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Airway inflammation in patients with symptoms suggesting asthma but with normal lung function

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Airway inflammation in patients with symptoms suggesting asthma but with normal lung function. P. Rytilä, T. Metso, K. Heikkinen, P. Saarelainen, I.J. Helenius, T. Haahtela. ©ERS Journals Ltd 2000.

ABSTRACT: The hypothesis that eosinophilic airway inflammation is present in many patients presenting with respiratory symptoms suggestive of asthma but with normal lung function was tested.

Thirty-six consecutive patients presenting with these features were studied. Twenty-five asthmatics and 43 healthy volunteers served as control groups. Signs of eosinophilic inflammation in blood and induced sputum were studied. Patients with respiratory symptoms were single-blindly treated with inhaled beclomethasone dipropionate (BDP), 800 μg daily, or placebo for 3 months, and re-examined at 3 months and 1 yr.

Patients with respiratory symptoms had higher numbers of blood and sputum eosinophils than healthy persons ($p<0.0001$), but the degree of eosinophilic inflammation was less pronounced than in asthmatics ($p<0.01$). Three-month's treatment with BDP significantly reduced total symptom score ($p<0.001$), cough score ($p<0.0001$), and the number of blood eosinophils ($p<0.01$). For cough alone, the improvement was significant compared with placebo ($p<0.05$). The patients were followed-up for 1 yr, and 17 (55%) still had symptoms but retained normal lung function. Four (13%) patients had developed asthma and another 10 (32%) had become free of symptoms.

Using lung function measurements and induced sputum analyses, a group of patients with symptoms suggestive of asthma and signs of eosinophilic airway inflammation but without enough airflow variability to be diagnosed as asthmatics were detected. They seemed to respond favourably to inhaled beclomethasone dipropionate treatment.

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Asthma is characterized by an influx of inflammatory cells, especially eosinophils, into the bronchial mucosa, as well as by variable airflow limitation. Diagnosis is based on establishing the lung function abnormality: improvement of airway narrowing (>15% increase forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF)), either spontaneously or after using a bronchodilator, indicates asthma [1]. Reversibility to bronchodilators and variability of lung volumes or peak flow, however, show a continuous distribution [2], and the cut-off limit of 15% is more or less arbitrary. The association between the degree of lung function abnormality and underlying inflammation is not straightforward [3]. Airflow limitation and increased bronchial responsiveness are, however, outcomes of the inflammatory process, and it may be argued that, at the time asthma is diagnosed, detection of eosinophilic bronchial inflammation is late.

Eosinophilic bronchial inflammation, sometimes also called eosinophilic bronchitis, is found in patients with newly detected or mild intermittent asthma [4, 5] and in some patients with chronic cough but normal lung function [6–8]. Patients with chronic cough responsive to corticosteroids have resembled patients with asthma in their gene expression of some cytokines found in cells from bronchoalveolar lavage [9].

Asthma is often suspected if a patient new to their doctor complains of prolonged symptoms such as cough, chest tightness, wheezing or dyspnoea. Lung function measurements are taken, and, if variable airway obstruction is established, treatment of asthma is initiated. In practice, many patients present with symptoms causing suspicion of asthma, but their lung function results do not fulfil criteria for significant variability. Consequently, these patients are usually left without specific diagnosis and may suffer from ineffective treatment.

It was decided to test the hypothesis that eosinophilic inflammation is a common pathophysiological feature in patients with prolonged respiratory symptoms suggestive of asthma irrespective of lung function. The patients with respiratory symptoms were treated with either inhaled beclomethasone diproprionate (BDP) or placebo for 3 months, and followed-up for 1 yr.

Subjects and methods

Patients

Thirty-six consecutive patients with respiratory symptoms referred to the Outpatient Clinic of the Department of

Allergology, Helsinki University Central Hospital during the winter period October 1996–March 1997 were studied. The clinic receives patients from general and private practitioners in the greater Helsinki region, which has a population of 1.2 million. The patients are referred if asthma is suspected to be the cause of symptoms and evaluation of their allergic status is needed. Therefore, the clinic receives patients with variable symptom severity, not just those who are difficult to treat. Twenty-five patients diagnosed as asthmatics during the same period and 43 healthy persons were recruited as control groups.

The patients with respiratory symptoms suggestive of asthma had to be symptomatic at the time they were studied. Only patients that had reported at least two of the six respiratory symptoms (cough, chest tightness with wheezing, shortness of breath, sputum production, wheezing or cough at exercise, and disturbed sleep) for >2 months but <1 yr were included. Each of the six symptoms was graded on a scale ranging from 0 (asymptomatic) to 9 (the most severe discomfort). Patients who had been treated with anti-inflammatory asthma medication (corticosteroids, disodium cromoglycate, nedocromil sodium or theophylline) were excluded. The healthy persons had no respiratory symptoms or history of chronic pulmonary diseases. Patients or healthy persons who had had a clinically diagnosed respiratory infection during the preceding 8 weeks were excluded. Possible causes of chronic cough, such as postnatal drip and lung parenchymal diseases, were excluded by means of chest and sinus radiography and careful interview of the patients. Special attention was paid to ruling out gastro-oesophageal reflux while taking the patient history. Patients who had used histamine H_2-blockers were excluded. None of the smokers included had a history of chronic bronchitis [10].

Table 1. – Characteristics of the study groups

	Respiratory symptoms	Asthma	Healthy persons
Subjects n	36	25	43
Age yrs	39 (19–60)	38 (15–75)	36 (23–54)
Sex male/female	3/33	9/16	16/27
Smoking*	8 (22)	9 (36)	4 (9)
Atopy#	19 (53)	14 (56)	10 (23)
History of allergic rhinitis	7 (19)	6 (24)	4 (9)
History of atopic eczema	3 (8)	2 (8)	0 (0)
FEV1 % pred+	95.4 (73–119)	78.6 (57–105)	98.2 (77–121)
Increase in FEV1 %‡	2.5 (0–6)	11.2 (0–38)	nd
PEF variability %§	5.2 (0–11)	21.1 (11–60)	nd
PD15 mg¶	>1.6	0.40 (0.02–1.25)	>1.6

Data are presented as means with ranges in parentheses or as absolute numbers with percentages in parentheses. *: all current smokers with mean (range) cumulative cigarette exposure of 8.6 (1–20) pack-yrs for respiratory symptoms, 8.4 (0.2–20) pack-yrs for asthma and 74 (2–15) pack-yrs for healthy controls. There were more smokers in the asthma than in the healthy control group ($p<0.01$, Chi-squared test); #: at least one positive allergy skin-prick test, see *Clinical methods* section. There were more atopic subjects in the respiratory symptoms and asthma than in the healthy control group ($p<0.01$, Chi-squared test); +: reference values of VILJANEN [12]; ‡: 15 min after inhalation of 200 mg salbutamol; §: between morning and evening; ¶: reference values of of SOVIJÄRVI *et al.* [11]. FEV1: forced expiratory volume in one second; PEF: peak expiratory flow; PD15: provocative dose of histamine causing a 15% fall in FEV1; % pred: percentage of the predicted value; ND: not determined.

Clinical methods

Asthma was diagnosed if the patient showed, on resting flow/volume spirometry (Medikro, Kuopio, Finland), a ≥12% increase in FEV1 15 min after inhalation of 200 μg salbutamol (Buventol Easyhaler 100 microg/dose®; Orion Pharma, Espoo, Finland), or PEF (Mini-Wright peak flow meter; Clement Clarke International, London, UK) varied by >12% from morning to evening for ≥3 days during a 2-week follow-up period. In addition, they had to show increased bronchial responsiveness to inhaled histamine [11]. Patients who did not show significant airflow variability and were not hyperresponsive were given an operational diagnosis of "respiratory symptoms". The healthy persons all showed normal lung function (table 1).

Skin-prick tests were performed using 11 common inhalant allergens (Soluprick SQ® (10 histamine equivalent potency (HEP)); ALK-Abello, Hørsholm, Denmark), and positive (histamine dihydrochloride, 10 mg·mL^{-1}) and negative control solutions (solvent). A subject was classified as atopic if any allergen caused a weal of ≥3 mm in diameter while control solution gave expected results [13]. Blood samples were taken by venepuncture and serum separated under standardized conditions permitting release of leukocyte activation markers. Sputum was induced by inhalation of nebulized 5% hypertonic saline using an ultrasonic nebulizer (Spira Ultra®; Hengityshoitokeskus, Hämeenlinna, Finland) as previously described [14]. No premedication was used. To ensure the safety of the procedure, PEF measurements were performed before and after inhalation. The method of sputum examination described by PIZZICHINI *et al.* [15] was used. Briefly, all sputum macroscopically free of salivary contamination was selected and treated with dithiothreitol (Sputolysin® 10% concentration; Calbiochem Corporation, San Diego, CA, USA) in phosphate-buffered saline. The resultant suspension was centrifuged, and the supernatant aspirated and stored in Eppendorf tubes at -20°C for later assay. The cell pellet was resuspended, and the absolute number of cells per milligram of processed sputum calculated. Coded cytospins were prepared and stained using May-Grünwald Giemsa stain and toluidine blue in order to obtain a differential cell count. The sputum sample was considered adequate if it contained <80% squamous epithelial cell contamination from saliva [16]. The results are expressed as a percentage of the total nonsquamous cell count.

Concentrations (in μg·L^{-1}) in thawed serum and sputum supernatant of two eosinophil activation markers, eosinophil cationic protein (ECP) and eosinophil peroxidase (EPO), as well as of two markers of neutrophil activation, myeloperoxidase (MPO) and human neutrophil lipocalin (HNL), were measured. ECP and MPO concentrations were determined using commercially available immunoassay kits (Pharmacia & Upjohn, Diagnostics, Uppsala,

Sweden), and EPO and HNL concentrations using prototype immunoassay kits (Pharmacia & Upjohn, Diagnostics) as previously described [17]. All analyses were performed blind to the clinical characteristics of the subjects.

The Ethics Committee of Helsinki University Central Hospital approved the study, and all subjects gave informed consent to participate in the study.

Follow-up

In order to study the effects of inhaled steroid as well as the course of respiratory symptoms, the 36 patients without variable airway obstruction were randomized to inhale single-blindly BDP, 400 μg twice daily, from a multidose powder inhaler (Beclomet Easyhaler 200 microg/dose®; Orion Pharma), or placebo (lactose) for the first 3 months. Randomization was performed using a computerized randomization list based on a block size of 10. Compliance was checked by collecting the dry powder inhalers after the 3-month treatment and checking whether they had been used adequately. After the first 3-month period, patients were allowed to take symptomatic medication (inhaled salbutamol, Buventol Easyhaler 100 microg/dose®) if needed. Their symptoms, lung function, and blood and sputum samples were studied at 3 months and after 1 yr. Patients with asthma and normal subjects were not followed.

Statistical analyses

Data are presented as mean and SEM or range. The significance of the differences between the three study groups was analysed using Kruskal-Wallis one-way analysis by ranks. Comparisons of the two patients groups were analysed by the Mann-Whitney U-test or the Chi-squared test, as appropriate. Wilcoxon's test for paired data was used to analyse the follow-up data in patients with respiratory symptoms. Two-tailed p-values of <0.05 were considered significant. The reference (normal) range for sputum eosinophil number was calculated as mean±3SD for the healthy control group.

Results

The clinical characteristics of the study groups are shown in table 1. There were more females than males, especially in the group with respiratory symptoms. The mean ages of the three study groups did not differ significantly.

Baseline

Patients with asthma had higher total symptom scores than patients with respiratory symptoms (p=0.005, Mann-Whitney U-test) (table 2). The asthma patients had significantly more blood eosinophils and higher concentrations of serum EPO compared with the patients with respiratory symptoms (p=0.002 and p=0.008, respectively), and the healthy persons (p<0.0001 for both analyses) (table 3). Also, patients with respiratory symptoms had more blood eosinophils and higher concentrations of serum EPO than the healthy persons (p=0.01 and p=0.02, respectively).

Table 2. – Symptoms of patient groups at baseline

	Respiratory symptoms	Asthma	p-value*
Subjects n	36	25	
Total symptom score (0–54)	10.6 (4–24)	16.5 (6–35)	0.005
Individual symptom scores (0–9)			
Cough	3.2 (0–9)	3.4 (1–9)	NS
Chest tightness with wheezing	0.9 (0–6)	2.6 (0–6)	<0.0001
Shortness of breath	1.6 (0–4)	3.0 (1–9)	0.006
Sputum production	2.2 (0–9)	2.3 (0–6)	NS
Exercise symptoms	1.6 (0–4)	3.5 (0–9)	0.0003
Symptoms at night	1.2 (0–6)	1.8 (0–6)	NS
Duration of symptoms months	9 (5–12)	9 (2–12)	NS

Data are presented as mean (range). *: Mann-Whitney U-test. NS: nonsignificant.

All subjects tolerated the sputum induction procedure well. Thirty-four (94%) of the patients with respiratory symptoms, 21 (84%) of the patients with asthma and 37 (86%) of the healthy persons produced an adequate specimen of sputum for analysis at baseline (table 3). Mean squamous epithelial cell contamination was 16% (range 0–73%) for all subjects. The three groups differed significantly in the percentage of sputum eosinophils and the concentrations of sputum EPO and ECP (table 3, fig. 1). No significant differences were observed between the three study groups in the percentage of sputum neutrophils or in the serum and sputum concentrations of MPO and HNL.

Based on the sputum values of the healthy persons, the upper limit for sputum eosinophils (mean±3SD; 0.7%) was calculated. Fourteen (67%) of the asthma patients who produced a sample for sputum analysis showed increased sputum eosinophils, compared with 13 (38%) of the patients with respiratory symptoms and one (3%) of the healthy persons.

Atopic asthmatics had more blood eosinophils than nonatopic asthmatics (0.51×10^9 *versus* 0.27×10^9 cells·L^{-1}, p=0.04). There were no other significant differences in clinical characteristics or measures of inflammation between atopic and nonatopic subjects in any of the groups. Smokers and nonsmokers did not differ significantly from each other in clinical characteristics or measures of inflammation. If smokers were omitted from the analyses, the differences between the groups remained the same.

Follow-up

Of the 36 patients with respiratory symptoms, 31 (86%) were re-examined both at 3 months and 1 yr (table 4, fig. 2). Four of the five patients who were not available for re-examination had used a placebo.

At 3 months, cough and total symptom scores and blood eosinophil number had decreased significantly from baseline in the BDP-treated group (table 4). In the placebo-treated group, only total symptom score decreased

Table 3. – Serum and sputum measurements in the three study groups at baseline

	Respiratory symptoms	Asthma	Healthy persons	p-value*
Subjects n	36	25	43	
Blood eosinophils 10^9 cells·L^{-1}	0.17±0.02	0.41±0.06	0.11±0.01	<0.0001
Serum ECP μg·L^{-1}	11.8±1.5	15.2±2.1	8.1±0.7	0.003
Serum EPO μg·L^{-1}	13.8±1.7	30.0±5.3	10.6±2.2	<0.0001
Serum MPO μg·L^{-1}	254±20	251±22	200±20	NS
Serum HNL μg·L^{-1}	112±11	104±6.7	94.5±3.6	NS
Sputum cells 10^3 cells·mg^{-1}	8.9±2.0	8.5±4.1	3.7±0.7	NS
Sputum eosinophils %	2.5±0.9	15.5±6.1	0.07±0.03	<0.0001
Sputum neutrophils %	39.8±4.6	39.6±6.4	32.5±4.2	NS
Sputum lymphocytes %	0.7±0.2	0.5±0.1	0.4±0.1	NS
Sputum macrophages %	55.4±4.4	42.5±6.3	61.5±3.9	0.02
Sputum epithelial cells %	1.5±0.5	1.9±1.0	5.4±2.0	NS
Sputum mast cells %	0.02±0.01	0.31±0.23	0±0	0.003
Sputum ECP μg·L^{-1}	644±229	1119±351	181±50	0.02
Sputum EPO μg·L^{-1}	89.1±32.5	292±164	17.6±11.6	<0.0001
Sputum MPO μg·L^{-1}	180±59	198±126	85±8.7	NS
Sputum HNL μg·L^{-1}	12596±3048	6568±1062	5598±785	NS

Data are presented as mean±SEM. *: Kruskal-Wallis test. Serum measurements were available from all subjects. Sputum measurements were obtained from 34 patients with respiratory symptoms, 21 asthmatics and 37 healthy persons. ECP: eosinophil cationic protein; EPO: eosinophil peroxidase; MPO: myeloperoxidase; HNL: human neutrophil lipocalin; NS: nonsignificant.

significantly. The cough score decreased significantly more in the BDP-treated group compared with the placebo-treated group ($p<0.05$) (fig. 2).

After 1 yr, 17/31 (55%) of the patients with respiratory symptoms continued to be symptomatic with normal lung function. Four (13%) patients, two in the BDP and two in the placebo group, had developed asthma. Another 10 (32%), six in the BDP and four in the placebo group, were free of symptoms, *i.e.* they did not fulfil the symptom criteria (see *Clinical methods* section). In the BDP-treated group, the total symptom score had decreased from 9.9–5.7, and, in the placebo group, from 11.8–7.0. Two of the patients (both in the placebo group) that had developed asthma had received inhaled steroid treatment after the first 3-month period and were omitted from the 1-year analysis. At 1 yr, the mean percentage of sputum eosinophils had decreased in the BDP-treated group from the baseline 3.0% to 1.3% and in the placebo group from the baseline 2.3%–0.3% (table 4). Of the 29 patients that were included in the 1-yr analysis, 11 of the 28 (39%) with adequate sputum samples showed increased sputum eosinophil number at the start of the study. At 1 yr, in 50% of them, eosinophils persisted. Of the 17 (61%) patients that had no sputum eosinophils at the first examination, 33% showed sputum eosinophils at 1 yr.

Discussion

A patient group with respiratory symptoms causing suspicion of asthma, many of them showing signs of eosinophilic airway inflammation, but whose lung function does not fulfil the criteria for asthma are described [1, 10]. Compared with healthy persons, these patients had higher numbers of blood and sputum eosinophils and higher concentrations of the eosinophil activation marker EPO. The degree of eosinophilic inflammation was not as pronounced as in the patients who could be diagnosed as having asthma.

Eosinophilic airway inflammation is a fluctuating process, and signs of it may be apparent at one time point but

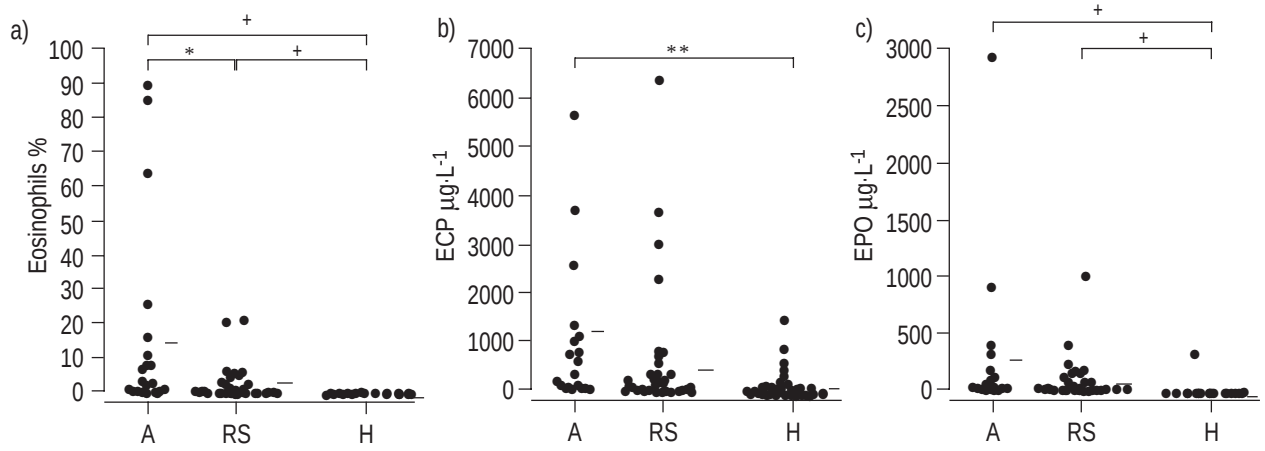

Fig. 1. – Sputum measurements in the three study groups at baseline: a) eosinophils; b) eosinophil cationic protein (ECP); and c) eosinophil peroxidase (EPO). Horizontal bars represent means. A: asthma; RS: respiratory symptoms; H: healthy. **: $p<0.01$; +: $p<0.0001$.

Table 4. – Changes in lung function, symptom score and eosinophil number in 31 patients with respiratory symptoms

	BDP[+]	Placebo[+]
Subjects n	16	15
Sex male/female	2/14	0/15
Age yrs	36±2.6	41±2.5
FEV_1 L		
Baseline	3.3±0.2	3.0±0.2
Change after 3 months	-0.06±0.05	-0.05±0.04
Change after 1 yr	-0.11±0.04	-0.03±0.04
PEF variability %		
Baseline	7.9±1.0*	4.8±0.9
Change after 3 months	-2.9±1.7	-1.3±1.2
Change after 1 yr	-3.1±1.2[#]	0.3±1.6
Total symptom score 0–54		
Baseline	9.9±1.3	11.8±1.2
Change after 3 months	-5.1±0.8[‡]	-4.2±1.7[#]
Change after 1 yr	-4.2±2.3	-4.4±2.7
Cough score		
Baseline	3.4±0.5	3.3±0.7
Change after 3 months	-1.9±0.6*,[§]	-0.9±0.8
Change after 1 yr	-1.5±0.7[§]	-0.7±1.2
Blood eosinophils 10^9 cells·L^{-1}		
Baseline	0.19±0.04	0.16±0.4
Change after 3 months	-0.07±0.04[#]	-0.02±0.02
Change after 1 yr	-0.04±0.04	-0.02±0.03
Sputum eosinophils %		
Baseline	3.0±1.3	2.3±1.7
Change after 3 months	-1.2±1.3	-1.0±1.1
Change after 1 yr	-1.7±1.5	-0.5±0.5
Sputum ECP µg·L^{-1}		
Baseline	896±449	496±211
Change after 3 months	-345±466	-21±282
Change after 1 yr	-871±630	-147±119
Sputum EPO µg·L^{-1}		
Baseline	136±68	50±22
Change after 3 months	-44±48	6.0±40
Change after 1 yr	-84±80	-2.7±4.0

Data are expressed as mean±SEM. [+]: the single-blind treatment with inhaled beclomethasone dipropionate (BDP), 800 µg daily, or placebo was given for 3 months. Sputum measurements were obtained from 26 patients (15 in the BDP and 11 in the placebo group) at both baseline and 3 months, and from 20 patients (13 in the BDP and seven in the placebo group) at both baseline and 1 yr. FEV_1: forced expiratory volume in one second; PEF: peak expiratory flow; ECP: eosinophil cationic protein; EPO: eosinophil peroxidase. *: $p<0.05$ *versus* placebo (Mann-Whitney U-test); [#]: $p<0.05$; [‡]: $p<0.001$; [§]: $p<0.0001$ *versus* baseline (Wilcoxon's test).

absent at another. This may be especially true in mild cases. It can be argued that the patients with respiratory symptoms had mild asthma, but, according to the present functional definition, are not diagnosed as such. The diagnosis of asthma can be difficult, since lung function measurements can long be normal or conflicting [18]. In order not to include asthmatics in the patient group with respiratory symptoms, the low 12% PEF and FEV_1 variability criteria and increased bronchial responsiveness were used for discriminating between the patient groups. In patients with respiratory symptoms, FEV_1 increased by only 2.5% 15 min after inhaling salbutamol mean morning and evening variability was 5.2% during PEF monitoring, and no increased responsiveness to inhaled histamine was detected.

The term eosinophilic bronchitis has been used for patients with isolated chronic cough and sputum production, but without wheeze or other symptoms suggestive of asthma, and with increased sputum eosinophil number [6–8, 19]. It has also been used in subjects with work-related asthma-like symptoms without asthma and with sputum eosinophils [20]. Recently, the limit of 3% sputum eosinophils has been suggested [8, 19]. Only 21% (seven of 34) of the present patients with respiratory symptoms suggestive of asthma fulfilled this criteria for marked eosinophilia. In the authors' experience, healthy and truly asymptomatic persons have very low eosinophil numbers in their sputum (mean 0.07%, see table 3). By using the 3-SD (0.7%) cut-off limit, 38% of the present patients with respiratory symptoms showed eosinophilia but 67% of the patients with asthma. These results support the present view that, in cross-sectional surveys, variable airflow limitation can be observed without signs of eosinophilic inflammation, which can also occur without functional abnormality [6–8, 19].

Atopic subjects without asthma and patients with seasonal allergic rhinitis not currently exposed to allergen may have airway eosinophilia [21, 22]. In the present study, the decree of airway inflammation did not differ between atopic and nonatopic individuals. Airway eosinophilia may occur in otherwise healthy persons during and after viral infection [23]. It was attempted to exclude the effects of any viral infection by including only patients with no signs of a respiratory infection during the preceding 8 weeks. The three study groups did not differ in the percentages of sputum neutrophils or in the concentrations of the neutrophil activation markers, MPO or HNL [24].

There are no population-based surveys on the prevalence of eosinophilic airway inflammation. Many people may experience episodes of symptomatic eosinophilic bronchial inflammation associated with allergen exposure and infections, but are not accurately diagnosed or treated if their lung function does not significantly deviate from reference values. In a recent study, the prevalence of eosinophilic bronchitis in a sample of 91 patients with isolated chronic cough was 12% [8].

It has previously been shown that lung function measurements, combined with assessment of eosinophil activation, increase the sensitivity of asthma diagnosis [14]. Eosinophilic airway inflammation can be readily studied from induced sputum, which has been shown to be similar to lower respiratory secretions expectorated spontaneously and to give results comparable to those obtained by more invasive bronchoscopic methods [25, 26]. The methodology of sputum processing used in the present study has been reasonably reproducible and is valid [15]. The presence of eosinophils in sputum is a more sensitive marker of asthmatic airway inflammation than blood eosinophils or serum ECP [27, 28].

In the patients with respiratory symptoms, 3 month's treatment with inhaled BDP suppressed the symptoms and eosinophils more than placebo, and, for the most important symptom, cough, the difference between treatments was significant. In asthma, eosinophilic inflammation is reversed or suppressed, along with lung function improvement, by inhaled corticosteroids [29, 30]. In eosinophilic bronchitis, inhaled steroid treatment has been shown to

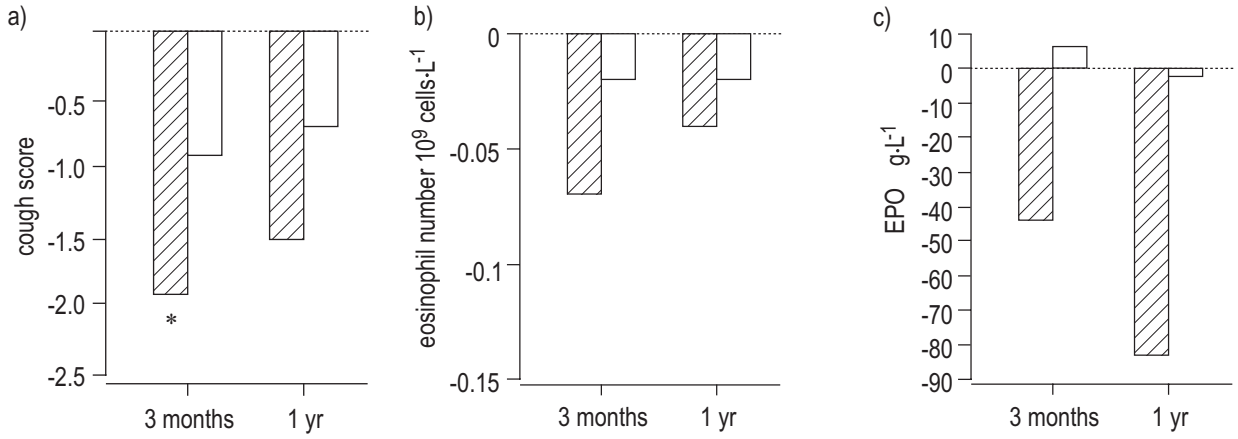

Fig. 2. – Changes (Δ) in: a) cough score; b) blood eosinophil number; and c) sputum eosinophil peroxidase (EPO) concentration after 3 months and 1 yr in patients with respiratory symptoms (▨: beclomethasone dipropionate treatment; □: placebo). Data are mean change from baseline. *: $p<0.05$ *versus* placebo.

suppress symptoms and decrease sputum eosinophils [7, 8]. However, these studies were not placebo-controlled.

A general consensus exists as to the treatment of moderate and severe asthma, but treatment of mild asthma is much debated. Introduction of anti-inflammatory therapy is usually not recommended until the patient uses a short-acting β_2-agonist several times a week [1]. The current situation is largely due to lack of knowledge of the natural history of these conditions. Do patients with respiratory symptom suggestive of asthma later develop asthma? In the present study, four (13%) patients developed asthma during the follow-up year, irrespective of their treatment during the first 3 months. In a Finnish study of children aged 7–12 yrs who had symptoms suggestive of asthma but normal lung function, one-third developed clinical asthma during a 2-yr follow-up [31]. Early detection of eosinophilic inflammation would improve treatment with anti-inflammatory medication. This approach might have an impact on disease progression and risk of asthma. In general practice, the bronchial inflammation that may underlie the symptoms is usually not characterized. Clinical judgement is based on indirect information concerning bronchial status. As a consequence, symptomatic patients without apparent lung function abnormality are left without accurate diagnosis, often leading to repeated courses of antibiotics, expectorants, antitussives, antihistamines and β_2-agonists. These medications do not essentially affect the eosinophilic process.

It is concluded that there are patients who have symptoms suggestive of asthma and signs of eosinophilic inflammation without significant airflow limitation. They respond to inhaled corticosteroid treatment. This condition lacks agreed definition and diagnostic criteria. It could be called eosinophilic bronchitis or asthma-like inflammation. The latter refers to the same kind of inflammation characteristics as found in asthma. The occurrence of this disorder and the effects of various treatments have not been studied systematically.

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