The clinical significance of focal active colitis and inflammatory bowel disease

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Abstract

Purpose

Focal active colitis (FAC) is a non-specific histological diagnosis of uncertain clinical significance. There is potentially a causal relationship between FAC and inflammatory bowel disease (IBD) in children, but this has not been adequately explored in adults. We sought to evaluate whether FAC is a reliable predictor of developing IBD in adults.

Methods

43 patients with FAC were retrospectively identified between October 2014 and May 2019 and reviewed using the electronic pathology database at our institution. Patients with known chronic colitis were excluded. Patients were followed up for a mean period of 36 months +/- 16. Clinical data and final diagnoses were recorded, and categorical analysis performed with Fisher's exact χ^2.

Results

43 patients (11 male: 32 female, mean age 53 years +/- 18) were included. 14 (33%) with FAC were subsequently diagnosed with infective colitis, 5 (12%) with IBD, of which 4 (80%) were diagnosed with ulcerative colitis and 1 (20%) was diagnosed with undetermined IBD. Of 34 patients (79%) with neither raised faecal calprotectin (FC) levels nor suspicious endoscopic findings, 1 (3%) patient subsequently developed IBD. This was statistically significant by Fisher's exact ($p = 0.0046$), and the phi coefficient of 0.53 demonstrated that patients with neither raised FC levels nor suspicious endoscopic findings were statistically unlikely to develop IBD.

Conclusion

Our results suggest that having normal FC levels and endoscopic findings reduces the risk of future development of IBD in adults. Furthermore, a raised FC level and endoscopic features suggestive of IBD with histological FAC may predict progression to IBD.

Introduction

Focal Active Colitis (FAC) is histopathologically characterised by the presence of neutrophilic infiltration in crypt spaces of colorectal mucosa in the absence of other significant defects [1]. Histopathological changes such as cryptitis or crypt abscesses, either focal or as discrete multiple foci, are also included in the definition of FAC [2]. While not an uncommon finding in gastrointestinal clinical practice, there is conflicting and limited evidence of its significance and predictive utility as an individual finding for the

various subsets of colitis and particularly inflammatory bowel disease (IBD). Given that outcomes in IBD are worse with delayed diagnosis [3], it is imperative that patients at risk of progression to IBD are adequately followed-up, and that the patients who can be reassured are reassured and avoid unnecessary and emotionally taxing investigations.

To date, there have only been 6 studies that have explored the clinical implications FAC. Of these, 2 studies were conducted on paediatric populations, and 4 studies have been retrospective studies of small sample sizes. The adult studies found IBD, drug-induced colitis and infectious colitis to be the most significant ramifications of FAC. The 2 paediatric studies demonstrated that FAC may represent early stages of IBD, but this relationship has not been demonstrated in adults [4–5]. Other differentials among paediatric cases included infectious colitis, Irritable Bowel Syndrome (IBS), and allergic colitis. Incidental findings of FAC in all studies were also common (8–29%).

In 1997 Greenson *et al* [2] reported no clinical correlation between FAC and IBD based on retrospective data obtained on 42 patients with colorectal biopsies where FAC was the only histopathological abnormality. Notably, a majority of these patients were found to have an acute self-limiting infectious colitis. However, subsequent studies have demonstrated a link between FAC and IBD. Volk *et al* [6] found that 13% of 31 patients with FAC developed Crohn's disease (CD), while Xin *et al* [4] found that 31% of 31 paediatric patients with FAC developed CD. More recently, Shetty *et al* [2] published the first prospective study and concluded that 16% of 90 adult patients with FAC developed IBD and therefore FAC may be an important predictor for future IBD in all age groups. This was further supported by Sinagra *et al* [7] who demonstrated that 23% of 30 FAC patients progressed to IBD.

In summary, these studies support FAC, although a non-specific diagnosis, as an independent predictor of IBD in children. There is, however, no consensus agreement on the clinical relevance of FAC in adult patients, and whether further investigation or ongoing surveillance for IBD is indicated. The aims of this paper are therefore:

1. To assess the clinicopathological implications of FAC.
2. To establish whether the presence of FAC in adult patients represents a significant risk for the development of IBD
3. To investigate whether additional investigations improved the specificity of FAC for an eventual diagnosis of IBD.
4. To identify those patients with FAC who have low risk of progression to IBD.

Design

A computer search of the electronic pathology archives at our institution between October 2014 and May 2019 was used to generate a list of all colorectal biopsies coded for 'colitis' (specimen code M41000). From this search, all patients under the age of 18 were excluded from the study, identifying a total sample

size of 226 biopsies. The histological reports from all 226 specimens were reviewed individually, identifying a total of 56 samples with a histological diagnosis of FAC (Fig. 1).

All 56 cases of FAC were retrospectively analysed by two separate clinicians using both electronic medical records and patient notes and charts when available. Of these 56 patients, 11 patients with an established diagnosis of chronic colitis were excluded from the study, including 10 patients with an antecedent diagnosis of ulcerative colitis (UC) or CD and 1 patient with known collagenous colitis. 2 patients were excluded from the study because no identifiable history was available. In total 43 patients were followed-up for between 11 months to 70 months (mean follow-up period of 36 months +/- 16) after a histological diagnosis of FAC. Presenting symptoms, duration of symptoms, past medical history and drug history were recorded. Both serum samples (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white cell count (WCC), thyroid function (TFT) and coeliac screen) and faecal samples (faecal calprotectin and microscopy, culture and sensitivity) that were taken within 2 weeks of the onset of symptoms were also recorded. Endoscopy indications, preparations, and findings were identified. Prior and subsequent colorectal biopsies as well as any relevant imaging were reviewed when available.

Results are expressed as mean ± standard deviation (SD), absolute numbers (n) and frequencies (%). Comparisons have been made between those that developed IBD and those that did not. Statistical analysis of the above demographic data was performed by Fisher's exact test for nominal data (presenting complaints, symptom duration and whether or not there was elevated faecal calprotectin or suspicious endoscopic findings) and by student's t-test for the continuous values (CRP, ESR and WCC). The association of an eventual diagnosis of IBD and elevated faecal calprotectin or endoscopic features of IBD were also analysed by Fisher's exact. Results with a p-value < 0.05 were considered statistically significant.

Any identifiable patient information used was removed to ensure anonymity and therefore does not fall under the remit of the National Health Service (NHS) ethics and research committee. For the purpose of this study, only histology reports were reviewed and no separate special body parts analysis was undertaken. This study therefore fell under the remit of a hospital audit (CB634). Approval was obtained from the Research & Audit Department at Wexham Park Hospital, Frimley Health NHS Foundation Trust, United Kingdom.

Results

We identified 43 patients who were diagnosed with FAC between 2014 and 2019. Of these, 11 patients (26%) were male, and 32 patients (74%) were female (Table 1). The age of patients ranged from 19 to 82 years old, with a mean age of 53 years old (56 years old in males, 48 years old in females. Relevant other past medical history of patients included 4 (9.3%) with IBS, 1 (2.3%) with lactose intolerance, 2 (4.7%) with known diverticular disease, 7 (15.3%) with hypothyroidism, 1 (2.3%) with Grave's disease. None of these patients were later diagnosed with IBD.

Table 1
Demographics and baseline comparisons of patients with focal active colitis diagnosed either with or without inflammatory bowel disease

	IBD (n = 5)	Non-IBD (n = 38)	Total Cohort (n = 43)	P value
Age (mean ± SD)	23–60 (42±18)	19–82 (53±18)	19–82 (53±18)	*0.2061*
Sex (Male : Female)	2 : 3	9 : 29	11 : 32	*0.5891*
Presenting issue				
PR bleeding	3 (60%)	12 (32%)	15 (35%)	*0.3236*
Diarrhoea	4 (80%)	19 (50%)	23 (53%)	*0.3508*
Anaemia	1 (20%)	2 (5%)	3 (7%)	*0.3164*
Weight loss	1 (20%)	3 (8%)	4 (9%)	*0.4019*
Change in bowel habit	0	4 (11%)	4 (9%)	*1.0000*
Abdominal pain	3 (60%)	13 (34%)	16 (37%)	*0.3437*
Mucus discharge	1 (20%)	2 (5%)	3 (7%)	*0.3164*
Frequency	0	2 (5%)	2 (5%)	*1.0000*
Urgency	0	1 (3%)	1 (2%)	*1.0000*
Symptom duration				
< 7 days	0	7 (18%)	7 (16%)	*0.5716*
< 28 days	1 (20%)	4 (11%)	5 (12%)	*0.4786*
> 28 days	2 (40%)	16 (42%)	18 (42%)	*1.0000*
> 6 months	2 (40%)	11 (29%)	13 (30%)	*0.6299*
C-Reactive Protein (mg/L)	20±33*	4±13*	9±18*	*0.1100*
Erythrocyte Sedimentation Rate (mm/hr)	32±37*	22±21*	24±23*	*0.4995*
White Cell Count (x10^9/L)	8.51±2.35*	7.53±2.17*	7.71±2.19*	*0.9000*
Raised Faecal Calprotectin (> 50 µg/g) (n)	3 (60%)	5 (13%)	8 (19%)	*0.0372*
Endoscopic features suspicious of IBD (n)	4 (80%)	1 (3%)	5 (12%)	0.0002
Raised calprotectin with suspicious endoscopy (n)	3 (60%)	1 (3%)	4 (9%)	0.0031

	IBD (n = 5)	Non-IBD (n = 38)	Total Cohort (n = 43)	P value
Neither raised calprotectin nor suspicious endoscopy (n)	1 (20%)	33 (87%)	34 (79%)	0.0046
*mean values, SD = standard deviation, IBD = inflammatory bowel disease				

7 (16.3%) patients underwent flexible sigmoidoscopy, and 36 (83.7%) patients underwent colonoscopy for diagnosis. 38 (88.4%) patients received an elective outpatient endoscopy, and 5 (11.6%) patients received an urgent inpatient endoscopy within 48 hours of admission. For bowel preparation patients were administered phosphate enema for flexible sigmoidoscopy and citramag and senna for colonoscopy.

7 (16.3%) patients were taking non-steroidal anti-inflammatory drugs (NSAIDs) at the time of endoscopy. 8 (18.6%) were taking thyroid medication (1 on carbimazole, 7 on thyroxine replacement therapy), 13 (30.2%) taking proton-pump inhibitor, 5 (11.6%) taking metformin, and 4 (9.3%) taking iron replacement therapy.

17 patients (39.5%) had a stool culture sent, of which 2 were confirmed with *Clostridium difficile* infection, 1 with *Shigella dysenteriae*, and 1 with *Campylobacter jejuni* infection. Of the 3 patients diagnosed with drug induced FAC, 2 were attributed to NSAIDs use, and 1 due to proton pump inhibitor (PPI) use.

20 (46.5%) patients were screened for coeliac disease, of which all were negative (19 confirmed serologically with tissue transglutaminase test and immunoglobulin A levels, and 1 confirmed with a second part of duodenum (D2) biopsy). All 41 (95%) patients screened for thyroid dysfunction were found euthyroid.

Following appropriate assessment and investigation, 5 (12%) patients were diagnosed with IBD, of which 4 had UC and 1 had undetermined IBD. Of those diagnosed with ulcerative colitis, 1 patient had previous rectal cancer treated surgically with anterior resection (Table 2).

14 patients (33%) were diagnosed with infective colitis, 8 (19%) with IBS, 1 (2%) with microscopic colitis, 3 (7%) with drug-induced colitis, and 1 (2%) was lost to follow-up. 11 (26%) cases were identified as being ‘incidental’. Subgroup analysis of patients labelled as ‘incidental’ identified 2 (18%) patients with history of chronic constipation, 2 (18%) with diverticular disease, 1 (9%) taking NSAIDs, 3 (27%) taking PPIs, 2 (18%) taking metformin, and 2 (18%) taking a statin. 20% of patients with IBD and 29% patients without IBD had endoscopic features of diverticular disease.

Table 2
Clinical categorization for all cases of focal active colitis

Clinical diagnosis	Male	Female	Total	%
Infective colitis	7	7	14	33
Incidental (no cause identified)	2	9	11	26
Irritable Bowel Syndrome	0	8	8	19
Inflammatory Bowel Disease	2	3	5 (4 UC, 1 UIBD)	12
Drug-induced colitis	1	2	3	7
Microscopic colitis	0	1	1	2

UC = ulcerative colitis, UIBD = undetermined inflammatory bowel disease

17 patients (39.5%) had a faecal calprotectin level tested, of which 1 had a level between 50–150 µg/mg (normal range 10–50 µg/mg), and 8 had a level > 150 µg/mg. Of these 8 patients, 4 (50%) were diagnosed with infectious colitis, 3 (37.5%) with ulcerative colitis, and 1 (12.5%) lost to follow-up. 1 patient with a pre-endoscopic faecal calprotectin of < 50 µg/mg had a repeated level of 691 µg/mg and was later diagnosed with undetermined IBD.

No statistically significant difference in symptom presentation or symptom duration was identified in patients with FAC later diagnosed with IBD or not. No statistically significant difference in the mean CRP or ESR levels was seen in patients with FAC later diagnosed with either IBD or not. However, a trend towards a raised CRP and ESR level was observed in patients with FAC later diagnosed with IBD.

Given 5 of 43 patients (12%) went on to develop IBD, FAC may indeed be an early predictor for IBD. 8 of 43 (19%) patients had raised calprotectin, of which 3 (7%) developed IBD (Fisher's exact: $p = 0.0372$). Furthermore, 5 of 43 patients (12%) had suspicious endoscopic findings, of which 4 (80%) developed IBD (Fisher's exact: $p = 0.0002$) On analysing patients having both a raised calprotectin and suspicious endoscopic findings in the presence of FAC, 4 of 43 patients (9%) had both, of which 3 (75%) developed IBD (Fisher's exact: $p = 0.000033$).

Of the 34 cases (79%) that had neither raised calprotectin nor suspicious endoscopic findings only 1 (3%) developed IBD. This was also statistically significant by Fisher's exact ($p = 0.0046$), and the phi coefficient of 0.53 strongly supports that having neither raised calprotectin nor suspicious endoscopic findings in the context of FAC is statistically very unlikely to represent potential future IBD.

Discussion

There is increasing evidence to suggest that FAC may represent early stages of IBD. This causal relationship appears most prevalent in children and less so in adult patients. This is likely because of

fewer confounding factors, such as recommendations for children not to receive bowel preparations prior to endoscopy [8] and less long-term treatment with drugs linked to colitis, such as NSAIDs, PPIs and corticosteroids, in this population [9–15]. Furthermore, children are less likely to suffer from bowel ischaemia and diverticulosis that may predispose patients to infective colitis [16]. Due to the apparent higher rates of IBD in children with FAC, Osmond et al suggested that FAC warrants more aggressive follow-up in children compared to adults. However, there is growing evidence that FAC may also be associated with IBD in adults, although distinguishing between high and low risk groups remains challenging.

Due to the relatively low diagnostic yield and the non-specific nature of FAC, most studies have been limited to retrospective data collection and small sample sizes. To date, our study is the largest retrospective study performed in an adult population that analyses the eventual clinical outcome following a diagnosis of FAC. In addition, this is the first study to explore the relationship of endoscopic and biochemical predictors with the eventual clinical evolution and outcome of FAC.

Consistent with previous studies, a large proportion of patients had FAC related to infection. Only 3 of 14 (21%) patients had a definitive diagnosis of infective colitis from stool cultures, of which 2 (67%) cases were secondary to *Clostridium difficile* infection, and 1 (33%) case was related *to Shigella dysenteriae* infection. Other studies have identified *Entamoeba histolytica* and *Campylobacter jejuni* as infective causes of FAC [2, 7], and the heterogeneity of microbiological detection between studies emphasises the nonspecific histology of FAC in infective colitis. The higher ratio of infective colitis seen in adults compared to children may be due to higher incidence of diverticulosis and bowel ischaemia, as well as higher usage of antibiotics and anti-acid secretion medications, all of which predispose to colonic dysbiosis[17].

Due to the high rates of ‘incidental’ findings of FAC among different studies, various bowel preparations have been speculated to be implicated in the pathogenesis of localised mucosal inflammation and resulting histological findings consistent with FAC [18–20]. Although difficult to categorically exclude this, the low detection rates of FAC in the UK population, where bowel preparations for both sigmoidoscopy and colonoscopy are standardised, makes this hypothesis less credible [2].

Contrary to other studies, we detected a relatively low number of patients who were later diagnosed with drug-induced FAC. All 3 (7%) patients diagnosed with drug-induced FAC were taking NSAIDs and symptoms improved upon drug cessation. Interestingly, 4 out of 10 (40%) patients diagnosed with incidental FAC were on acid suppressive medication, and 2 of 10 (20%) patients were prescribed statins. Both classes of drugs have been implicated in the development of drug-induced colitis and this may have been a contributory factor to these patients’ symptoms and histological findings. It is well-established that NSAIDs are associated with colitis, and therefore the low detection rates of drug-induced colitis in our cohort may reflect a paucity of awareness amongst clinicians of alternative drugs as a cause of colitis [9, 14].

Our study identified 5 patients (12%) with FAC who were later diagnosed on follow up with IBD (endoscopy and histology), of which 4 (80%) were diagnosed with UC and 1 (20%) with unspecified IBD. This is in contrast to other studies where there has been a stronger correlation between FAC and CD. This discrepancy, and the underrepresentation of UC, may be incidental and reflect the small sample sizes of each study. Another explanation is that FAC may actually be an early finding consistent with all forms of IBD. However, given the close proximity of clinical presentation and histological findings, it is unlikely that the presence of FAC in patients later diagnosed with IBD is incidental.

90% of patients with UC have been shown to have at least 1 episode of relapse and remission from diagnosis. The relapse/remission rate is prognostically important, and early changes in disease activity (within 2 years) have been associated with a more aggressive trajectory [21–22]. In our study, all 5 patients diagnosed with IBD were followed up for more than 2 years after diagnosis, and none developed symptoms necessitating hospital admission, biological therapy or surgical resection. Although not statistically significant, we observed a trend towards milder disease course when FAC is associated with IBD.

Due to our limited sample size, we could not identify any statistical significance in differentiating a causal relationship between FAC and IBD and non-IBD pathologies based on symptoms, duration of symptoms, or blood markers. Nonetheless, we identified that adult patients with an eventual diagnosis of IBD had raised inflammatory markers (CRP and WCC) when initially presenting with FAC, in contrast to non-IBD patients, these findings being consistent with Osmond et al in the paediatric population. We postulate that markers of inflammation, namely CRP and WCC levels may be additional diagnostic markers for IBD in the context of FAC.

In addition, and most importantly, our study found that adult patients with a histological diagnosis of FAC were statistically unlikely to develop IBD if at presentation the endoscopic features and faecal calprotectin levels were normal. These findings augment clinical decision making, particularly with respect to active surveillance for IBD. The worried well can be reassured without unnecessary further investigations and follow-up.

Based on the 2017/18 Archived Reference Costs published by NHS Improvement [23], the average cost per unit for an outpatient lower gastrointestinal flexible sigmoidoscopy and colonoscopy with biopsies are £176 and £370, respectively. The cost of a follow-up clinic ranges from £90 to £149 depending on whether these are conducted face to face. In a large district general hospital such as our institution, serving 450,000 patients, FAC is diagnosed on average once per month. Factoring in a £36 per unit cost of FC level [24], a total of £3709 to £4347 can be saved per annum by eliminating costs of unnecessary repeated endoscopy and follow-up clinics. Extrapolating this nationally, we estimate an annual cost savings to be between £533,000 and £638,000 for the UK. This is likely to be an underestimate as unanticipated inpatient spells surrounding procedures are not included.

Conclusion

We therefore suggest that non-invasive faecal biomarkers such as calprotectin levels could be used as adjunctive surrogate markers alongside endoscopic findings to identify those patients with FAC who are at risk of developing IBD. There are accompanying positive impacts on healthcare service burden and costs. Larger prospective studies are required to validate these conclusions.

Declarations

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COMPETING INTERESTS

No potential conflict of interest was reported by the authors.

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CONTRIBUTORSHIP

Tom Hosack and Cameron Griffiths conceptualised the study. Tom Hosack, Cameron Griffiths and Rohith Kumar collected the data. Tom Hosack and Cameron Griffiths performed the statistical analysis. Tom Hosack, Cameron Griffiths and Amit Mandal performed the literature search and prepared the first draft of the manuscript. Imroz Salam and Constantinos Missouris edited subsequent versions and all five authors approved the final submission. Amit Mandal, Imroz Salam and Constantinos Missouris are acting as guarantors of the submitted work.

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Figures

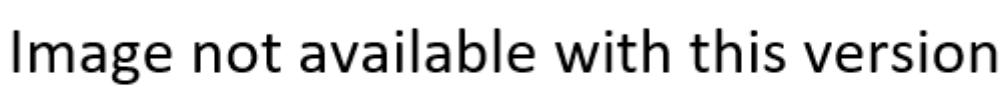

Figure 1

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