is quantitative and can measure values >60 mg/kg. However, in clinical practice, it is not important to assess how high the FC levels are but to assess whether FC expression is high or very high. Moreover, this rapid test may be easily performed in the clinical setting. Calprotectin in stool is stable for up to 7 days in samples stored at room temperature [8]: it is therefore possible to collect stool samples at home and bring them to the physician for evaluation or post them by mail, avoiding the use of a more complex laboratory FC assessment. Of course, intrinsic limits of this technique should lead to care being taken when interpreting the results of this test.

In conclusion, the present study showed that increased FC is a predictor of diverticulitis recurrence.

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