

Observational study of the natural history of eosinophilic bronchitis

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Summary

Background Eosinophilic bronchitis is an important cause of chronic cough. Treatment with inhaled corticosteroids is associated with a short-term improvement in cough and reduced sputum eosinophil count but the long-term outcome is uncertain.

Objective To determine the long-term outcome in patients diagnosed with and treated for eosinophilic bronchitis.

Methods We have performed a longitudinal study of symptoms, eosinophilic airway inflammation, spirometry and airway hyper-responsiveness in all patients diagnosed with eosinophilic bronchitis over 7 years.

Results We identified 52 patients with eosinophilic bronchitis and longitudinal data of greater than 1 year (mean 3.1 years) was available in 32 patients, all of whom were treated with inhaled steroids. Three (9%) patients developed symptoms consistent with asthma and a methacholine PC₂₀ < 8 mg/mL on one or more occasion. Five (16%) patients developed fixed airflow obstruction defined by a persistent post-bronchodilator forced expiratory volume in 1 s (FEV₁)/forced vital capacity < 70%. One (3%) patient had complete resolution of symptoms and eosinophilic airway inflammation off treatment. The remaining patients had ongoing eosinophilic airway inflammation and/or continuing symptoms. Multiple linear regression identified smoking, female gender and area under the curve of sputum eosinophil count over time as the most important predictors of decline in FEV₁.

Conclusions The most common outcome in eosinophilic bronchitis is continuing disease and complete resolution is rare. Asthma and fixed airflow obstruction developed in relatively few patients. The most important factors associated with a more rapid decline in FEV₁ were female gender, smoking and prolonged eosinophilic airway inflammation.

Keywords asthma, eosinophilic bronchitis

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Introduction

Eosinophilic bronchitis in the absence of asthma was originally described by Gibson et al. [1] and has subsequently been recognized as an important cause of chronic cough [2], being present in 10–15% of patients referred for specialist investigation. Asthma and eosinophilic bronchitis are associated with a similar T-helper type 2 cytokine driven airway inflammation [3, 4]; however airway hyper-responsiveness and variable airflow obstruction, which are the defining features of asthma, are not present in eosinophilic bronchitis.

Eosinophilic bronchitis responds well to treatment with inhaled corticosteroids in the short-term, with a reduction in symptoms and fall in sputum eosinophil count [5], however the long-term outcome of the disease is unclear. In a 10 year follow-up study of the eight of the patients originally described by Gibson, complete resolution of symptoms and eosinophilic airway inflammation was the most common outcome but a minority of patients had developed fixed

airflow obstruction [6]. Brightling has also described a patient with eosinophilic bronchitis who developed fixed airflow obstruction in association with prolonged uncontrolled eosinophilic airway inflammation [7]. Others have speculated that eosinophilic bronchitis is an early stage in the development of an asthma phenotype [8] although there is less evidence that evolution to more typical asthma occurs.

More definite information on the natural history of eosinophilic bronchitis is necessary to guide best clinical management. The aim of this prospective observational study was to investigate the outcome in patients with eosinophilic bronchitis who were diagnosed in our institution over 7 years. We have investigated annual decline in forced expiratory volume in 1 s (FEV₁) and have attempted to identify variables that might be associated with this.

Methods

Subjects

We studied all patients diagnosed with eosinophilic bronchitis at Glenfield Hospital between December 1996 and June 2003. These represented 10% of the patients referred for specialist

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investigation of chronic cough. Eosinophilic bronchitis was defined as a cough for greater than 2 months, a sputum eosinophil count $>3\%$, normal FEV₁ and FEV₁/forced vital capacity (FVC) ratio ($>80\%$ predicted and $>70\%$ respectively), an increase of less than 15% in FEV₁ 20 min following inhalation of 200 µg of salbutamol, within single day peak flow amplitude as percent of mean of less than 20% with twice daily measurements over 2 weeks and methacholine PC₂₀ >16 mg/mL. The study was approved by the Leicester-shire and Rutland research ethics committee and all patients gave written informed consent before inclusion.

Measurements

FEV₁ and FVC were measured using a rolling seal spirometer (vitalograph®, Maids Moreton, UK), which is calibrated daily. Methacholine Challenge Test was performed using the standard tidal breathing method [9] and the concentration of methacholine causing a 20% fall in FEV₁ recorded as the methacholine PC₂₀. Induced sputum was obtained using 3%, 4% and 5% saline administered via an ultrasonic nebulizer and processed as previously described [10]. Sputum eosinophil and neutrophil differential counts were expressed as a percentage of total non-squamous cells. Symptom visual analogue scores were assessed using a 100 mm scale fixed at both ends by no symptoms and worst symptoms ever [11].

Protocol

We measured FEV₁, FVC, visual analogue score, sputum differential cell count and methacholine PC₂₀ annually. If, at the end of the study period, patients had no significant symptoms and their sputum eosinophil count was less than our normal range (1.9%) [12] then an assessment of symptoms, airway responsiveness and sputum induction was repeated after withholding inhaled corticosteroid treatment for 2 months.

Analysis

Patients were assigned four different outcomes: Continuing disease, defined as evidence of significant ongoing symptom of cough and/or a sputum eosinophil count of more than 3% on or off treatment or after a 2 month withdrawal of budesonide. Disease remission, defined as no significant symptoms and no evidence of eosinophilic airway inflammation after a 2 month withdrawal of budesonide. Asthma was defined as symptoms other than cough that were consistent with asthma and a methacholine PC₂₀ of less than 8 mg/mL at any point during follow-up. Fixed airflow obstruction was defined as a FEV₁/FVC ratio of less than 70% following inhalation of 200 µg of salbutamol that persisted throughout the subsequent observation period. All available data on FEV₁ was used in a linear regression analysis to calculate the annual change in post-bronchodilator FEV₁, which was then adjusted for height by dividing by height in metres squared [13]. Area under the curve for sputum eosinophil count over time was calculated using the trapezium method [14]. Multiple independent linear regression was used to identify factors associated with rate of decline in FEV₁; gender and age were entered into the model as factors which are known to be associated with rate of decline in FEV₁. Sputum eosinophil counts were Log transformed prior to analysis, as they

assume a Log normal distribution, and sputum neutrophil counts were corrected for age [15]. All statistical tests were performed using SPSS 10 for Windows.

Results

We identified 52 patients (29 Male) with eosinophilic bronchitis. Patient characteristics are given in Table 1. Longitudinal data of greater than 1 year was obtained in 32 patients (Table 1). The diagnosis was made less than 1 year ago in nine patients, six patients declined inclusion in the longitudinal study and five patients were lost to follow-up. The mean duration of follow-up was 3.1 years (range 1–6 years) and the mean number of observations of spirometry, PC₂₀ and sputum eosinophil count were; 4.8, 2.6 and 3.2, respectively. There was no significant correlation between baseline cough visual analogue score and sputum eosinophil count ($r = -0.148$, $P = 0.43$). All patients received treatment with inhaled budesonide 200–400 µg twice daily from the time of diagnosis. Twenty (63%) patients had a reduction in cough visual analogue score that was outside the 95% range for repeat measures (15 mm) [11] following treatment and overall there was a mean improvement of 16 mm (95% CI 7, 25; $P = 0.002$). Complete resolution of symptoms occurred in six (18%) patients. There was a significant improvement in sputum eosinophil count from baseline (9.8%) to first measurement following treatment with inhaled corticosteroids (1.5%, mean fold difference 6.4%, 95% CI 2.9, 13.8; $P < 0.001$). Two patients had sufficient ongoing symptoms and eosinophilic airway inflammation to justify the addition of oral corticosteroids, which led to resolution of symptoms and eosinophilic airway inflammation in both cases. No patients received treatment with long acting β_2 -agonists.

Three (9%) patients developed symptoms other than cough that were consistent with asthma and a PC₂₀ <8 mg/mL at some point during follow-up. Five (16%) patients developed a persistent post-bronchodilator FEV₁/FVC $<70\%$. One

Table 1. Demographic data at diagnosis of all patients identified with eosinophilic bronchitis

	Cross-sectional group	Longitudinal group
Number (male)	52 (29)	32 (19)
Age (years)*	53 (17–83)	54 (17–80)
FEV ₁ (% of predicted)	99.2 (17.5)	101 (17.1)
FEV ₁ /FVC	79.2 (7.5)	79.5 (6.6)
Sputum eosinophil count (%)†	8.23 (0.23)	9.8 (0.32)
Sputum neutrophil count (%)	53 (22)	55 (21)
PC ₂₀ (mg/mL)	>16	>16
IgE (ku/L)†	46 (1.2)	43 (1.0)
Blood eosinophil count ($\times 10^9/L$)	0.31 (0.25)	0.35 (0.29)
Atopic (%)	45	38
Smokers (%)	23	19
Potential occupational dust exposure (%)	44	48
Cough visual analogue score (mm)	39 (28)	36 (21)

Values are given as mean(standard deviation) except where marked *mean (range) and †geometric mean (log standard deviation).

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PC₂₀, provocative concentration of methacholine causing a 20% drop in FEV₁.

(3%) patient had complete resolution of symptoms and eosinophilic airway inflammation off treatment. Of the 23 (72%) remaining patients 13 had ongoing symptoms and a sputum eosinophil count $>3\%$ on one or more occasion, seven had ongoing otherwise unexplained cough and a persistent sputum eosinophil count $<3\%$ (of which three were cigarette smokers) and three had no symptoms and a sputum eosinophil count on one or more occasion of $>3\%$. The mean height corrected change in FEV₁ for the group was -19 mL/year (95% CI: 9.8, 28.6). The mean height corrected change in FEV₁ was -18 mL/year in patients who did not develop fixed airflow obstruction and -26 mL/year in those that did (mean difference 8% mL, 95% CI -16 , 34; $P = 0.5$). Multiple linear regression identified smoking ($B = -30.7$; SE 9.0; $P = 0.004$), female gender ($B = -17.3$; SE 7.1; $P = 0.028$) and area under the curve of sputum eosinophil count over time ($B = -3.0$; SE 1.1; $P = 0.013$; model statistics; $R^2 = 0.713$, $P = 0.009$) as the most important predictors of decline in FEV₁.

Discussion

This is the largest longitudinal study of outcome in eosinophilic bronchitis. We identified 52 patients over 7 years representing 10% of patients seen in our institution with chronic cough over this time. As reported before [16], subjects with eosinophilic bronchitis were predominantly middle aged, non-atopic and non-smokers. In our series there was a small excess of male patients in contrast to other cough syndromes where female preponderance is common [17]. Exposure to occupational dust was no more common than would be expected in the general population [18]. The most common outcome was continuing symptoms and eosinophilic airway inflammation, although a significant minority of patients developed fixed airflow obstruction. Few patients developed symptoms and objective evidence of asthma.

Our finding that ongoing disease is the most common outcome contrasts with the findings of Hancox et al. [19], who in a 10 year follow-up of eight patients found that complete resolution of symptoms and eosinophilic airway inflammation was the most common outcome. Some of the difference may be as a result of the shorter follow-up period in our study. However our results are consistent with the outcome in atopic cough, a condition with many features in common with eosinophilic bronchitis [20]. In a longitudinal study of outcome in atopic cough only one out of a series of 63 patients with atopic cough went on to develop symptoms and objective evidence of asthma.

We have gone further than these earlier studies by estimating annual decline in FEV₁. This was not significantly different from that expected in a healthy age matched non-smoking population [13]. Our entry criteria may have biased our findings because we only recruited patients with normal spirometry values and it is possible that the population may have a reduced rate of decline in FEV₁ (i.e. the healthy smoker phenomenon). All of our patients were taking inhaled budesonide throughout the study period so we are unable to exclude the possibility that untreated individuals have a more rapid decline in FEV₁. The fact that a persistently elevated

sputum eosinophil count was related to decline in FEV₁ would be consistent with this. Our findings that female gender and as well as prolonged eosinophilic inflammation was associated with a more rapid decline in FEV₁ are consistent with our earlier observation that non-smokers with fixed airflow obstruction are predominantly female and commonly have a sputum eosinophilia [21]. Smoking was unusual in our population, perhaps reflecting referral bias because smokers with cough are unlikely to be referred for specialist opinion. However, we have shown that smoking also has an independent effect on decline in FEV₁ suggesting that smokers with eosinophilic bronchitis might be particularly likely to develop COPD. We [22] and the others [23] have shown that up to 40% of smokers or ex-smokers with moderate to severe COPD who are not taking inhaled steroids have a sputum eosinophilia supporting the view that the presence of eosinophilic bronchitis might be linked to the development of fixed airflow obstruction in some smokers.

Opinion on the nature of eosinophilic bronchitis ranges from the condition being part of an asthma spectrum to it being a clinically and pathologically distinct condition [24–26]. Our demonstration that in most patients the clinical expression of disease is unchanged over up to 7 years and that the development of features of asthma was unusual is more consistent with the latter view; although we recognize that the outcome might have been different in untreated patients. Inhaled corticosteroid treatment was associated with improvement in cough and reduction in eosinophilic airway inflammation in most patients although complete resolution of these features was uncommon. Persistent cough was present in 23 of the patients in our series, the majority of whom had ongoing eosinophilic airway inflammation. Treatment concordance was not formally assessed in our study and we cannot discount the possibility that persistent cough was because of poor treatment concordance; another possibility is the presence of relative inhaled corticosteroid resistance – the complete response to oral corticosteroids in two cases would support this. An interesting observation was that some of our patients had persistent cough but no evidence of eosinophilic airway inflammation. In some cases this may have reflected the presence of other triggers for cough such as smoking or rhinitis. However this observation suggests that cough might not be directly causally associated with eosinophilic airway inflammation. The lack of association between cough symptoms and sputum eosinophil counts at baseline is consistent with this view. A plausible explanation for the persistent cough is the presence of activated mast cells in the superficial airways, because studies have shown that sputum mast cell mediator concentrations are high [27, 28] and bronchial brushing mast cell numbers are increased in eosinophilic bronchitis [29].

In summary we have shown that eosinophilic bronchitis is usually a stable disease phenotype that remains clinically distinct from asthma. A subgroup of patients with treated eosinophilic bronchitis may have a more rapid decline in FEV₁. Smoking, female gender and prolonged sputum eosinophilia are probably associated with this outcome. Further work is necessary to determine whether more widespread investigation of airway inflammation and more aggressive anti-inflammatory treatment will lead to a reduction in the development of fixed airflow obstruction.

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