Sputum neutrophilia can mask eosinophilic bronchitis during exacerbations

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BACKGROUND: Exacerbations of airway disease are eosinophilic, neutrophilic, both or neither. The primary objective of the present study was to identify whether the treatment of a neutrophilic bronchitis can unmask an associated eosinophilia.

METHODS: A retrospective survey of 2160 consecutive sputum cell counts from 1343 patients with airway disease was conducted to identify patients with an isolated neutrophilic bronchitis, which was defined as a sputum total cell count of greater than or equal to 12×10^6 cells/g of sputum and a proportion of neutrophils of 80% or greater. The characteristics of the patients who subsequently demonstrated sputum eosinophilia (3% or greater) within eight weeks of resolving the neutrophilia were compared with the patients who subsequently did not have sputum eosinophilia.

RESULTS: Two hundred thirty-seven patients had 273 neutrophilic exacerbations. The sputum was re-examined within eight weeks in 65 patients (27.4%), of whom 38 (58.5%) had resolution of the neutrophilic bronchitis after treatment with an antibiotic. Of these 38 patients, 13 (34%) showed eosinophilia.

CONCLUSIONS: A neutrophilic exacerbation of airway disease was observed to mask sputum eosinophilia in one-third of patients who had sputum cell counts available before and after antibiotic therapy. Hence, the absence of sputum eosinophilia during an infective exacerbation should not be used as an indication to reduce the dose of corticosteroids. To optimize therapy, repeat sputum cell count measurements are recommended after antibiotic treatment before changing corticosteroid treatment.

Key Words: *Eosinophilic bronchitis; Neutrophilic bronchitis; Sputum cell counts*

Une neutrophilie des expectorations peut masquer une bronchite à éosinophiles pendant des exacerbations

HISTORIQUE : Les exacerbations des maladies des voies aériennes sont causées par des éosinophiles, des neutrophiles, ces deux substances ou aucune d'entre elles. Le principal objectif de la présente étude consistait à établir si le traitement de la bronchite à neutrophiles peut révéler une éosinophilie connexe.

MÉTHODOLOGIE : On a mené une étude rétrospective d'après 2 160 dénombrements cellulaires consécutifs d'expectorations auprès de 1 343 patients atteints d'une maladie des voies aériennes afin de repérer les patients atteints d'une bronchite à neutrophiles isolée, définie comme un dénombrement cellulaire total des expectorations égal ou supérieur à $12x10^6$ cellules/g d'expectorations et une proportion de neutrophiles de 80 % ou plus. Les caractéristiques des patients qui ont ensuite démontré une éosinophilie des expectorations (3 % ou plus) dans les huit semaines suivant la résorption de la neutrophilie ont été comparées à celles des patients qui n'avaient pas développé d'éosinophilie des expectorations.

RÉSULTATS : Deux cent trente-sept patients ont souffert de 273 exacerbations à neutrophiles. On a réexaminé les expectorations dans les huit semaines chez 65 patients (27,4 %), dont 38 (58,5 %) ont guéri de leur bronchite à neutrophiles après une antibiothérapie. De ces 38 patients, 13 (34 %) ont présenté une éosinophilie.

CONCLUSIONS : On a observé qu'une exacerbation à neutrophiles des maladies des voies aériennes masquait une éosinophilie des expectorations chez le tiers des patients pour qui on disposait du dénombrement cellulaire des expectorations avant et après une antibiothérapie. Par conséquent, l'absence d'éosinophilie des expectorations pendant une exacerbation infectieuse ne doit pas servir d'indicateur pour réduire la dose de corticoïdes. Pour optimiser la thérapie, il est recommandé de reprendre le dénombrement cellulaire des expectorations après l'antibiothérapie, avant de modifier le traitement aux corticoïdes.

Exacerbations of airway disease are common in tertiary care clinics (1-3). They are a major cause of morbidity and mortality, and are an economic burden to the patient and society (1,2). Exacerbations are heterogeneous in nature, and can be associated with a neutrophilic, eosinophilic, or combined neutrophilic and eosinophilic bronchitis (4,5). Neutrophilic exacerbations are common, and are usually associated with bacterial or nonbacterial infections (6). Noninfective exacerbations are usually eosinophilic (7). When exacerbations are noneosinophilic, the condition is unlikely to benefit from added corticosteroid treatment (8-10). However, when there is an infection with an increase in both total cell count and neutrophil differential, it is possible that the airway neutrophilia may mask an eosinophilic bronchitis and lead to an inappropriate reduction of corticosteroid treatment. We examined the frequency and clinical predictors of such masking in a retrospective survey of exacerbations over a two-year period.

PATIENTS AND METHODS

Subjects

Patients referred for sputum cell counts between January 2004 and January 2006 from the clinics of eight respiratory physicians at the Firestone Institute for Respiratory Health, Hamilton, Ontario, were enrolled in the present study. Patients were 30 to 81 years of age and had an exacerbation of physician-diagnosed asthma, chronic airflow limitation, bronchiectasis or chronic cough.

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TABLE 1
Characteristics of patients at the time of a neutrophilic exacerbation

Characteristics	Masking effect (n=13)	No masking effect (n=25)	P
Male, n (%)	4 (30.8)	14 (56)	NS
Age, years, mean ± SD	60.2±15.3	60.5±14.4	NS
Current or former smokers, n (%)	2 (15.4)	5 (20)	NS
Asthma, n (%)	10 (76.9)	5 (20)	
Chronic airflow limitation, n (%)	2 (15.4)	14 (56)	
Bronchiectasis, n (%)	0	1 (4)	
Chronic cough, n (%)	1 (7.7)	5 (20)	
FEV_1, L, mean ± SD	1.9±0.5	2.0±1.1	NS
FEV_1, % predicted, mean ± SD	72.0±17.5	65.5±22.9	NS
Atopy, %	61.5	41.7	NS

FEV_1 Forced expiratory volume in 1 s

Design

A retrospective survey of a computerized database of spontaneous or induced sputum cell counts was designed. The database was used to identify those patients with neutrophilic bronchitis who were treated with an antibiotic for seven to 10 days and whose sputum cell counts were re-examined within eight weeks. The patient's clinical characteristics, including atopy and spirometry, were documented at baseline, as well as their medications on both occasions. The patients were divided into two groups: those who subsequently demonstrated sputum eosinophilia and those who did not. The study was approved by the Research Ethics Board of St Joseph's Healthcare, Hamilton, Ontario.

Study definitions

Neutrophilic bronchitis, which is suspected to mask an eosinophilia, was defined as that with a total cell count of greater than or equal to 12×10^6 cells/g of sputum and a proportion of neutrophils of 80% or greater (11). Eosinophilic bronchitis, which is not usually associated with a raised total cell count, was defined as a percentage of sputum eosinophils of 3% or greater (12,13). Asthma was defined as variable airflow limitation as described by Scadding (14). The presence of moderate or many macrophage smokers' inclusions was used to indicate that the patient was a current or former smoker. Chronic airflow limitation included patients who were diagnosed with chronic obstructive pulmonary disease as indicated by a postbronchodilator forced expiratory volume in 1 s/slow vital capacity of less than 70% (15). The masking effect of neutrophilic bronchitis was identified by the presence of sputum eosinophilia after the sputum neutrophilia had resolved with antibiotic treatment.

Procedures

Sputum induction and examination for total and differential cell counts were performed by the methods described by Pizzichini et al (16). Spontaneous sputum was considered appropriate if the viability of the sample was more than 50% (17). Spirometry was performed according to the standards of the American Thoracic Society, before or 10 min after the administration of 200 µg of salbutamol (18). Reference values were taken from Crapo et al (19). An exacerbation was defined by an increase in cough, dyspnea, sputum volume or purulence, or a fall in forced expiratory volume in 1 s by at least 20% that, in the opinion of the physician, required an adjustment to therapy (4). Allergy skin tests were performed by the modified skin prick technique with 14 common allergen extracts (20), and atopy was defined as one or more wheals of larger than 3 mm in diameter.

Analysis

Descriptive statistics were used to identify the demographic characteristics of the patients. Normally distributed data were summarized by the arithmetic mean ± SD. Variables with non-normal distributions, such as the dose of corticosteroid, percentage of eosinophils and absolute eosinophil count, were summarized using the median and interquartile range. Student's *t* tests were used for comparisons between normally distributed groups. Mann-Whitney U tests were used to compare non-normally distributed data. A multiple logistic regression model was used to determine the predictive value of clinical features in patients who showed the masking effect. The statistical software used was SPSS Graduate Pack 13.0 (SPSS Inc, USA).

RESULTS

The sputum database consisted of 2160 cell counts from 1343 patients. Two hundred thirty-seven patients had 273 neutrophilic exacerbations, of whom only 65 (27.4%) had sputum cell count measurements repeated within eight weeks. Of these 65 patients, 38 (58.5%) had a resolution of the neutrophilic bronchitis after seven to 10 days of antibiotic treatment, and of these, 13 (34%) had eosinophilia, suggesting a masking effect of the previous neutrophilia (Tables 1 and 2).

The predictive values of the disease diagnosis, atopy and decrease in total steroid dose between the two visits were assessed for a masking effect. Only diagnosis was a significant predictor (P=0.009); the odds of demonstrating the masking effect was lower in patients with chronic airflow limitation than in those with asthma (OR 0.07, 95% CI 0.01 to 0.44; P=0.005). Atopy and decrease in total steroid dose between the two visits were not predictors of the masking effect.

DISCUSSION

The results show that among patients with an exacerbation of neutrophilic bronchitis (presumed to be infective) and a normal percentage of sputum eosinophils, approximately one-third had sputum eosinophilia after the neutrophilia was treated. This demonstrates that the previous neutrophilia had masked the eosinophilia. These observations are relevant in clinical practice when having to choose the appropriate therapy to treat neutrophilic exacerbations.

The strengths of the present study are the excellent reliability, validity and responsiveness of quantitative sputum cell count measurements. The major weaknesses are the retrospective design and failure to ensure that corticosteroid dose was left unchanged between the two measurements. Furthermore, as sputum measurements were not repeated in all patients who had neutrophilic bronchitis, the results may not be representative of the entire sample of patients with isolated neutrophilic bronchitis. The mean length of time between the end of antibiotic treatment and the second sputum examination in both groups of patients was between 23 and 26 days, close to the required time period of four to six weeks for symptomatic and physiological recovery to occur (21). The present study did not include patients whose exacerbations were severe enough to warrant hospitalization, and therefore, the findings are limited to mild to moderate exacerbations of airway disease. Also, while

TABLE 2
Sputum cell counts and concomitant corticosteroid treatment at the time of the exacerbation and after antibiotic treatment

	At the time of the exacerbation			After antibiotic treatment		
	Masking effect (n=13)	No masking effect (n=25)	P	Masking effect (n=13)	No masking effect (n=25)	P
Sputum total cell count, x10^6/g, mean ± SD	53.6 (49.5)	44.1 (37.8)	NS	7.2 (5.1)	5.1 (3.2)	NS
Neutrophils, %, mean ± SD	93.3 (5.2)	91.2 (4.4)	NS	51.6 (23.3)	62.8 (26.7)	NS
Neutrophils, ×10^6/g, mean ± SD	51.3 (48.8)	40.4 (35.5)	NS	4.1 (3.5)	4.0 (3.0)	NS
Eosinophils, %, median (interquartile range)	0.5 (0.3 to1.3)	0 (0 to 0.3)	0.006	17.8 (6.5 to 30.4)	0.3 (0 to 1.2)	<0.001
Eosinophils, ×10^6/g, median (interquartile range)	0.2 (0.1 to 0.4)	0 (0 to 0.2)	0.011	1.0 (0.3 to 2.7)	0 (0)	<0.001
Inhaled steroid, n (%)	13 (100)	20 (80)	NS	13 (100)	20 (80)	NS
Dose of Inhaled steroid, µg, median (interquartile range)	1000 (900 to 1800)	1000 (500 to 1300)	NS	1000 (1000 to 1800)	1000 (500 to 1300)	NS
Prednisone, n (%)	8 (61.5)	9 (36)	NS	7 (53.8)	9 (36)	NS
Dose of prednisone, mg, median (interquartile range)	10 (0 to 27.5)	0 (0 to 8.8)	NS	5 (0 to 15)	0 (0 to 5)	NS

The masking effect of neutrophilic bronchitis was identified by sputum eosinophilia after the sputum neutrophilia had resolved with antibiotic treatment

we considered the exacerbations to be infectious because of the raised total cell count, their bacterial or viral cause was not examined, and this might have been important with respect to the associated eosinophilia (6). Hence, the accuracy and elaboration of the results require further prospective evaluation.

In patients with asthma, an eosinophilic bronchitis is usually characterized by an increase in the percentage of sputum eosinophils, while the total cell count remains within the normal range (4). Hence, when there is infective neutrophilia with an increase in total cells and percentage of neutrophils, eosinophilia may be masked. Such eosinophilia might have been present before the infection, because treatment was suboptimal, or it may have been induced by the infection. Activated neutrophils secrete mediators such as platelet activation factor, leukotriene B4, and tumour necrosis factor alpha, which can augment the accumulation of eosinophils (22). Papi et al (6) have suggested that viral infection can cause an increase in airway eosinophils. However, this has not been observed in another similar study (7), and might just have been a result of coincidental uncontrolled eosinophilic bronchitis due to exposure to allergen (23) or chemical sensitizer (24). We observed that the masking effect was less common in patients with chronic airflow limitation. This is supported by observations that only one-third of patients with stable moderate to severe chronic obstructive pulmonary disease have associated eosinophilic bronchitis (15).

Sputum cell count measurements are still not available for routine clinical management of airway diseases in Canada, except in a few academic centres in Hamilton (Ontario), Quebec City and Montreal (Quebec), and Calgary (Alberta). The major limitations are perceived technical difficulties and a lack of financial support. The present observations suggest that if sputum cell counts are available, overwhelming neutrophilic bronchitis can mask underlying eosinophilia. Therefore, both the absence and a normal percentage of sputum eosinophils during such neutrophilic exacerbations do not indicate that there is no associated eosinophilic bronchitis. If the exacerbation is severe, corticosteroid treatment may need to be added or increased. Otherwise, to optimize therapy, we recommend that sputum cell count measurements be repeated after antibiotic treatment and before changing corticosteroid treatment.

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