Respiratory Medicine (2014) 108, 1761–1770

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Clinical characteristics and airway inflammation profile of COPD persistent sputum producers

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Received 24 April 2014; accepted 30 September 2014
Available online 8 October 2014

KEYWORDS
COPD;
Chronic bronchitis;
Persistent sputum producer

Summary
Background: COPD patients with chronic bronchitis include a subgroup with persistent sputum production on most or every day. We hypothesized that COPD patients with persistent sputum production have a different profile of airway inflammation, and more severe clinical characteristics.
Objective: To compare the airway inflammation profile and clinical characteristics of COPD persistent and non-persistent sputum producers.
Methods: COPD persistent sputum producers ($n = 26$) and non-persistent sputum producers ($n = 26$) underwent sputum induction and pulmonary function tests. Exacerbation history was recorded; the St. George's Respiratory Questionnaire, Modified Medical Research Council Dyspnoea scale and COPD Assessment Tool were completed. 33 COPD patients provided sputum for bacteriology.
Results: Persistent sputum producers had lower post-bronchodilator FEV_1% predicted ($p = 0.01$), diffusion capacity ($p = 0.04$), 6 min walk test distance ($p = 0.05$), and higher closing volume ($p = 0.01$), BODE index ($p = 0.01$), rate of bacterial colonization ($p = 0.004$) and exacerbations ($p = 0.03$) compared to non-persistent sputum producers. The mean SGRQ and CAT scores were higher in persistent sputum producers ($p = 0.01$ and 0.03 respectively). Sputum neutrophil and eosinophil total cell counts were higher in persistent sputum producers ($p = 0.02$ and 0.05 respectively). Sputum levels of eotaxin ($p = 0.02$), MCP-1 ($p = 0.02$), TNF-α ($p = 0.03$) and IL-6 ($p = 0.05$) were higher in persistent sputum producers.

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http://dx.doi.org/10.1016/j.rmed.2014.09.020

Conclusion: COPD persistent sputum producers have more severe clinical characteristics and increased concentrations of some inflammatory mediators in the airways.

Introduction

The hallmark features of COPD are poorly reversible airflow obstruction and persistent pulmonary inflammation [1]. It is recognized that disease phenotypes exist, comprising subgroups of patients with distinct clinical or pathological characteristics associated with different prognosis or response to treatment [2].

Chronic bronchitis is defined as a productive cough for $\geq$3 months for $\geq$2 consecutive years. There is evidence that chronic bronchitis is associated with more severe airflow obstruction and breathlessness [3,4], an excessive decline in FEV_1 [5], and higher exacerbation [6—8] and mortality rates [9—11]. However, recent large observational studies have not consistently reproduced these findings; The COPD Gene Cohort study showed that chronic bronchitis is associated with more exacerbations but not with other clinical characteristics [12], while the ECLIPSE study only showed that COPD patients with chronic bronchitis had worse general health status [13]. These different outcomes may be due to the broad range of symptom severity covered by the definition of chronic bronchitis; Some COPD patients fall into the category of 'chronic bronchitis' due to a productive cough for a few months, while others have a persistent productive cough for most or every day of the year. The inclusion of patients with mild chronic bronchitis in clinical studies, as opposed to those with severe and persistent sputum production, is likely to reduce the chance of observing positive findings.

Mucins are glycosylated proteins secreted by the airway epithelia that form gels that are key components of mucus in the lungs [14]. MUC5AC and MUC5B are the major mucin subtypes expressed in the lungs, with epithelial MUC5AC expression upregulated in COPD patients [15,16]. A number of cytokines upregulate mucin expression [17], and may cause mucus hypersecretion in COPD. Previous studies evaluating cytokine levels in COPD patients with chronic bronchitis have used healthy control groups [18—20]. However, the optimal study design to investigate cytokines associated with the presence of chronic bronchitis in COPD is to compare COPD patients with and without chronic bronchitis. This approach has been used for airway inflammatory cells; eosinophil numbers were increased in induced sputum and decreased in the bronchial submucosa of COPD patients with chronic bronchitis [21], suggesting that eosinophil chemotaxis is altered.

The primary aim of this study was to investigate clinical characteristics and sputum inflammatory biomarkers in COPD patients with chronic bronchitis. The novel aspects were to focus on COPD patients with symptoms of persistent sputum production, in order to maximize the chance of finding differences between groups, and to use a control group of COPD patients without chronic bronchitis, in contrast to previous studies of sputum cytokines that have used healthy controls [19,20,22]. We processed sputum using a 'two-step' procedure [23], using phosphate buffered saline (PBS) processing first to obtain supernatant followed by dithiothreitol (DTT) to obtain cells. This avoids any effect of DTT on cytokine analysis from sputum supernatant. A secondary aim of this study was to compare results from induced and spontaneous sputum samples from persistent sputum producers, in order to determine which type of sample provides better sample quality and reproducibility in this patient group.

Methods

Subjects

COPD patients, diagnosed according to current criteria [24], were recruited from the clinical research database of the Medicines Evaluation Unit, University Hospital of South Manchester Foundation Trust. Patients were excluded if they had experienced a respiratory tract infection or exacerbation of COPD in the preceeding 6 weeks. Fifty two COPD patients participated in the main study where clinical characteristics and sputum cytokine levels were assessed. Thirty three COPD patients, including 22 from the main study, participated in a follow-on study where bacterial colonization in sputum was assessed. All patients provided written informed consent, and the local ethics committee approved the study.

Patients were identified as persistent sputum producers using the validated American Thoracic Society questionnaire [25]; Patients bringing up phlegm at least twice a day for four or more days of the week were categorized as persistent sputum producers. Non-persistent sputum producers were defined as patients who did not produce phlegm except during an exacerbation.

Study design

Measurements of pulmonary function including spirometry, lung volumes, gas transfer (KCO), single breath nitrogen washout were performed, and six minute walk test (6 MWT) and sputum induction. Full details of the methods are in the online data supplement. Exacerbation history using patient recall verified by primary care records in the previous 12 months was recorded. An exacerbation was defined as an acute change in dyspnoea, cough or sputum requiring treatment with antibiotics, oral corticosteroids or both. St. George's Respiratory Questionnaire (SGRQ), Modified Medical Research Council dyspnoea scale (MMRC) and COPD Assessment Tool (CAT) were completed, and the BODE index calculated [26]. High resolution CT scan (HRCT) (GE Medical Systems, Light Speed L52002) had been performed on 26 patients in the previous year; we did not specifically