Comparison of Airway Wall Remodeling in Asthma and COPD: Biopsy Findings

Justyna Kosciuch MD PhD, Rafal Krenke MD PhD, Katarzyna Gorska MD PhD, Wojciech Baran PhD, Marek Kujawa MD PhD, Katarzyna Hildebrand MD PhD, and Ryszarda Chazan MD PhD

BACKGROUND: Bronchial remodeling is currently known to affect not only patients with asthma, but also COPD patients. Some studies have demonstrated that basement membrane thickening and destruction of the bronchial epithelium are also found in COPD. The aim of the study was to compare the basement membrane thickness (BMT) and epithelial damage in biopsy specimens from patients with asthma and COPD. METHODS: The study was performed in 20 subjects with asthma and 12 subjects with COPD, who had not been treated with corticosteroids for at least 3 months before study enrollment. Subjects' characteristics were based on the results of clinical assessment, allergic skin-prick tests, lung function testing, and methacholine bronchial challenge. All subjects underwent bronchoscopy with forceps biopsies of bronchial mucosa. Light-microscope and semi-automatic software were used to measure BMT in hematoxylin-eosin stained sections. Total (denudation) and partial epithelial damage were assessed independently by 2 pathologists. RESULTS: The mean BMT in subjects with asthma was 12.54 ± 2.8 μm, and only 7.81 ± 2.0 μm in COPD patients ($P < .001$). Overall percentage of the basement membrane length lined with damaged epithelium was 45 ± 20% in the asthma group and 47 ± 22% in the COPD group (difference not significant). Complete and partial epithelial damage did not differ between the groups. CONCLUSIONS: BMT might be a histopathological parameter helpful in distinguishing asthma and COPD patients, whereas the extent and pattern of epithelial damage is not. *Key words: asthma; COPD; biopsy; basement membrane; epithelium; bronchoscopy.* [Respir Care 2012;57(4):557–564. © 2012 Daedalus Enterprises]

Introduction

The first reports of bronchial remodeling in patients with asthma date back to the early 1900s.[1] Many subsequent observations have confirmed the results of those early studies.[2,3] Introduction of fiberoptic bronchoscopy in the early 1990s resulted in further extensive research on airway inflammation and remodeling in patients with asthma.[4,5] Several structural abnormalities have been shown to be important and relatively constant features of airway remodeling in asthma patients. They include epithelial desquamation, basement membrane (BM) thickening, hypertrophy of the goblet cells and mucous glands, increased proliferation of blood vessels, hyperplasia, and smooth muscle cell hypertrophy.[6,7] Airway remodeling is regarded as a major cause of airway hyper-responsiveness, progressive loss of lung function, resistance to corticosteroid therapy, more severe course of the disease, and only partial reversibility of air-flow limitation observed in some asthma patients.[6]

Bronchial remodeling is currently known to affect not only patients with asthma, but also patients with COPD. Several studies have demonstrated that BM thickening and

Drs Kosciuch, Krenke, Gorska, and Hildebrand, and Prof Chazan are affiliated with the Department of Internal Medicine, Pneumonology, and Allergology; Dr Baran is affiliated with the Department of Biophysics and Human Physiology; and Dr Kujawa is affiliated with the Department of Histology and Embryology, The Biostructure Centre, Medical University of Warsaw, Warsaw, Poland.

The authors have disclosed no conflicts of interest.

Correspondence: Justyna Kosciuch MD PhD, Department of Internal Medicine, Pneumonology, and Allergology, Medical University of Warsaw, Banacha 1A, 02–097 Warsaw, Poland. E-mail: j_kosciuch@o2.pl.

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destruction of the bronchial epithelium are found also in patients with COPD.[8,9]

Since asthma and COPD are distinct diseases, it might be expected that they result in different patterns of airway remodeling. Differences in airway remodeling in these 2 diseases might be associated with different anatomical and pathophysiological consequences. The aim of our study was to compare morphological components of airway remodeling (epithelial damage and basement membrane thickness [BMT]) in patients with asthma and COPD.

QUICK LOOK

Current knowledge

Airway remodeling is regarded as a major cause of airway hyper-responsiveness, progressive loss of lung function, resistance to corticosteroid therapy, more severe course of the disease, and only partial reversibility of air-flow limitation observed in patients with asthma.

What this paper contributes to our knowldege

Basement membrane thickening was the only significant difference in the bronchial mucosa morphology between patients with asthma and patients with COPD. Basement membrane thickening might be a histopathological parameter that is helpful in distinguishing patients with asthma from patients with COPD.

Methods

A total of 32 patients, 20 with asthma and 12 with COPD, participated in this prospective study. Inclusion criteria for both groups were mild to moderate and stable (defined as the absence of exacerbations for at least one month prior to study onset) disease. Since the aim of the study was to evaluate the features of airway remodeling in the natural course of the diseases, only patients who had not been treated with inhaled corticosteroids (ICS) for at least 3 months before study onset were enrolled. Patients who were treated with ICS within 3 months before the recruitment period were excluded. None of the patients included into the study had discontinued ICS treatment for the study purpose.

The diagnosis of asthma and the assessment of its severity were performed in accordance with the Global Initiative for Asthma (GINA).[10] Patients had to meet the following criteria to be included in the asthma group:

- Manifestations consistent with asthma
- Evidence of airway obstruction and a positive bronchial reversibility test
- Positive result of methacholine bronchial challenge

Mild asthma was defined as daytime symptoms occurring more frequently than once a week but less than once a day, nocturnal dyspnea more frequent than twice a month but less than once a week, and $FEV_1 \geq 80\%$ of predicted. Patients with moderate asthma had daytime symptoms at least once daily, nocturnal symptoms more often than once a week, and FEV_1 between 60–80% of predicted.

The diagnosis of COPD was made in accordance with the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[11] The following criteria were applied to select COPD patients for the study:

- Current or past smokers
- Symptoms and signs consistent with COPD
- Evidence of bronchial obstruction (FEV_1% of vital capacity < 70) in post-bronchodilator spirometry

Subjects with $FEV_1 > 80\%$ of predicted were classified as mild COPD, whereas those with FEV_1 50–80% of predicted as moderate COPD.

All subjects underwent extensive clinical evaluation, including medical history and physical examination, chest x-ray, lung function testing, arterial blood gas analysis, skin prick tests (Allergopharma, Reinbek, Germany) and basic biochemistry panel including total serum immunoglobulin E.

Lung function testing comprised flow-volume curve (Lungtest 1000, MES, Cracow, Poland) with obstruction reversibility test (albuterol 200 μg) interpreted according to European Respiratory Society standards,[12] body plethysmography with the measurement of bronchial resistance and diffusion capacity for carbon monoxide (Vmax Series 229/V6200, SensorMedics, Yorba Linda, California), and methacholine challenge in accordance with the American Thoracic Society guidelines.[13]

Fiberoptic bronchoscopy was performed under local anesthesia (2% lidocaine) after premedication with atropine sulfate 0.5 mg intramuscular, diazepam 10 mg intramuscular, and inhaled albuterol 400 μg. An endotracheal tube with small bore, in-built tracheal catheter (Bronchoflex, Rusch, Kernen, Germany) was inserted to secure the airways and enable continuous endotracheal oxygen administration. A large bore channel of this tube was used to introduce the flexible bronchoscope (11004 BC, Storz, Germany). After visual inspection of the lower airways, bronchoalveolar lavage (BAL) was performed (200 mL of 0.9% NaCl), and 2–4 forceps biopsies were taken from the segmental and subsegmental bronchi of the middle lobe or lower lobes. Oxygen saturation was continuously monitored throughout the whole procedure (400 HS pulse oximeter, TridentMed, Warsaw, Poland).

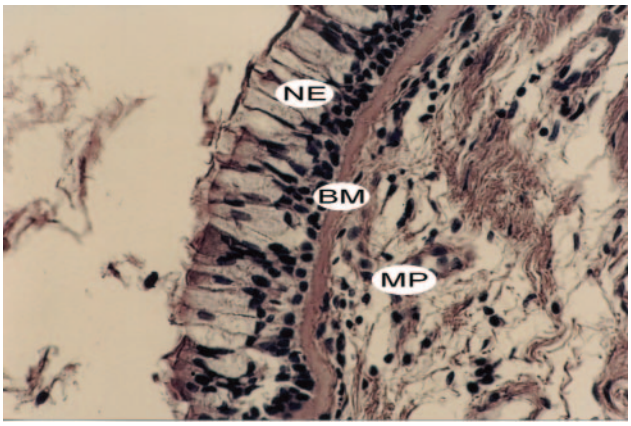

Fig. 1. Mucosa specimen collected from a patient with asthma. BM = basement membrane. NE = normal epithelial bronchial layer. MP = mucosa propria. Light microscope, ×400 magnification.

The specimens were fixed in 4% buffered formalin solution and routinely processed to paraffin blocks. Four-μm-thick sections were stained with hematoxylin and eosin and used to evaluate BMT and the epithelium. The slides were assessed by light microscopy (Olympus, Tokyo, Japan) at ×400 magnification (×40 objective lens, ×10 eyepiece). Only sections perpendicular to the epithelial surface and the BM were selected for measurement (Fig. 1). Computer software (MultiScan Base 08.98 CSS Video Frame Grabber v.5.10, Computer Scanning Systems, Warsaw, Poland) was used to measure BMT. At least 40 measurements at 20-μm intervals were taken in each subject, in accordance with the method developed by Sullivan et al.[14] Two independent pathologists, who were blinded to subjects' diagnoses, were involved in the evaluation of the biopsy specimens. The mean BMT in an individual subject was calculated as a mean of all measurements by both raters, provided they did not differ by more than 10%. If the measurements differed by more than 10%, the pathologists repeated their measurements and discussed their results in order to reach a consensus on the final BMT value. In order to avoid excessive tissue injury during biopsy, all bronchoscopies were performed according to the same protocol, accounting for the operator, type of biopsy forceps, as well as the method of fixation specimen staining. Macroscopically inadequate specimens (small, squashed) were excluded from analysis.

To quantify the extent of epithelial injury, the length of BM lined by normal respiratory epithelium and the length of BM covered by damaged epithelium were measured. The latter was further classified into 2 subcategories: partial epithelial shedding, defined as the BM length covered by a single layer of basal cells with no ciliated epithelial cells, and complete epithelial shedding being the length of denuded BM, lacking any epithelial cells. The results of these measurements were expressed as a percentage of the total length of the measured BM.

All statistical calculations were performed using software (Statistica 6.0, StatSoft, Tulsa, Oklahoma). Numeric values were presented as mean ± standard deviation. Ranges were also provided for selected variables. The Mann-Whitney U test and Kruskal-Wallis analysis of variance test were applied to compare 2 or more unrelated samples, respectively. If each of the variables had 2 values only, the chi-square test with the Yates correction for continuity or the exact Fisher test was used. The Wilcoxon test was used to analyze the differences between related variables (a comparison by 2 raters). The Spearman rank correlation coefficient was applied to test potential correlations between different variables. *P* values below .05 were considered statistically significant.

The study was part of a research project approved by the Bioethics Committee of the Medical University of Warsaw, Poland (approval no. 172/2003). All subjects had signed an informed consent.

Results

Comparative Clinical Characteristics of the Study Groups

All subjects with asthma had a history of dyspnea and wheezing. There were 2 subjects with intermittent asthma, 9 with mild persistent asthma, and 9 with moderate persistent asthma. All COPD subjects complained of exertional dyspnea, and the majority (75%) had chronic productive cough. In 7 subjects disease severity was classified as mild, and in the remaining 5 as moderate. The detailed comparative characteristics of the study groups are described in Table 1.

Bronchoscopy was well tolerated, and no major complications were noted in asthma or in COPD subjects. Mucous gland enlargement with moderate mucus hypersecretion were the most common endobronchial abnormalities in COPD subjects. In asthmatics, various grades of increased mucosal vascularity and edema, in some subjects progressing during the bronchoscopic procedures, were observed.

Histological Assessment of Bronchial Biopsies

The mean number of collected biopsy specimens was 3 ± 1 per patient. There were 6 ± 1 slides with perpendicular mucosal sections available for every subject. The mean number of BMT measurements was similar in both groups (53 ± 16 and 58 ± 24 per subject, respectively (P = .60). No significant differences were found with respect to the BMT as assessed by 2 independent raters (the sign test and Wilcoxon test were not significant).

Table 1. Comparative Characteristics of Subjects With Asthma and COPD (n = 32)

	Asthma (no. = 20)	COPD (no. = 12)	P
Sex, M/F, no.	10/10	8/4	.80
Age, mean ± SD, y	37 ± 15	54 ± 11	< .001
BMI, mean ± SD, kg/m^2	24.5 ± 3	26.0 ± 5	.20
Age at onset of symptoms, mean ± SD, y	19 ± 21	50 ± 12	.001
Duration of symptoms, mean ± SD, y	14.5 ± 13	4.0 ± 3	.02
Atopy, no. (%)	12 (60)	3 (25)	.007
Allergic rhinitis, no. (%)	7 (33)	2 (17)	.04
Non-smokers, no. (%)	11 (50)	0	.001
Ex-smokers, no. (%)	6 (35)	4 (33)	.15
Current smokers, no. (%)	3 (15)	8 (67)	.005
Total number of pack-years, mean ± SD	6 ± 12	39 ± 15	< .001
FEV_1, % predicted	81.6 ± 18	72.8 ± 20	.06
FEV_1/VC, %	69 ± 9	59 ± 6	.002
FVC, % predicted	100 ± 14	100 ± 25	.50
TLC, % predicted	107 ± 20	114 ± 15	.20
R_{aw}, cm H_2O/L/s	3.3 ± 3.6	3.8 ± 1.7	.055
RV, % predicted	127 ± 44	151 ± 40	.001
D_{LCO}, % predicted	88 ± 14	72 ± 28	.01
PC_{20}, mg/mL	2.3 ± 3.1	9.3 ± 7.8	.004

BMI = body mass index
TLC = total lung capacity
R_{aw} = resistance of the airways
RV = residual volume
D_{LCO} = diffusing capacity of the lung for carbon monoxide
PC_{20} = provocational concentration that produced a 20% decrease in FEV_1

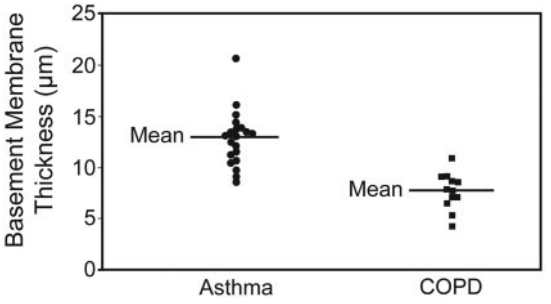

Fig. 2. Mean basement membrane thickness (BMT) in individual subjects (data points), and mean BMT in the asthma and COPD groups (horizontal lines).

BMT in Subjects With Asthma and COPD

The results of mean BMT in individual subjects are presented in Figure 2. A significant difference in BMT was found. The mean BMT in subjects with asthma was 12.54 ± 2.8 µm, and only 7.81 ± 2.0 µm in subjects with COPD (P < .001, see Fig. 2). Significant differences were also noted in BMT between subjects with mild asthma and subjects with mild COPD and between subjects with moderate asthma and subjects with moderate COPD. Table 2 summarizes the comparison of BMT between the groups.

BMT in Asthma Subjects

No relationships were revealed between BMT and the duration of the disease or the subjects' age. There was also no correlation between BMT and asthma severity. The mean BMT was 15.3 ± 2.0 µm, 11.5 ± 1.9 µm, and 13.0 ± 3.4 µm in subjects with intermittent, mild, and moderate asthma, respectively (P = .10). The mean BMT in subjects with atopy was comparable with the mean BMT in non-atopic subjects (12.3 ± 2.1 µm vs 13.0 ± 4.2 µm, respectively, P = .20). In allergic rhinitis subjects the BMT was slightly higher than in subjects without rhinitis, but the difference was not statistically significant (13.2 ± 1.4 µm vs 12.3 ± 3.3 µm, P = .08).

BMT in COPD Subjects

No relationship was found between BMT and age or the duration of disease. The mean BMT in subjects with mild and moderate disease did not differ significantly, equaling 7.7 ± 1.5 µm and 8.0 ± 2.8 µm, respectively (P = .19). In 3 atopic COPD subjects the mean BMT did not differ from that found in subjects without atopy (7.5 ± 4.0 µm vs 7.6 ± 1.3 µm, P = .20). In 2 COPD subjects with chronic allergic rhinitis, the mean BMT was slightly higher than the mean BMT in subjects without rhinitis (9.2 ± 2.9 µm vs 7.5 ± 1.8 µm, P = .07).

Epithelial Damage in Subjects With Asthma and COPD

There were no significant differences in the extent of epithelial damage in subjects with asthma and those with COPD. The comparative data are shown in Table 3. The overall percentage of the BM length lined with damaged epithelium was 45 ± 20% in the asthma group and 47 ± 22% in the COPD group (P = .40).

Epithelial Damage in Asthma Subjects

Analysis of the severity of epithelial damage did not reveal any differences among subjects with intermittent, mild, and moderate persistent asthma. The percentage of the length of damaged epithelium was 47 ± 24% in intermittent asthma, 45 ± 20% in mild persistent asthma, and 43 ± 20% in moderate persistent asthma (P = .20). Similarly, the percentage of complete epithelial shedding did not differ significantly between the various severity groups, and was 18 ± 9%, 18 ± 11%, and 13 ± 11% in intermittent, mild, and moderate asthma, respectively,

Table 2. Comparison of Basement Membrane Thickness Between Asthma and COPD Subjects ($n = 32$)

	Asthma		COPD		P
	no.	BMT (mean ± SD μm)	no.	BMT (mean ± SD μm)	
Intermittent	2	15.32 ± 2.0	0	0	NA
Mild	9	11.46 ± 1.9	7	7.66 ± 1.5	.001
Moderate	9	13.00 ± 3.4	5	8.02 ± 2.8	.006
Mean value for the group	20	12.54 ± 2.8	12	7.81 ± 2.0	< .001

BMT = basement membrane thickness
NA = not applicable

Table 3. The Extent of Bronchial Epithelial Damage (Comparison of Histological Evaluation of Biopsies in the Study Groups)

	Asthma	COPD
Normal epithelium	55 ± 20	53 ± 22
Damaged epithelium	45 ± 20	47 ± 22
Partial epithelial shedding	29 ± 15	33 ± 15
Complete epithelial shedding	16 ± 10	14 ± 11

Values are mean ± SD percent. None of the differences are significant.

($P = .25$). However, the percentage of damaged epithelium was considerably higher in atopic versus non-atopic asthma (50 ± 19% vs 32 ± 17%, $P = .06$).

Epithelial Damage in COPD Subjects

No differences were found in the extent of epithelial damage in subjects with mild and moderate disease. However, a significant, positive correlation was revealed between the extent of damaged epithelium and the age of COPD patients ($r = 0.79$, $P < .01$, Fig. 3).

Discussion

Our results confirm the presence of structural changes in the airways in asthma and COPD patients. The change that merits special attention in asthma patients is the considerable thickening of BM. This is a well recognized feature of airway wall remodeling in asthmatics.[3,5,15–17] It has been shown that BM thickening may develop in COPD patients as well.[8,9,18] However, there are only a few studies directly comparing BMT in patients with asthma and COPD. The results of these studies and studies comparing BMT in asthmatics or COPD subjects and healthy subjects are shown in Table 4.

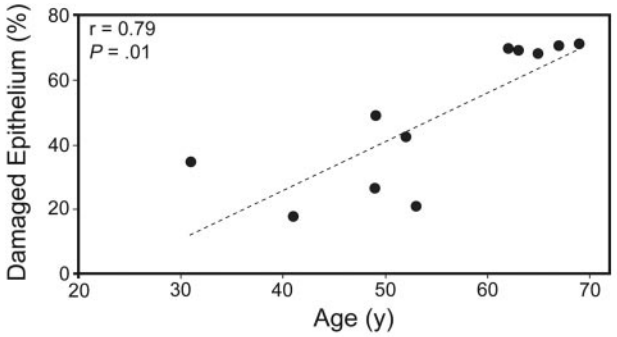

Fig. 3. Relationship between the extent of total bronchial epithelial damage and the age of subjects with COPD.

Our findings seem to be consistent with the results of others.[18,19] The mean BMT in subjects with asthma was significantly higher than in COPD subjects (12.5 ± 2.8 μm and 7.8 ± 2.0, respectively). In fact, this was the only significant difference in the morphology of the bronchial mucosa in asthma and COPD subjects found in our study. We did not observe any relationship between BMT and asthma duration or severity. We cannot exclude that the inability to show these relationships was associated with a limited number of subjects in our study and that significant correlations between these variables could have been demonstrated in a larger sample. On the other hand, it should be stressed that our results seem to confirm earlier observations of other authors. According to Jeffery, the BM thickening is already present in the initial stages of asthma and does not appear to increase considerably with age, duration, or severity of the disease.[22] BM thickening has been reported in very early asthma[20] and even before recognition of the disease.[23] The factors underlying significant variability in the pattern of remodeling reported by different authors remain unknown. Although higher BMT has been noted in patients with asthma and atopy,[24] our findings are consistent with those of Vignola et al, who reported similar BMT in both types of asthma.[25] Bronchial wall remodeling, particularly BM thickening, has relevant clinical implications. This issue has been a subject of numerous studies in asthma patients. BM thickening was found to lead to airway hyper-responsiveness and more severe airway obstruction.[5,26] An important observation is that in asthma patients ICS can reduce BMT, and, as a consequence, bronchial hyper-responsiveness[4,26] Thus, not only eosinophilic inflammation, but also at least some components of airway remodeling might be a (direct or indirect) target for these potent anti-inflammatory agents. This can explain the effectiveness of ICS in achieving asthma control.

While BMT in patients with asthma has long been recognized,[3] features and clinical relevance of airway wall remodeling in COPD patients have been less recognized.[15,21] BMT in COPD patients has usually been found

Table 4. Basement Membrane Thickness in Healthy Individuals, Subjects With Asthma, and Subjects With COPD

First Author	Year	Healthy		Asthma		COPD		Staining Method	Microscopy
		BMT, mean ± SD	*n*	BMT, mean ± SD	*n*	BMT, mean ± SD	*n*		
Roche[3]	1989	4.17 ± 0.59	3	7.95 ± 1.79	8	ND	ND	Immunohisto-chemistry, labeling of collagen I, III, V	Electron microscopy
Ollerenshaw[15]	1992	ND	ND	12 ± 2	10	ND	ND	Hematoxylin and eosin	Light microscopy
Jeffery[16]	1992	8.2 ± 1.7	12	11.25 ± 2.9	11	ND	ND	Toluidine blue	Light microscopy
Trigg[17]	1994	ND	ND	23.13 ± 3.44	12	ND	ND	Immunohisto-chemistry, labeling of collagen III	Electron microscopy
Milanese[19]	2001	ND	ND	10.1 ± 3.7	11	5.2 ± 0.7	9	Hematoxylin and eosin	Light microscopy
Payne[20]	2003	Adults 4.4 Range 3.2–6.3 Children 4.9 Range 3.7–8.3	8 adults 10 children	Adults 8.1 Range 5.8–10 Children 8.2 Range 5.4–1.1	10 adults 19 children	ND	ND	Toluidine blue	Light microscopy
Köksal[21]	2005	4.1 ± 1.7	8	ND	ND	3.6 ± 1.4	14	Hematoxylin and eosin	Light microscopy

ND = no data provided

to be comparable to that in healthy individuals, and considerably lower than that found in asthmatics.[18,19] The lack of significant BM thickening in the majority of COPD patients indicates that different mechanisms, including lung parenchyma remodeling and loss of lung elastic recoil, play an important role in airway obstruction. This is associated with limited effectiveness of ICS in COPD treatment, as compared to asthma. It should be stressed, however, that in some patients with COPD, eosinophilic airway inflammation as well as significant BM thickening can be found.[8,9,27] As these patients might respond to ICS treatment, this might have relevant therapeutic implications. In our study significant BM thickening (11.3 μm) was found in only one COPD subject. Chanez et al reported thicker BM in COPD subjects with eosinophilia in BAL fluid, and a positive response to steroid reversibility test.[8] Our subject with substantial BM thickening may have belonged to the "subgroup" of COPD patients who show a positive response to corticosteroids, as described by Chanez et al.[8] Thus, we believe evaluation of the predominant type of airway inflammation along with BMT might have a practical value in considering an optimal treatment choice for COPD patients.

Since in our study the range of the BMT was 8.6–21.1 μm in asthmatics and 4.3–11.3 μm in COPD subjects, there was a partial overlap of BMT in these 2 diseases. On the other hand, BMT was lower than 10 μm in only 3 subjects with asthma and higher than 10 μm in only one subject with COPD. An estimation of the accuracy of BMT as a parameter differentiating asthma and COPD (ROC curve with cutoff level 10 μm) demonstrated the sensitivity and specificity of this parameter to be 85% and 91.7%, respectively. In contrast, Bourdin et al reported only 48% sensitivity and 80% specificity of the pathological diagnosis of COPD based on the evaluation of bronchial biopsy samples. None of the evaluated features (basement membrane thickening, epithelial destruction, squamous metaplasia, inflammatory infiltrate in the epithelium, and mucosa propria) was a sensitive and specific marker enabling a distinction between COPD and asthma.[9] These results are not difficult to explain, given that the evaluation of endobronchial biopsies in asthma and COPD is not an easy task and the results could be influenced by artifacts, uneven distribution of inflammatory cells, and a wide range of BMT even in healthy individuals (2.4–9.9 μm).[3,16,20]

The second parameter assessed in our study was the extent of epithelial damage. Since bronchial epithelial cells in patients with COPD and asthma are chronically exposed to noxious factors (eg, reactive oxygen metabolites, infectious agents, proteolytic enzymes, inflammatory mediators), one might expect similar epithelial destruction in both diseases. It has been reported that in both asthma[28] and COPD, abnormal regeneration of damaged epithelium may occur and that cigarette smoke inhibits regenerative processes.[29]

Epithelial injury has been extensively studied in asthma patients. Some earlier studies have suggested that it is a common and specific feature of asthma.[25,30] Epithelial destruction has been observed in post-mortem examinations[2] and also in bronchial biopsies taken during fiberoptic bronchoscopies.[25,31] Abnormalities in epithelial cell adhesion and intercellular junctions have been suggested to increase sensitivity of the "asthmatic" epithelium to various noxious agents. This hypothesis was supported by an increased number of epithelial cells occasionally found in BAL fluid

in asthma patients.[30] However, numerous studies with larger control groups have not confirmed this hypothesis, demonstrating similar epithelial layer destruction in asthmatics and healthy individuals.[32,33] In both groups, only approximately 50% of bronchial mucosa surface was covered with intact epithelium.

Fewer studies have quantitatively evaluated epithelial damage in COPD. Cohen et al were unable to find any differences in epithelial damage between healthy individuals, asthmatics, and subjects with chronic bronchitis.[32] As far as asthma and COPD subjects are concerned, our study produced similar results. Both patterns of epithelial injury (partial and complete epithelial shedding) were present in asthma and COPD, and the percentages of bronchial mucosa with various types of epithelial injury were equally distributed in both groups (see Table 3). Ordoñez et al reported a similar percentage of complete denudation in subjects with asthma (11.4 ± 9.8%) but a higher percentage of the BM lined by a single layer of basal cells (54.5 ± 9.8%).[33] Köksal et al observed more extensive epithelial cell injury in smokers with chronic bronchitis than did our study (62 ± 33%).[21] Turcotte et al reported that, even in healthy subjects, as much as 24% of the bronchial mucosa length might reveal partial epithelial desquamation.[34]

Although epithelial damage may be caused by eosinophilic proteolytic enzymes, no epithelial desquamation has been observed in animal asthma models, despite marked eosinophilic infiltrates.[35] Similarly, in asthma subjects allergen challenge did not result in damage to epithelial integrity, despite marked respiratory eosinophilia.[36] Considering these findings, epithelial damage might, at least, be regarded as an artifact associated with the collection and preparation of bronchial biopsy samples. It has been shown that bronchoscopy technique, the type and size of biopsy forceps, and the fixation and staining methods may all affect the integrity of the epithelial layer in evaluated samples.[37] Therefore, all bronchoscopies in this study were performed according to the same protocol, accounting for the operator, type of biopsy forceps, as well as the method of fixation and staining of the specimens.

Contrary to the potential "false positive" enhancement of the epithelial injury caused by the bronchoscopic procedure per se, ICS can produce an opposite, beneficial effect on epithelial regeneration and BMT in asthmatics.[16,38] To exclude the influence of this factor, only patients not treated with steroids were included in the study. A similar criterion was used by Cohen et al.[32]

In our asthma group we did not observe any relationship between the extent of epithelial damage and asthma severity or duration. However, we found a significantly higher percentage of epithelial damage in atopic compared to non-atopic asthmatics. A similar finding has already been reported by Amin et al.[24]

It is worth noting that COPD subjects in our study demonstrated a strong correlation between the extent of epithelial damage and the subject's age, but not duration of symptoms.

Our study has numerous limitations. The study groups were relatively small. The main limiting factors affecting sample sizes were patient consent to flexible bronchoscopy and requirement not to use corticosteroids in the pre-study period. There were some demographic and clinical differences between the asthma and COPD group (eg, mean age, duration of symptoms), which could affect our findings. No control group of healthy subjects participated in our study. Given the primary aim of the study, no control group was necessary, although it might have added valuable comparative data. The other important limitation is that all COPD and asthma subjects were only in mild to moderate stages. Biopsy findings could be different in severe and very severe stages of asthma and COPD, but in order to avoid the risk of bronchofiberoscopy we did not perform this procedure in patients with more severe disease. It should also be emphasized that classification of asthma and COPD severity has been based on different parameters. Daytime and nocturnal symptoms, as well as spirometric values, were used to assess asthma severity, while FEV_1 percent of predicted was the only parameter classifying severity of COPD. Thus, patients with mild or moderate asthma do not necessarily reflect similar stages of COPD severity, and comparison of these patients might be questionable. On the other hand, there were no other easily applicable and commonly accepted severity assessment methods at the time of study onset. The wide clinical application of the classifications recommended by GINA and GOLD and their association with proposed treatment algorithm[10,11] seemed to be their advantage.

Conclusions

In conclusion, BMT was the only significant difference in the bronchial mucosa morphology between asthmatics and COPD subjects. BMT might be a histopathological parameter that is helpful in distinguishing asthmatics and COPD patients. The pattern and the extent of epithelial damage are similar in both diseases. In COPD the extent of epithelial damage is related to the patient's age. These results need to be confirmed in larger study groups.

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