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SHORT REPORT

Prevalence of inflammatory bowel disease in patients with airways disease

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Summary
Background: Case reports and case series have suggested an association between inflammatory bowel disease (IBD) and airways disease, but there are no data demonstrating a higher prevalence of IBD among patients with airways disease. Furthermore, no consistent radiological, pulmonary or pathological abnormalities have been demonstrated in patients with both conditions.
Aims: To determine the prevalence of IBD among patients with airways disease and to evaluate clinical and pathophysiological features.
Methods: A retrospective analysis of outpatients with airways disease over a 10-year period.
Results: IBD was four times more prevalent among patients with airways disease compared with published local IBD prevalence [Odds Ratio 4.26, 95% CI 1.48, 11.71, $p = 0.006$; Crohn's disease OR 5.96, 95% CI 1.94, 18.31, $p = 0.002$ and ulcerative colitis OR 4.21, 95% CI 1.71, 10.41, $p = 0.001$]. IBD was more frequent in all types of airways disease except asthma; the association was particularly strong for conditions associated with productive cough. All except 1 patient had established IBD before the onset of respiratory symptoms. There were no obvious radiological differences between ulcerative colitis and Crohn's disease cases. There was a trend for a higher lymphocyte count (despite a tendency to lower blood lymphocyte count) but lower sputum neutrophil count in patients with Crohn's disease compared with ulcerative colitis. There were no significant differences in physiological measurements of pulmonary function between the two types of IBD.
Conclusion: Our findings support an association between airways disease and inflammatory bowel disease, particularly non-asthmatic airways disease with productive cough.

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Introduction

25% of patients with inflammatory bowel disease (IBD) have evidence of extra-intestinal manifestations.[1] The best known include pyoderma gangrenosum, erythema nodosum, anterior uveitis, arthropathy, sacroileitis, ankylosing spondylitis and primary sclerosing cholangitis. Lung involvement in IBD was first reported in 1976.[2] Since then numerous case reports and several case series have suggested an association between IBD and a variety of bronchopulmonary pathologies including: tracheal stenosis,[3] chronic bronchitis with and without suppuration,[2,4] bronchiectasis,[5–8] bronchiolitis [9] and asthma.[10] Less commonly reported associations include bronchiolitis obliterans organising pneumonia (BOOP),[8,11] granulomatous lung disease,[12] pulmonary vasculitis,[13] necrotic pulmonary nodules, drug-induced pneumonitis and serositis.[14]

An intact colon and ongoing bowel inflammation are not necessary for the pathogenesis of respiratory disease associated with IBD, since there are reports of respiratory disease developing after patients have undergone colectomy. In common with many other extra-intestinal manifestations of IBD, the activity of the bowel disease is not thought to be linked to the development and progression of IBD-associated airways disease.

Most reported cases of airways disease are in patients with ulcerative colitis. However, there has been no systematic evaluation of IBD prevalence among patients with airways disease and the apparent strong association between ulcerative colitis and airways disease may arise because ulcerative colitis is more prevalent than Crohn's disease.[15] In support of this we have shown a threefold increase in prevalence of cough, breathlessness and sputum production among patients with either ulcerative colitis or Crohn's disease compared with controls.[16] Moreover, subclinical abnormalities of pulmonary function[17–19] and airway responsiveness[20,21] are common in both conditions, although lymphocytic alveolitis has been demonstrated only in patients with Crohn's disease without respiratory symptoms.[22–24]

The mechanisms for the pathogenesis of lung disease associated with IBD are unknown. A better understanding of the types of airways disease associated with IBD may aid identification of key factors involved in the pathogenesis. We have, therefore, retrospectively identified IBD sufferers among patients presenting to a respiratory clinic with airways disease, in order to determine both prevalence and to investigate patterns of airways disease.

Methods

We reviewed all clinic letters of patients attending one consultant's (IDP) respiratory clinic between 1995 and 2005 to determine IBD prevalence among patients diagnosed with airways disease. Numbers of patients seen were recorded for all patterns of airway diseases. Clinical notes were obtained and reviewed for all patients with a diagnosis of IBD, history of bowel surgery (for IBD, or indication not stated), use of 5-aminosalicylates or immunomodulators (if indication not stated) recorded in the clinic letter.

Diagnosis of IBD was confirmed on the basis of a consistent clinical picture with endoscopic and histological confirmation, or characteristic radiological appearances.

Airways disease was classified on the following grounds: *asthma*: a consistent clinical picture with objective evidence of variable outflow obstruction and/or airway hyperresponsiveness (requiring at least one of the following: $>15\%$ rise in FEV_1 20 min after 200 μg inhaled salbutamol, $>20\%$ maximum PEF variability obtained from twice daily PEF over 14 days, a positive methacholine provocation test [$PC_{20} < 8$ mg/ml]).[25] *COPD:* a consistent clinical picture with evidence of airflow obstruction ($FEV_1 < 70\%$ of predicted and $FEV_1/FVC < 70\%$), and no significant improvement in FEV_1 after 200 μg inhaled salbutamol ($<15\%$, or if $FEV_1 < 1$ l, <200 ml improvement).[26] *Bronchiectasis*: consistent clinical picture with CT evidence of abnormal bronchial dilatation.[27] *Chronic bronchitis*: productive cough for more than 3 months a year for more than 1 year in the absence of radiological features of bronchiectasis and physiological criteria for COPD.[28] *Chronic cough*: persistent cough without sputum for $>$ 8 weeks, with no evidence of asthma and no response to proton pump inhibitors, nasal steroids or ACE Inhibitor withdrawal.[29] *Bronchiolitis obliterans*: a consistent clinical picture with progressive airflow obstruction, CT features of peribronchiolar inflammation and fibrosis, and/or fibrosis of submucosal and peribronchiolar regions.

Duration of respiratory symptoms, absence or presence of shortness of breath (SOB), wheeze, cough and sputum were documented, as well as smoking history. The duration, type, extent and where possible activity, using the Simple Clinical Colitis Activity Index and the Crohn's Disease Activity Index,[30,31] of IBD was sought. In addition, information on surgery for IBD, type of surgery and length of time since surgery, was also obtained.

Spirometry was performed with a Vitalograph spirometer (Vitalograph, Buckinghamshire, UK). Lung function tests were performed with a benchmark (PK Morgan, Chatham, UK). Sputum induction was performed 10–30 min after pretreatment with inhaled salbutamol 200 μg. However, 3%, 4% and 5% saline was inhaled sequentially, each for 5 min via an ultrasonic nebuliser with an output of 0.9 ml/min and median mass diameter of 5.5 μm (Medix, Harlow, UK). FEV_1 was measured after each inhalation, a fall $>$ 20% of best post-bronchodilator value resulted in discontinuation of the procedure; a fall $>10\%$ but $<20\%$ resulted in the administration of the same concentration of saline for the subsequent inhalation.

Analysis of data

Demographic characteristics were expressed as mean $\pm$standard error of mean (SEM) values. Comparisons between ulcerative colitis and Crohn's disease patients; for sputum and peripheral blood mean differential cell counts, pulmonary function tests, mean duration of respiratory symptoms and IBD, were undertaken using unpaired Student's *t*-tests for parametric data χ^2 tests and Fisher's exact test were used for comparisons between Crohn's disease and ulcerative colitis patients for prevalence of respiratory symptoms, smoking, medication use and abnormal radiology results. Odds ratios were calculated to

Table 1 Cases of IBD in respiratory clinic compared with expected cases [prevalence of UC 243 per 100 000: CD 130 per 100 000, IBD 396 per 100 000).[15]

Airways disease	Patients seen in clinic	IBD cases (%)	Odds ratio observed/expected	95% Confidence interval of odds ratio	*p*-Value
Chronic bronchitis	66				
UC		1	6.39	0.85–47.98	0.000
CD		3	36.58	10.18–131.52	0.07
All IBD		4 (10)	16.07	3.92–65.76	0.006
Bronchiectasis	215				
UC		4	7.88	2.71–22.91	0.000
CD		2	7.21	1.62–32.2	0.01
All IBD		7 (19)	8.38	2.43–28.89	0.001
Chronic cough	426				
UC		6	5.94	2.41–14.60	0.000
CD		2	3.62	0.82–16.11	0.09
All IBD		8 (22)	4.76	1.43–15.90	0.011
COPD	588				
UC		5	3.57	1.30–9.38	0.01
CD		4	5.26	1.71–16.19	0.04
All IBD		9 (24)	3.87	1.19–12.62	0.025
Asthma	893				
UC		6	2.81	1.15–6.9	0.02
CD		2	1.74	0.39–7.65	0.47
All IBD		9 (24)	2.54	0.78–8.26	0.123
Total	2192				
UC		22	4.21	1.71–10.41	0.001
CD		13	5.96	1.94–18.31	0.002
All IBD		37	4.26	1.48–11.71	0.006

UC, ulcerative disease; CD, Crohn's disease.

determine the ratio of IBD cases in the airways disease population compared with the predicted number of cases in a theoretical similar-sized general population cohort, using published local IBD prevalence data[15]; this was calculated in 2002 from 15 general practices in the Trent region, with a combined list size of 86 801; prevalence of IBD was 396 per 100 000, Crohn's disease 130 per 100 000 and ulcerative colitis 243 per 100 000. All tests were two-sided and a p value < 0.05 was considered statistically significant. All analysis was performed using SPSS 12 for Windows.

Results

Altogether, 2192 patients with airways disease were seen, representing 79% of all respiratory patients seen. Forty-eight had a diagnosis of IBD recorded in their clinic letter. Eleven were excluded from subsequent analysis for the following reasons: IBD not confirmed by histology ($n = 2$); lung disease other than airways disease ($n = 5$), including 1 case of pneumonitis secondary to mesalazine therapy; no underlying chronic bronchopulmonary pathology after investigation ($n = 4$: symptoms of breathlessness only, $n = 1$; acute respiratory tract infection, $n = 2$; pneumonia, $n = 1$).

There were significantly more cases of IBD in patients with airways disease than would be expected in a similar sized general population cohort, using local IBD prevalence data[15] [OR 4.26, 95% CI 1.48, 11.71, $p = 0.006$]. This was true for both Crohn's disease [OR 5.96, 95% CI 1.94, 18.31, $p = 0.002$] and ulcerative colitis [OR 4.21, 95% CI 1.71, 10.41, $p = 0.001$]. IBD was more prevalent in all patterns of airways disease except asthma; the association was particularly strong with airways disease associated with productive cough (Table 1). There were significantly more cases of ulcerative colitis than expected in all patterns of airways disease, although this just failed to reach significance in chronic bronchitis (Table 1). Crohn's disease was more prevalent in COPD and bronchiectasis, just failing to reach significance in chronic bronchitis and chronic cough.

Ulcerative colitis was the diagnosis in 62% of cases, whilst 32% had Crohn's disease, and 6% had indeterminate colitis. There were no significant differences in baseline characteristics between subjects with ulcerative colitis and Crohn's disease (Table 2). IBD diagnosis preceded onset of respiratory symptoms in all patients except 1 with Crohn's disease. A colectomy, predating the onset of respiratory symptoms in all cases, had been performed in 24% of cases. There

Table 2 Subject demographics.

	UC	CD
N (% female)	22 (59)	13 (54)
Age in years	61 (3)	60 (4)
Non-smokers *n* (%)	9 (45)	4 (31)
Ex-smokers *n* (%)	10 (50)	6 (46)
Current smokers *n* (%)	1 (5)	3 (23)
Duration of respiratory symptoms in months	30 (10)	33 (6)
Length of IBD diagnosis in years	16 (2)	15 (3)
SOB *n* (%)	11 (65)	8 (62)
Wheeze *n* (%)	9 (56)	5 (38)
Cough *n* (%)	13 (76)	12 (92)
Sputum *n* (%)	7 (41)	9 (69)
Using azothioprine/6MP *n* (%)	5 (21)	1 (8)
On 5 ASA *n* (%)	15 (79)	6 (46)
Colectomy *n* (%)	5 (28)	4 (31)
On oral steroids for IBD at initial consultation *n* (%)	0 (0)	2 (15)
Normal CT *n* (%)	1 (14)	3 (23)
Normal CXR *n* (%)	11 (73)	8 (62)

Values expressed as mean (SEM), except where stated. Denominator varies according to number of patients with relevant information documented.

were insufficient clinical details at the initial respiratory consultation to determine the Crohn's Disease Activity Index or the Simple Clinical Colitis Activity Index, but most patients appeared to have clinically inactive or mild disease at the time of consultation and did not relate respiratory symptoms to IBD activity.

Eighteen patients underwent induced sputum as part of their clinical work-up; 3 were unable to provide a sputum sample despite induction. There were no statistically significant differences between patients with ulcerative colitis and those with Crohn's disease. However, there was a non-significant trend for a higher sputum lymphocyte differential in patients with Crohn's disease compared with ulcerative colitis patients (Table 3). Crohn's disease patients also had a peripheral blood lymphocyte count at the lower end of normal range, and lower than ulcerative colitis subjects, although again statistical significance was not reached. There was no difference in use of Azathioprine, which can induce lymphopenia, between the two groups. There was a non-significant trend for a lower sputum neutrophil count in those with Crohn's disease with no differences in absolute sputum neutrophil count or peripheral blood neutrophil count (Table 3). Both groups had a higher sputum eosinophil count than the normal range, but there was no statistically significant difference between the groups.

Results of baseline spirometry were recorded in 33 patients and results of full pulmonary function tests in 11. There was a trend for a lower FEF_{25-75} among patients with Crohn's disease compared with those with ulcerative colitis (percentage predicted FEF_{25-75} 31% vs 65%, mean difference 34, 95% CI −6.7, 74, $p = 0.09$), but there were no other differences (Table 3).

Discussion

We have shown a fourfold increased prevalence of IBD in our cohort of patients with airways disease; prevalence of both Crohn's disease and ulcerative colitis was increased to a similar extent, particularly in non-asthmatic airways disease. The prevalence of ulcerative colitis was higher in all types of airways disease, whereas Crohn's disease prevalence was greater in patients with airways disease associated with productive cough. However, the small numbers of patients involved make it difficult to draw meaningful conclusions about differences in patterns of airways disease according to IBD type.

Whilst retrospective analyses are a less robust methodology than population studies, our findings strengthen the case for an association between IBD and airways disease, an association previously based on evidence from case reports and case series.[2–14] Moreover, our findings are in keeping with the predominance of non-asthmatic airways disease with productive cough seen in the majority of case series. However, further studies need to be conducted to determine whether our findings can be replicated in population-based studies. One weakness of our study is that adjustments for age or smoking status were not made, as this information was not available in either the airways disease population or the local general population sample, although the age of patients with IBD in both populations was comparable. It is unlikely that age accounted for the difference in IBD prevalence in the two populations, since the highest age-specific incidence rates of ulcerative colitis is 30–39 years and 20 −29 years for Crohn's disease [32–34] and almost all of our patients with IBD and airways disease had IBD of long duration. Similarly, differences in smoking prevalence between the 2 populations is unlikely to have accounted for the increased prevalence of ulcerative colitis amongst the population with airways disease since there is evidence that smoking protects against the development of ulcerative colitis, and the relative risk of ulcerative colitis occurring in non-smokers versus smokers is 2.6.[35] Smoking is associated with an increased risk of Crohn's disease, so we cannot exclude the possibility that the excess of Crohn's disease cases in our population with airways disease could be attributed to smoking. However, the proportion of current smokers in our cohort of patients with IBD and airways disease was very similar to that in the IBD patients in our general population cohort.

It is plausible that the increased IBD prevalence seen in our patients with airways disease results from patients with multiple diseases being referred more frequently to secondary care than those with just one disease. However, similarities between prevalence of respiratory symptoms in our earlier survey[16] and the current findings increase confidence that the association is real. It is more likely that the prevalence of IBD amongst our airways disease population has been underestimated as a limitation of our study was that the diagnosis of IBD was not systematically gathered and may not be reported by patients, particularly if their disease was of long duration and had been inactive for some time. Furthermore, our methodology meant that we were unable to identify patients no longer under active respiratory follow-up, who may subsequently have been diagnosed with IBD.

Table 3 Induced sputum and lung function results for all IBD and airways disease patients and by IBD type.

	IBD	UC	Number	CD	Number
Induced sputum: differential white cell count					
Neutrophils Normal 30.6 range (0–74.2)	67.1 (7.3)	76.9 (9.3)	7	58.6 (10.5)	8
Eosinophils Normal 0.15 range (0.2–0.6)	2.4 (1.7)	3.69 (3.50)	7	1.10 (0.38)	7
Lymphocytes Normal 1 range (0.3–2.2)	2.2 (1.4)	0.51 (0.15)	7	3.76 (2.47)	8
Induced sputum: Absolute cell count ($\times 10^4$/g)					
Neutrophils	587 (154)	613 (227)	6	556 (228)	5
Eosinophils	10.4 (5.7)	11.7 (10.4)	6	8.8 (3.9)	5
Lymphocytes	8.9 (4.1)	3.4 (2)	6	15.5 (8.3)	5
Total cell count ($\times 10^6$/mg)	7.0 (1.6)	7.1 (2.3)	6	6.9 (2.6)	5
Lung function					
FEV_1 (% predicted)	75 (4.7)	81 (6.4)	20	67 (6.3)	12
FEV_1/FVC Ratio %	68 (2.8)	70 (3.7)	20	67 (4.4)	12
RV (% predicted)	112 (9.7)	103 (8.8)	8	129 (20.1)	5
TLC (% predicted)	92 (4.4)	91 (4.6)	8	95 (9.6)	5
RV/TLC (% predicted)	119 (7.3)	110 (8.4)	8	134 (11.5)	5
KCO (% predicted)	106 (9.9)	115 (11.9)	8	92 (16.7)	5
FEF25–75 (% predicted)	49 (10.2)	65 (13.6)	6	31 (11.6)	5
Exhaled nitric oxide	11.9 (3.1)	14.85 (4.37)	11	7.37 (3.79)	7

Values expressed as mean (SEM).

Our results do not demonstrate any statistically significant difference in pulmonary function or pattern of airway inflammation between patients with ulcerative colitis and Crohn's disease. However, the study was not powered to detect such a difference and numbers of patients completing induced-sputum and full-lung function tests were small (15 and 11, respectively). Moreover, as this was a retrospective study there were neither healthy controls, non-IBD patients with the same airways disease, nor IBD patients without respiratory symptoms for comparison. Nonetheless, trends in the pattern of airway inflammation and lung function may suggest different mechanisms for the pathogenesis of airways disease in these two conditions. We had insufficient information on the extent of IBD and its activity to allow meaningful conclusions to be drawn on the relationship between bowel activity and airway disease. The different patterns of airways disease associated with different types of IBD, how they compare with patients with the same airways disease but without IBD and the relationship between activity of IBD, and airways disease have to be investigated further in an appropriately designed and powered prospective study.

In summary, we have found a significantly higher prevalence of both ulcerative colitis and Crohn's disease in our cohort of patients with airways disease compared with the expected population prevalence. The association was strongest in airways disease associated with productive cough and in patients with ulcerative colitis. The mechanisms for development of airways disease may differ between ulcerative colitis and Crohn's disease.

Conflict of Interest Statement

None of the authors has a conflict of interest to declare in relation to this work.

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