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Similarity and differences in elderly patients with fixed airflow obstruction by asthma and by chronic obstructive pulmonary disease

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Summary

Background: Epidemiologic studies have demonstrated that elderly patients with fixed airflow obstruction can be affected by asthma or chronic obstructive pulmonary disease (COPD).

Methods: We studied 49 consecutive elderly outpatients, presenting fixed airflow obstruction, by clinical history (smoking), pulmonary function tests, blood gas analysis, and induced sputum.

Results: The age was not different in patients with COPD ($n = 28$) and asthma ($n = 21$) (70.2 ± 3.9 years vs. 69.6 ± 3.7 years), also the degree of fixed airflow obstruction was similar (FEV_1: $58.3 \pm 1.5\%$ vs. $59.0 \pm 1.4\%$ of predicted). Patients with asthma had significantly more eosinophils in peripheral blood ($0.43 \pm 0.05 \times 10^{-3}\,\mu L$ vs. $0.27 \pm 0.1 \times 10^{-3}\,\mu L$, $P < 0.0001$), and in induced sputum (5.0% [(p25th and p75th) 5.0–6.0%] vs. 1.0% [(p25th and p75th) 0.01–1.0%]; $P < 0.0001$), as well as serum ECP ($18.6 \pm 4.9\,ng/mL$ vs. $7.7 \pm 4.7\,ng/mL$, $P < 0.0001$) and ECP in the induced sputum ($31.6 \pm 2.9\,ng/mL$ vs. $5.6 \pm 4.9\,ng/mL$, $P < 0.0001$). Finally, in induced sputum the eosinophils EG_2^+ were higher in patients with asthma than in patients with COPD (40.5 [(p25th and p75th) 39.3–44.3] MFI vs. 3.9 [(p25th and p75th) 0–11.4] MFI, $P < 0.0001$). They also had significantly higher

diffusing capacity, and a greater reversibility to steroids, after 14-day course of therapy, whereas the reversibility to 400 μg of salbutamol was similar.

Conclusion: Despite similar fixed airflow obstruction, elderly patients with asthma have distinct characteristics compared with patients with COPD.

Introduction

Airway diseases are a significant problem for older subjects. They cause a large burden of illness in the community, and, in primary settings, they present particular problems for diagnosis and management. Despite this, much of what we already know and do for asthma in older subjects is based on studies conducted in young people with asthma.

Lung function is not routinely measured and airflow obstruction is largely underestimated, particularly in the elderly.[1–3] However, distinguishing between asthma and chronic obstructive pulmonary disease (COPD) is difficult and may be impossible in some older patients, specially in those with fixed airflow obstruction.[4,5] Many elderly patients are often diagnosed as having COPD, even if the differential diagnosis between asthma and COPD, in patients with fixed airflow obstruction, may be important as the responses to treatment are different, depending on whether fixed airflow obstruction is due to asthma or COPD.[6,7] Epidemiologic studies have demonstrated that up to 30% of patients with fixed airflow limitation have a history of asthma.[8]

The goals of treatment are similar in asthma and COPD: to reduce symptoms, maintain lung function and normal activity, prevent exacerbation, and minimize the adverse effects of treatment.[9,10] Asthma is usually treated with anti-inflammatory medications, and bronchodilators are used as needed.[9] COPD is usually treated with bronchodilators, which provide small symptomatic benefits, and inhaled corticosteroids, which can reduce exacerbations and improve quality of life.[10,11]

We planned this study to investigate if fixed airflow obstruction in elderly subjects, by asthma or by COPD, can be differentiated through clinical and functional characteristics or through the evaluation of the cells in induced sputum, or both.

Methods

Patients

From January 2000 to December 2004, we evaluated 80 patients, older than 64 years, who consecutively presented at *Dipartimento di Medicina Clinica e delle Patologie Emergenti* of the University of Palermo (Italy), with fixed airflow obstruction.

Fixed airflow obstruction was defined as post-bronchodilator (salbutamol) FEV_1/FVC less than 70%.[12]

None of the patients received regular anti-inflammatory treatment at the time of the sampling. Smoking status was checked during patient interview.[13]

We excluded patients who had an exacerbation requiring pharmacologic treatment in the 6 months before the study.

The number and severity of exacerbations before the months preceding the study were not recorded.

Flow-volume curves were assessed at baseline and after 400 μg salbutamol by metered-dose inhaler, and diffusing capacity (diffusing capacity of carbon monoxide [DLCO]), and carbon monoxide transfer coefficient [KCO]) was measured. Equipment: Gould 2400 automated system (Bilthoven, Netherlands), and SensorMedics Vmax 229 V6200 Autobox Bodypletismograph with DLCO (Yorbalinda, CA, USA).

Atopic status was assessed by skin prick test (SPT) for pneumo-allergens in the Palermo area[14] (allergens used: Alk Abellò, Milan, Italy). The panel included the following extracts: pollens (grass [*Phleum pratense*], mugwort [*Artemisia vulgaris*], wall pellitory [*Parietaria judaica*], and trees [*Olea europea* and *Cupressus*]), house dust mites (*Dermatophagoides pteronyssinus* and *farinae*), molds (*Alternaria alternata* and *Aspergillus fumigatus*), animal danders (cat and dog), a negative (glycerinated saline), and a positive control (histamine, 10 mg/mL). A positive response was defined as any wheal with a diameter 3 mm greater than the negative control, 15 min after the application.[15]

Each patient also performed arterial blood gases analysis, eosinophils blood count, serum total IgE and ECP in serum and in induced sputum, according to the manufacturer's instructions. Equipment: pH/Blood Gas Analyzer, Instrumentation Laboratory 1306 (Lexington, MA, USA), Technicon-H1 blood cell counter (Bayer Leverkusen, Germany), and CAP[TM] SYSTEM (Phadia Diagnostics, Uppsala, Sweden).

In all patients were controlled the reversibility to corticosteroids (14-day course with oral prednisone, 50 mg/day).

Authorization of the study was not required according to our institutional policy and the ethical committees of our institution. However, written informed consent to the study was obtained from every patient, in compliance with our institutional policy.

All the measurements and clinical data collections were performed during the first visit.

Sputum induction and processing

After baseline FEV_1 and FVC measurements, salbutamol was given by inhalation (200 μg by metered-dose inhaler), and subjects then inhaled hypertonic (4.5%) saline nebulized solution for periods of progressively increasing length (1, 2, 4, 8, and 16 min). FEV_1 was measured 1 min after each inhalation. The hypertonic saline solution was administered with a MEFAR nebulizer (Markos, Monza, Italy). The collected sputum samples were examined within 2 h. Selected portions of the sputum sample originating from the lower respiratory tract were chosen through examination with an inverted

microscope, were weighed, and then, processed using 1% dithiothreitol (Sigma Chemicals, Poole, UK). Total cell count and viability (Trypan blue exclusion method) were determined with a Burkers chamber hemocytometer. The cell suspension was placed in a Shandon cytocentrifuge (Shandon Southern Ltd., Runcorn, UK) and cytospin preparations were made at 450 rpm for 6 min. Cytospin slides were fixed with methanol, stained with May-Grunwald-Giemsa for an overall differential cell count of 500 nucleate nonsquamous cells, and examined, under oil immersion by light microscopy, at magnification of $400 \times$, by an observer unaware of the clinical characteristics of the subjects. Only samples with a cell viability $>50\%$ and $<20\%$ squamous cell contamination were considered.[16]

EG$_2^+$ cells in induced sputum

A flow cytometric technique, based on fixation with formaldehyde and permeabilization with octyl-glucopyranoside of eosinophils from induced sputum, was used according to Hallden et al. with minor modifications, previous described.[17,18] The results were expressed as mean fluorescence intensity (MFI) ratio of positive cell populations.[17–19]

Statistical analysis

Data have been presented as mean $\pm$ S.D. and as median and 25–75th percentile, and analyzed with Student's test for unpaired data, or with Mann–Whitney U-test, on the basis of the distribution of the data. For statistical analyses a value of $P<0.05$ was considered statistically significant.

Receiver operating characteristic (ROC) curve analysis was performed for all the functional/pathologic parameters that were thought to define the capability/power of each variable (predictive value) to recognize patients with a history of asthma within our study population. The area under the ROC curves was determined, and a value above 0.80 was considered a good discrimination.[20] ROC curve analysis also allowed (sensitivity vs. one minus specificity) selection of the best cut-off point of each variable for discriminating between the two groups.

Results

On the whole, the subjects were elderly, with fixed airflow obstruction. From the 80 patients recruited, we report the results obtained in the 49 patients who agreed to participate in the study. Each patient was characterized by medical history and physical examination. Of the 49 patients studied, 21 had a history of asthma and 28 had a history of COPD.

All asthma patients had a clear clinical history of recurrent wheezing or breathlessness episodes that reversed spontaneously or after treatment, and a familial history of asthma.[9] None of these patients was a smoker. All patients with COPD had a clear history of smoking, with more than 20 pack-years, chronic productive cough or sputum, no history of asthma, even in their familial, and no reported allergic diseases.[10]

In Table 1, we have been reported gender, age, duration of disease (years), smoking (pack-years), previous treatments, total serum IgE, and rate of SPT positivity. The patients with history of asthma differed from patients with history of COPD for smoking (no asthmatic was a smoker), previous treatments, total serum IgE (209 kU/L [162–331] vs. 36 kU/L [27.5–63.0], $P<0.0001$), and rate of SPT positivity (47.6 vs. 7.1, $P = 0.001$).

In Table 2, we reported the pulmonary function and diffusing capacity. FEV$_1$, FVC, and FEV$_1$/FVC have been reported as value obtained and as percentage of theoretical value. These parameters did not differ between the 21 patients with asthma and the 28 patients with COPD. Patients with asthma had higher diffusing capacity (DLCO

Table 1 Demographic and clinical features of patients.

	Asthma group ($n = 21$)	COPD group ($n = 28$)	P-value
Gender (M/F)	10/11	16/12	0.5
Age (years)*	70.2 ± 3.9	69.6 ± 3.7	0.6
Duration of disease (years)*	11.9 ± 3.7	11.7 ± 4.3	0.9
Previous treatments			
Inhaled steroid (%)	71.4	60.7	0.4
β_2-short-acting (%)	100	100	
β_2-long-acting (%)	61.9	46.4	0.2
Oral steroids (%)	100	100	
Cromones (%)	52.0	3.5	<0.0001
Anticholinergic (%)	14.2	42.8	0.03
Mucolytic (%)	9.5	100.0	<0.0001
Antileukotrienes (%)	66.6	42.8	0.1
Ketotifen (%)	33.3	7.1	0.02
Serum total IgE (kU/L)†	209 (162–331)	36 (27.5–63)	<0.0001
Rate of skin prick test positivity (%)	47.6	7.1	0.001

*Data have been reported as mean ± S.D.
†Data have been reported as median with lower quartile (25th) and higher quartile (75th) shown in parentheses.

Table 2 Pulmonary function of patients.

Parameters	Asthma group (n = 21)	COPD group (n = 28)	P-value
DLCO (mL/min/mmHg)	23.2±1.5	15.7±1.5	<0.0001
KCO (mL/min/mmHg/L)	4.1±0.2	3.3±0.2	<0.0001
FEV_1 (L)	1.29±0.23	1.37±0.21	0.1
FEV_1 (%)	58.3±1.5	59.0±1.4	0.1
FVC (L)	2.13±0.37	2.23±0.35	0.2
FVC (%)	76.0±2.3	76.7±2.8	0.09
FEV_1/FVC (%)	60.5±2.1	61.3±4.1	0.9
FEV_1 after bronchodilator (400 μg of salbutamol) (L)	1.40±0.24	1.48±0.22	0.2
Increasing of FEV_1 (mL) after bronchodilator (400 μg of salbutamol)	106.4±16.5	112.5±16.8	0.09
Δ % of FEV_1 after bronchodilator (400 μg of salbutamol)	8.3±1.2	8.3±1.6	0.7
FEV_1 after steroid (50 mg of prednisone) (L)	1.47±0.05	1.51±0.04	0.4
Increasing of FEV_1 (mL) after steroid (50 mg of prednisone)	165.8±52.9.5	144.6±34.5	0.1
Δ % of FEV_1 after steroid (50 mg of prednisone)	13.1±5.0	10.7±3.0	0.04

Data have been reported as mean±S.D. Δ = change.

Table 3 The results of arterial blood gas analysis.

Parameters	Asthma	COPD	P-value
pH	7.43±0.02	7.43±0.01	0.7
PO_2 (mmHg)	86.9±1.2	85.5±2.0	0.006
PCo_2 (mmHg)	38.4±0.6	38.5±0.7	0.9
SaO_2 (%)	94.9±1.9	93.5±6.0	0.01

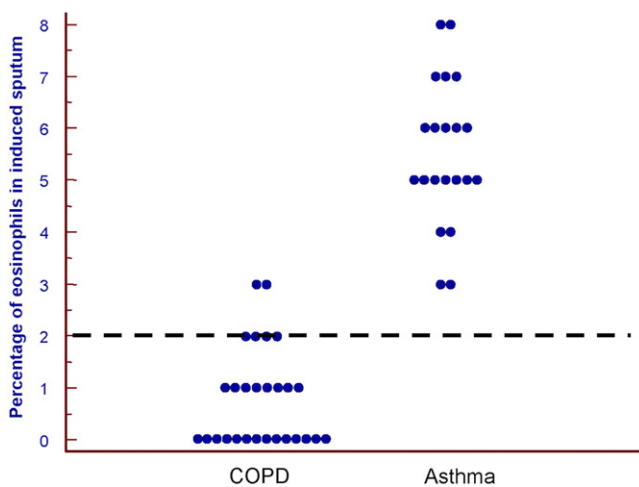Data have been reported as mean±S.D.

Figure 2 Percentage of neutrophils in induced sputum in patients with fixed airflow obstruction by COPD and asthma. The best cut-off points to discriminate between the two groups are ⩽21.0% neutrophils in induced sputum.
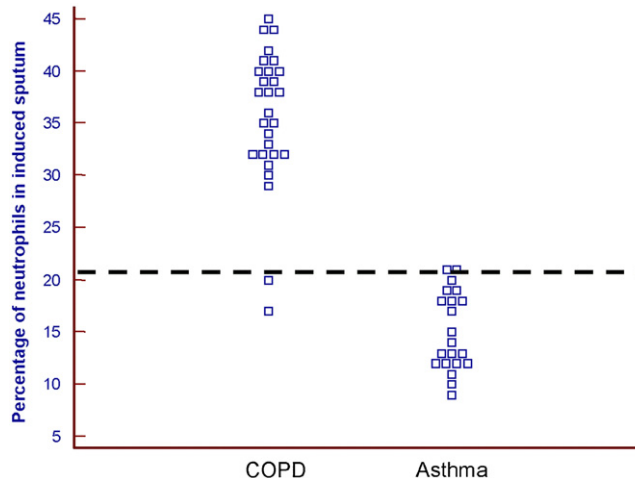

Figure 1 Percentage of eosinophils in induced sputum in patients with fixed airflow obstruction by COPD and asthma. The best cut-off points to discriminate between the two groups are >2.0% eosinophils in induced sputum.

and KCO). However, the patients with asthma differed from patients with COPD only for an increasing FEV_1 after steroids (14-day course), considered as Δ % of FEV_1 (13.1±5.0 vs. 10.7±3.0, P = 0.04).

In Table 3, have been shown the results of ABG analysis. Both PO_2 (86.9±1.2 mmHg vs. 85.5±2.0 mmHg, P = 0.006) and SaO_2 (94.9±1.9% vs. 93.5±6%, P = 0.01) significantly differed in patients with COPD respect to patients with asthma.

ECP in the serum (18.6±4.9 ng/mL vs. 7.7±4.7 ng/mL, P<0.0001) and in the induced sputum (31.6±2.9 ng/mL vs. 5.6±4.9 ng/mL, P<0.0001) was higher in patients with asthma than in patients with COPD.

Also the number of eosinophils in the blood was higher in patients with asthma than in patients with COPD (0.43±0.05 × 10^{-3} μL vs. 0.27±0.1 × 10^{-3} μL, P<0.0001). Compared with the patients with COPD, patients with asthma had more eosinophils (5.0% [(p25th and p75th) 5.0–6.0%] vs. 1.0% [(p25th and p75th) 0.01–1.0%]; P<0.0001), and fewer neutrophils in the induced sputum

Table 4 Inflammatory cells in the induced sputum in patients with fixed airflow obstruction.

	Asthma group ($n = 21$)	COPD group ($n = 28$)	P-value
Macrophages (%)	33.0 (26.0–36.0)	34.0 (28.0–36.0)	0.8
Neutrophils (%)	9.0 (8.0–11.0)	36.0 (32.0–40.0)	<0.0001
Eosinophils (%)	5.0 (5.0–6.0)	1.0 (0–1.0)	<0.0001
Eosinophils EG_2^+ (MFI)	40.5 (39.3–44.3)	3.9 (0–11.4)	<0.0001

Data have been expressed as median with lower quartile (25th) and higher quartile (75th) shown in parentheses.

(9.0% [(p25th and p75th) 8.0–11.0] vs. 36.0% [(p25th and p75th) 32.0–40.0]; $P<0.0001$) (Figures 1 and 2). No difference was found between patients with asthma (33.0% [(p25th and p75th) 26.0–36.0]) and COPD (34.0% [(p25th and p75th) 28.0–36.0], $P = 0.8$) as regards to percentage of macrophages. Finally, in the induced sputum, the MFI of eosinophils EG_2^+ was higher in patients with asthma than in patients with COPD (40.5 [(p25th and p75th) 39.3–44.3] vs. 3.9 [(p25th and p75th) 0–11.4], $P<0.0001$) (Table 4).

ROC curve analysis

None of the functional pulmonary parameters were able to recognize patients with asthma among subjects with fixed airflow obstruction due to asthma or COPD. The values of the area under the ROC curves (0.53 for reversibility to bronchodilators, 0.55 for reversibility to steroids, 0.59 for KCO, 0.70 for SaO_2, and 0.71 for PO_2) were below 0.80, suggesting that these parameters are poor predictors of the diagnosis of asthma.

In contrast, the percentage of eosinophils in sputum was good predictors of asthma, whereas the percentage of neutrophils in sputum was good predictors of COPD. The area under the ROC curve was 0.99 (CI 95%, 0.92–1.00) for the percentage of eosinophils in sputum. For sputum eosinophils, the best cut-off point was 2.0% [(with a sensitivity of 1.00 (CI 95% 0.83–1.00) and a specificity of 0.92 (CI 95% 0.75–0.98)], indicating that values higher to 3.0% predicted asthma, whereas values lower than 2% predicted COPD, among subjects with fixed airflow obstruction. The area under the ROC curve was 0.99 (CI 95%, 0.89–0.99) for the percentage of neutrophils in sputum. For sputum neutrophils, the best cut-off point was $\leqslant21\%$ [(with a sensitivity of 1.00 (CI 95% 0.83–1.00) and a specificity of 92.9 (CI 95% 0.75–0.98)], indicating that values lower or equal to 21% predicted asthma, whereas value higher than 21% predicted COPD, among subjects with fixed airflow obstruction.

Discussion

In this study, we showed that, within a group of elderly patients with fixed airflow obstruction, those with asthma have distinct airway inflammation as compared with those with COPD and history of smoking-induced airway disease. This finding suggests that asthmatic airway inflammation does not change with the development of fixed airflow obstruction and thus does not become similar to the airway inflammation characteristic of COPD. Therefore, our results indicate that, even when fixed airflow obstruction is present, asthma should be diagnosed as asthma and not as COPD.

Previous studies have compared airway inflammation in asthma and COPD.[21,22] All those studies compared young patients with asthma, who had variable airflow obstruction, with older COPD patients, who had fixed airflow obstruction. Thus, they did not address whether the issue of the pathology of asthma changes with the development of fixed airflow obstruction and becomes similar to that characteristic of COPD. In another study, the authors compared 27 patients with late-onset asthma and 24 patients with COPD. The reported values for FEV_1(%), FVC(%), and FEV_1/FVC(%), in their patients with COPD (43.79 ± 20.08, 59.54 ± 18.21, and 56.08 ± 14.36, respectively), were lower that the values of our patients with COPD (59.0 ± 1.4, 76.7 ± 2.8, and 61.3 ± 4.1, respectively). Moreover, the characteristics of the asthmatic patients were different between the studies: their asthmatic patients were smoker, and the comparisons between patients with asthma and patients with COPD were statistical significant for FEV_1%, FVC%, and FEV_1/FVC(%). On the contrary, our asthmatic patients were never smoker and we found no differences between FEV_1(%), FVC(%), and FEV_1/FVC(%) between asthmatic patients and patients with COPD.[23]

Indeed, in this study, the patients examined were clearly identified as suffering from COPD, and the differential diagnosis with asthma has not been even previously considered.[24,25]

In this study, we investigated the characteristics of airway inflammation in elderly patients of similar age and similar degree of fixed airflow obstruction, but with a different clinical history, asthma or COPD.

The relationship between airway inflammation and airflow obstruction is poorly understood, both in asthma and in COPD. The increased number of eosinophils in asthma and neutrophils in COPD seems to be the major determinant of airflow obstruction, therefore it may be a marker of two different inflammatory cascades for two diseases, asthma and COPD, that result in the same functional abnormality, i.e. fixed airflow obstruction. One limitation of our study is that no patients have been submitted to bronchial biopsies. Our Ethic Committee did not consider ethical performing bronchial biopsies in elderly subjects with the diagnosis of asthma or COPD.

The differential diagnosis between fixed airflow obstruction due to asthma or COPD is important in clinical practice, because the response to treatment of the two diseases are different.[26] The results of our study show that measurement of lung volumes, responsiveness to steroids, and even

diffusing capacity overlap considerably, making these tests of little use for distinguishing the two groups. Airway hyperresponsiveness to methacholine is with difficulty performing, considering the values of FEV_1 of these patients.[27] However, in previous study the airway hyperresponsiveness to methacholine was not significantly different between patients with asthma and with COPD, confirming that, once fixed airflow obstruction develops, measurement of airway responsiveness to methacholine is not useful for distinguishing asthma from COPD.[28]

Eosinophils in induced sputum are a well-established marker of airway inflammation in asthma, and also the most reliable objective measurement that helps to distinguish asthma from COPD once fixed airflow obstruction has developed.[28] Our results suggest that, in particular, the noninvasive measurements of eosinophils in induced sputum might be clinically useful in assessing the relative contributions of asthma.

Using the discriminating point of 2.0% sputum eosinophils, identified in our study, we found that only 6 of the 28 patients with COPD had sputum eosinophilia: 4 patients with 2% of eosinophils and 2 patients with 3%, respectively. These results confirm that eosinophilia in sputum may occur in only a minority of patients with COPD. Because these patients with COPD could be able to respond to steroids as asthma patients do, they should be properly identified and treated.[29,30] However, the eosinophils EG_2^+ and ECP in serum and sputum in patients with COPD were lower that in patients with asthma.

The diagnosis of asthma is more difficult in older patients and it could be responsible for a lower rate of asthma diagnosis in elderly subjects. Physicians may underdiagnose asthma, in older patients.[31,32] Therefore, it is a common misconception that adult-onset asthma is rare and that dyspnea is caused by aging.[23,31]

Considering the presented data, on the basis of a detailed clinical history, especially smoking habit, it should be possible to differentiate asthma from COPD. Whereas, it may not be possible to differentiate fixed airflow obstruction due to asthma or COPD, considering only pulmonary function examination, i.e. change of FEV_1 after 400 μg of salbutamol. In other words, common diagnostic tools are not helpful in elderly patients for discrimination between these two obstructive diseases. However, the results of our study demonstrate that, despite similar fixed airflow obstruction, subjects without history of smoking, i.e. with asthma, have distinct functional and pathologic characteristics compared with patients with a history of smoking, i.e. with COPD. These differences may explain the better response to steroids described in patients with fixed airflow obstruction due to asthma, compared with patients with fixed airflow obstruction due to COPD.[28]

Anyway, the principle limitation of our study is the small number of patients studied. Larger populations are needed to conclude more accurate interpretations. However, it is difficult to find elderly patients available to these kinds of investigations.

Finally, our study suggests that, in clinical practice, older patients with fixed airflow obstruction due to asthma should not be grouped under the general heading of COPD. Rather, they should be properly identified and treated. Our data shown that the atopy and the smoking predispose to chronic respiratory disease with a different effect on the prevalence of asthma and COPD, respectively.

Conflict of interest

The authors declare no competing interests.

Acknowledgments

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