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Airway inflammation in chronic obstructive pulmonary disease: Comparisons with asthma

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Chronic obstructive pulmonary disease (COPD) is a progressive syndrome of expiratory airflow limitation caused by chronic inflammation of the airways and lung parenchyma. The airway inflammatory response in COPD is initiated by smoking in the overwhelming majority of cases, and chronic exposure to cigarette smoke initiates a series of events that causes damage to central airways, peripheral airways, and terminal airspaces, leading to physiologic and clinical abnormalities. Although COPD shares some clinical features with asthma, another prevalent airway inflammatory disease, there are distinct differences in the phenotypic characteristics of airway inflammation between COPD and asthma. The eosinophil is the most prominent inflammatory cell in asthma, with mast cells, lymphocytes, and macrophages playing important but less prominent roles. In COPD the cellular composition of the airway inflammatory infiltrate differs, with neutrophils, macrophages, and lymphocytes assuming prominence and the eosinophil playing a minor role, except in the setting of exacerbations. The contrasting inflammatory phenotypes of asthma and COPD have important implications for clinical and physiologic manifestations of disease, as well as for therapy. (*J Allergy Clin Immunol* 2003;112:819-27.)

Key words: Inflammation, chronic obstructive pulmonary disease, small airway, asthma, lymphocyte

Chronic obstructive pulmonary disease (COPD) is a progressive syndrome of expiratory airflow limitation caused by chronic inflammation of the airways and lung parenchyma. Closely linked to smoking, COPD is a public health problem of epic proportions. In 2001, it was the fourth leading cause of death in the United States,¹ and it is predicted to become the fifth greatest public health problem worldwide by 2020.² Recent advances have improved our understanding of airway inflammation in COPD and have shed light on multiple features that distinguish this disorder from asthma.

Abbreviations used

COPD: Chronic obstructive pulmonary disease

MMP: Matrix metalloproteinase

CLINICAL MANIFESTATIONS AND PHYSIOLOGY

From the clinical perspective, COPD is a chronic process of progressive airflow limitation associated with symptoms such as cough, sputum production, and dyspnea. Recently, the Global Initiative for Chronic Obstructive Lung Disease defined COPD as “a disease state characterized by airflow limitation that is not fully reversible,” which is “progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases.”³ This definition underscores the fact that COPD is an inflammatory disease and reinforces the importance of airflow limitation in defining the clinical syndrome. Although airflow limitation is a cardinal feature of both COPD and asthma, there are differences between the 2 disorders (Table I). Whereas expiratory airflow limitation in asthma typically responds significantly (ie, $\geq 12\%$ and 200 mL)⁴ to inhaled bronchodilators, airflow limitation in COPD is generally poorly responsive to bronchodilators. However, inhaled bronchodilators do have an important role in the treatment of COPD in that they reduce symptoms and improve exercise tolerance by reducing hyperinflation.^{5,6}

Airway hyperresponsiveness is considered a hallmark of asthma, but it is also an important (albeit less prevalent) feature of COPD. The Lung Health Study evaluated airway hyperresponsiveness in smoking patients with COPD with moderate airflow limitation (FEV_1 /forced vital capacity ratio = $63\% \pm 5.5\%$ [mean $\pm$ SEM]) and demonstrated that the overall prevalence of airway hyperresponsiveness (defined as a methacholine PC_{20} of <25 mg/mL) ranged between 58.9% in men and 85.1% in women. Baseline degree of airflow limitation was associated with airway hyperresponsiveness, and women were more likely than men (46.6% vs 23.9%) to react to a methacholine concentration of less than 5 mg/mL.⁷ Subsequent follow-

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TABLE I. Clinical phenotypic differences between COPD and asthma

COPD	Asthma
Airflow limitation largely irreversible	Airflow limitation reversible
Airway hyperresponsiveness variable	Airway hyperresponsiveness significant
Destruction of lung parenchyma	Lung parenchyma intact
Steroid response varies	Steroid responsive

up of this cohort revealed that airway hyperresponsiveness to methacholine is an important predictor of progression in airflow limitation, independent of features such as age, sex, baseline lung function, baseline smoking history, and changes in smoking status.⁸

Traditionally, the terms *chronic bronchitis* and *emphysema* have been used to describe the 2 major clinical phenotypes of COPD.⁹ Chronic bronchitis results from chronic inflammation of the small and medium-sized airways and leads to a clinical presentation that includes airflow limitation, dyspnea, chronic cough, and sputum production. The inflammatory processes leading to emphysema destroy elastic tissue in the terminal airspaces and lung parenchyma, resulting in loss of lung elastic recoil, airflow limitation, dyspnea, and hypoxemia. Emphysema can be further characterized by the anatomic location of lung tissue destruction. Centrilobular emphysema is most commonly associated with cigarette smoking and is seen predominantly in the upper lobes of the lung, occurring as a result of inflammatory destruction of the respiratory bronchioles. Panlobular emphysema, seen primarily in patients with α_1 -antitrypsin deficiency, occurs as a result of a more uniform destruction of the secondary lobule and involves predominantly the lower lobes.¹⁰

ROLE OF SMOKING IN COPD PATHOGENESIS

Smoking is the primary risk factor for the development of COPD, and although the majority of cases of COPD occur in individuals who have smoked, the majority of smokers (approximately 80%) will not have this disorder.¹¹ Chronic exposure to cigarette smoke initiates a series of events that cause damage to the central airways,¹² peripheral airways,^{13,14} and terminal airspaces,¹⁵ leading to physiologic and clinical abnormalities (Fig 1). In chronic bronchitis the inflammatory process is characterized by mucosa infiltration with neutrophils, macrophages, and lymphocytes, which results in epithelial disruption, smooth muscle hypertrophy, and fibrosis. In emphysema a combination of inflammatory cell recruitment in the terminal airways, protease-mediated damage of the extracellular matrix, and ineffective matrix mechanisms¹⁶ cause inflammatory destruction of the respiratory bronchioles, alveolar ducts, and alveoli.

CELLULAR CHARACTERISTICS OF AIRWAY INFLAMMATION IN COPD

The eosinophil is the most prominent inflammatory cell in asthma, although mast cells, lymphocytes, and macrophages also play important roles. In COPD the cellular composition of the airway inflammatory infiltrate differs (Table II), with the eosinophil playing a minor role, except in the setting of exacerbations.¹⁷ Although they are minor contributors to the pathogenesis of COPD, the presence of significant numbers of eosinophils in induced sputum is associated with steroid responsiveness in patients with COPD.^{18,19}

Neutrophils have been hypothesized to have a significant role in COPD pathogenesis because of their ability to mediate tissue destruction by the release of elastases. In 1983, Hunninghake and Crystal²⁰ evaluated airway inflammatory cells in bronchoalveolar lavage fluid and lung biopsy specimens of smokers and nonsmokers who did not have evidence of COPD. They reported that smokers had an increase in lavage fluid neutrophils and macrophages when compared with nonsmokers and postulated that cigarette smoking induced macrophages to release neutrophil chemotactic factors.

Stanescu et al²¹ subsequently evaluated differences in induced sputum and lung function in a group of smokers and exsmokers. Patients were matched with regard to age (64 years) and had a smoking history of approximately 40 pack-years. Subjects who had greater airflow limitation (as measured by FEV₁/FVC ratio) had greater induced sputum neutrophilia than did those without airflow limitation. Sputum neutrophilia was also more prevalent in patients with chronic cough and sputum production, and increased sputum neutrophilia was associated with an accelerated decrease in FEV₁ over a 15-year follow-up period.

Macrophages also play an important role in directly mediating tobacco smoke-induced lung destruction, in part through macrophage-derived matrix metalloproteinases (MMPs). Although neutrophil influx is required for cigarette smoke-induced connective tissue matrix breakdown in mouse models and has been described in clinical studies, as noted previously, it appears to be dependent on the presence of macrophage-derived MMP-12, suggesting that both neutrophils and macrophages are required for the development of emphysema after smoke exposure.²² In mouse models of the acute response to tobacco smoke, the secretion of MMP-12 from macrophages has been reported to cause macrophages to release TNF- α , resulting in neutrophil influx, possibly through activation of vascular endothelial cells.²³

The important role of T lymphocytes, particularly CD8⁺ cells,^{14,24,25} in the pathogenesis of COPD is described below.

SMALL AIRWAY INFLAMMATION IN COPD VERSUS ASTHMA

Early studies of airway resistance in COPD demonstrated that much of the airflow limitation occurs in air-

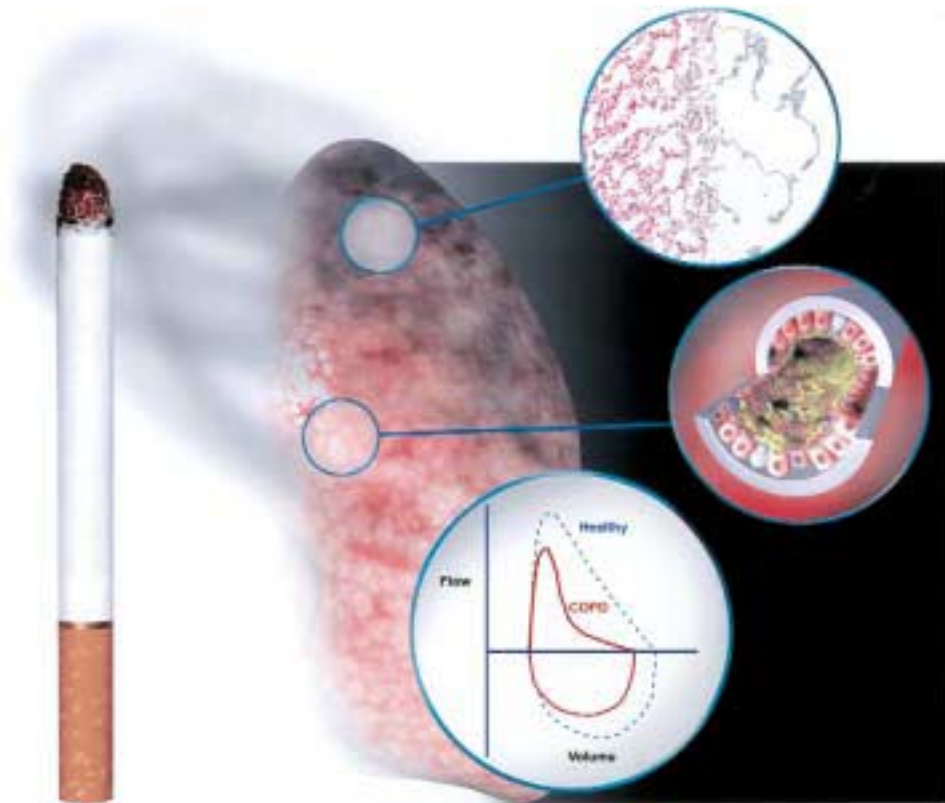


FIG 1. In COPD cigarette smoking initiates a series of inflammatory events that lead to emphysema (*top circle*) and airway inflammation with epithelial damage and mucus hypersecretion (*middle circle*), both of which combine to cause the hallmark physiologic abnormality of expiratory airflow limitation (red flow-volume loop, *bottom circle*).

ways of less than 2 mm in diameter. In 1968, Hogg et al²⁶ compared resistance to airflow in lung specimens obtained at autopsy from healthy subjects and subjects with COPD. They found that although total lung resistance was near normal in the specimens of patients with mild COPD, small airways resistance was increased 4-fold versus that of normal lungs. In moderate-to-severe COPD total lung resistance was significantly increased almost entirely as a result of an increase in small airways resistance. These physiologic abnormalities correlated significantly and positively with morphologic abnormalities of the small airways, including mucus plugging and airway inflammation and fibrosis.

In 1977, Cosio et al²⁷ further described the relationship between small airways inflammation and physiologic abnormalities in older smokers. Using biopsy specimens and physiologic measures of small airway function, including closing volume and single-breath nitrogen washout, they demonstrated that physiologic measures of small airway function worsened as small airway inflammation increased. The authors concluded that small airways inflammation was a significant contributor to the physiologic deterioration seen in patients with COPD. The small airway pathologic changes observed by Cosio et al were similar to but more extensive than those previously reported by Niewoehner et al.¹³ This difference

TABLE II. Inflammatory phenotypic differences between COPD and asthma, with cells listed in relative order of importance

COPD	Asthma
Neutrophils	Eosinophils
Macrophages	Mast cells
CD8 ⁺ T lymphocytes	CD4 ⁺ T lymphocytes
Eosinophils	Macrophages

was attributed to differences in age between the 2 study populations (44-63 years²⁷ vs 26 years¹³). This age-based difference in severity of inflammation suggested a dose-response relationship between duration of smoking and severity of small airways inflammation.

Although these studies demonstrated the relationship between airway inflammation and abnormal lung function in COPD, the mechanism by which inflammation altered lung function required further investigation. In 1990, Bosken et al²⁸ used morphometric analysis to evaluate small airway dimensions and to describe small airways structural alterations that occurred in response to chronic inflammation in smokers with and without airflow limitation ($FEV_1 = 76.6\% \pm 3.6\%$ of predicted value

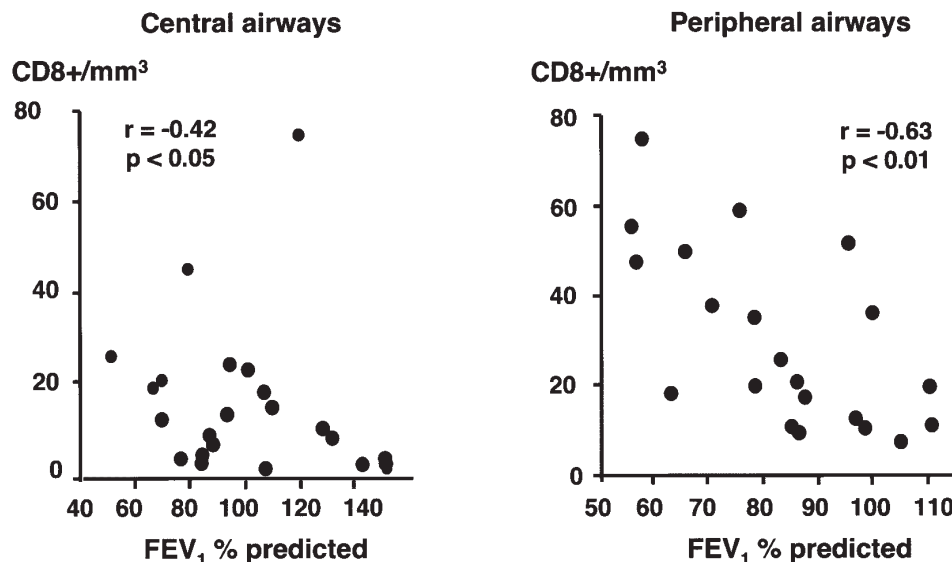


FIG 2. Inverse correlation between CD8⁺ cells per cubic millimeter and FEV₁ percent predicted in the central²⁴ (left) and peripheral¹⁴ (right) airways of subjects with COPD.

vs $54.9\% \pm 6.2\%$ of predicted value [mean $\pm$ SD]). They reported that smokers with airflow limitation had significantly smaller measured luminal diameter and significantly greater wall thickness in the small airways when compared with values seen in nonsmokers. Airway wall thickness correlated with the severity of inflammation and was due to increases in the thickness of the epithelium, connective tissue, and smooth muscle. Smokers also demonstrated evidence of parenchymal destruction, as manifested by increased emphysema scores.

In 1997, O'Shaughnessy et al²⁴ reported the results of a study evaluating airway inflammation in endobronchial biopsy specimens from patients with chronic bronchitis without airflow limitation, patients with chronic bronchitis with airflow limitation, and healthy control subjects. Healthy control subjects and subjects with chronic bronchitis without airflow limitation had normal FEV₁ values (range, 98.5%-100.5% of predicted value), and patients with chronic bronchitis and airflow limitation had an FEV₁ of 59.7% of predicted value. In those patients who demonstrated airflow limitation, there was a significant increase in CD3⁺ T lymphocytes versus levels in healthy subjects. These individuals also demonstrated an increased number of CD8⁺ T lymphocytes and CD68⁺ macrophages versus numbers in healthy control subjects. Within the group of subjects who had a history of chronic bronchitis, those who demonstrated airflow limitation had increased macrophage counts when compared with those with chronic bronchitis without airflow limitation.

In the subgroup of patients with chronic bronchitis who smoked, there was a significant negative correlation between CD8⁺ T cells and FEV₁ percent predicted ($r = -0.42$, $P < .05$; Fig 2, left), neutrophils and FEV₁ percent predicted ($r = -0.46$, $P < .05$), and eosinophil counts and FEV₁ percent predicted ($r = -0.53$, $P < .05$). The authors

concluded that these data suggested an important role of T lymphocytes and macrophages in the pathogenesis of smoking-induced airflow limitation and suggested that COPD differs from asthma, particularly with regard to the importance of CD8⁺ T lymphocytes.²⁴

Although the study of O'Shaughnessy et al²⁴ evaluated pathologic changes in the more central airways, Saetta et al¹⁴ reported pathologic changes in the small airways of patients with COPD in 1998. The authors examined surgical specimens from 16 smokers who underwent lung resection for pulmonary nodules. Of these 16 subjects, 9 had evidence of clinical bronchitis with airflow limitation, and 7 were asymptomatic with normal lung function. The authors used immunohistochemical techniques to identify inflammatory cells in the airway wall and performed morphometric evaluation as well.

Subjects with a history of chronic bronchitis demonstrated an increased number of CD8⁺ T lymphocytes in the peripheral airways without significant differences in the numbers of neutrophils, macrophages, or CD4⁺ T lymphocytes. When all subjects were analyzed, there was a significant negative correlation between the number of CD8⁺ T lymphocytes and FEV₁ percent predicted, with an r value of -0.63 ($P = .01$; Fig 2, right). Morphometric evaluation revealed an increased smooth muscle area in patients with COPD, and when all subjects were evaluated, there was a significant inverse relationship between airway smooth muscle area and FEV₁ percent predicted ($r = -0.67$, $P = .01$). This study confirmed the importance of the CD8⁺ T lymphocyte in airway inflammation in smokers with chronic bronchitis and complemented the research of O'Shaughnessy et al²⁴ by demonstrating that this observation could be made not only in the larger airways but in the peripheral airways as well. It is interesting that the authors were unable to demonstrate a signif-

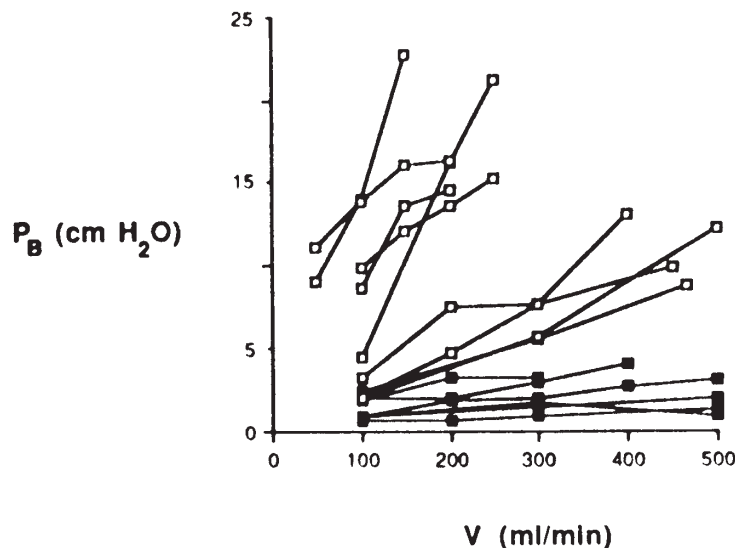


FIG 3. Increased peripheral airways resistance in patients with asthma. Reprinted with permission from Wagner et al.³²

icant increase in neutrophils in this subset of patients with chronic bronchitis. This can be explained in part by comparisons with prior studies in which neutrophils are found more prominently in bronchoalveolar lavage fluid rather than in airway biopsy specimens.

The small airways are also an important site of inflammation in asthma. In 1996, Kraft et al²⁹ evaluated alveolar tissue inflammation in patients with chronic stable asthma. They studied 21 subjects with asthma, 11 of whom had nocturnal asthma and 10 of whom had nonnocturnal asthma. Each subject underwent bronchoscopy with endobronchial and transbronchial biopsy at both 4 AM and 4 PM, and morphometric analysis was used to determine the number and type of inflammatory cells per unit volume in each lung compartment. The authors showed that in terminal bronchiolar and alveolar tissue biopsy specimens obtained at 4 AM there were significant increases in the number of eosinophils per unit volume in patients with nocturnal asthma when compared with values in patients with nonnocturnal asthma. Similar differences could not be demonstrated in proximal airway endobronchial biopsy specimens.²⁹

Furthermore, in subjects with nocturnal asthma, there was a circadian variation in the number of eosinophils seen in alveolar tissue, with a significantly greater number of eosinophils present at 4 AM versus 4 PM ($41.4 \pm 8.6 \times 10^3$ vs $12.9 \pm 4.3 \times 10^3$, $P = .005$). The number of macrophages was also greater in nocturnal asthmatic alveolar tissue at 4 AM than at 4 PM. No circadian differences in the number of proximal airway inflammatory cells were demonstrated, and the circadian differences seen in nocturnal asthma could not be demonstrated in patients with nonnocturnal asthma. Increases in alveolar eosinophils in patients with nocturnal asthma correlated with nocturnal decrements in FEV_1 ($r = -0.54$, $P = .03$); this relationship was not seen with cell counts from prox-

imal airway biopsy specimens. The authors concluded that eosinophilic inflammation in the small airways and alveolar tissue was an important component of the inflammatory phenotype in patients with nocturnal asthma.²⁹

T lymphocytes are also thought to play a central role in asthma pathogenesis.³⁰ Inflammatory cytokines, such as $\text{TNF-}\alpha$, IL-4, IL-5, and IL-13, are produced by T lymphocytes and facilitate eosinophil migration into tissues through vascular endothelium. In 1999, Kraft et al³¹ studied whether lymphocytes were responsible for the recruitment of eosinophils into the small airways and alveolar tissue in patients with nocturnal asthma. They demonstrated that at 4 AM, patients with nocturnal asthma had significantly greater numbers of CD4^+ lymphocytes in alveolar tissue than did patients with nonnocturnal asthma (median of $9.8/\text{mm}^2$ [interquartile range, 5.6-30.8] vs median of $1.5/\text{mm}^2$ [interquartile range, 0-6.3], $P = .04$ for the comparison). Alveolar CD4^+ cells correlated positively with the number of EG2^+ eosinophils ($r = 0.66$, $P = .01$) and inversely with FEV_1 ($r = -0.68$, $P = .0018$) at 4 AM.

Small airways inflammation in asthma also leads to significant airflow resistance at this level. Wagner et al³² used the technique of peripheral airways resistance measurement through a wedged bronchoscope to evaluate the distal lung in healthy subjects and subjects with mild asymptomatic asthma. In asthmatic subjects increases in airflow through the wedged bronchoscope resulted in increases in peripheral airways resistance (Fig 3). This finding was not seen in healthy control subjects, however, despite the fact that at baseline the 2 groups had similar lung function. The authors were also able to demonstrate a correlation between airway responsiveness and increased peripheral airways resistance. These observations demonstrated the importance of increased peripheral airways resistance in even the most mild of asthmatic subjects.³²

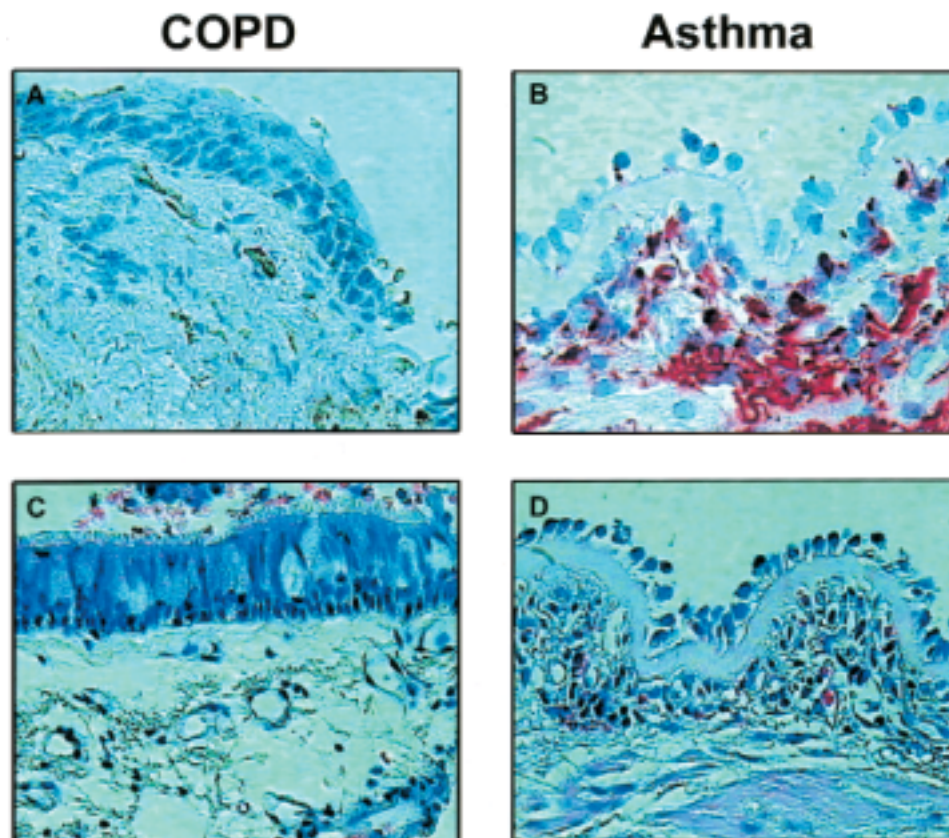


FIG 4. Pathologic changes in the airways of patients with COPD (*top and bottom left*) and asthma (*top and bottom right*). Immunostaining for eosinophils (EG2⁺) demonstrates subepithelial infiltration with these cells in asthma (*top right*) that is not seen in COPD (*top left*). Additionally, the reticular layer of the basement membrane is thicker in patients with asthma (*bottom right*) than in patients with COPD. Reprinted with permission.

FIXED AIRFLOW LIMITATION IN ASTHMA AND COPD

In 2003, Fabbri et al³³ reported the results of a study in which they evaluated pathologic and functional characteristics of patients with fixed airflow obstruction. They evaluated 46 subjects, 27 of whom reported a prior history of COPD and 19 of whom reported a prior history of asthma. Although these subjects had a similar degree of airflow limitation ($FEV_1 = 56\%$ of predicted value without significant bronchodilator responsiveness), there were distinct differences in airway inflammation between the 2 groups. Subjects with a history of COPD demonstrated an increased percentage of neutrophils in both induced sputum and bronchoalveolar lavage fluid, whereas patients with a history of asthma had a significantly increased percentage of eosinophils in the peripheral blood, bronchoalveolar lavage fluid, and airway mucosa. A prior history of asthma was also associated with an increased percentage of bronchoalveolar lavage fluid lymphocytes, with a higher proportion of those lymphocytes being CD4⁺ T lymphocytes, resulting in an increased CD4⁺/CD8⁺ ratio versus that seen in patients with a his-

tory of COPD. Pathologic evaluation of endobronchial biopsy specimens revealed that patients with a history of asthma had a thicker reticular layer of the basement membrane (Fig 4) and a higher level of exhaled nitric oxide.³³

These variations in inflammatory phenotype had implications for physiologic and radiographic phenotypes as well. Although subjects were well matched with regard to age, FEV_1 , and PC_{20} , those with a prior history of COPD had a lower PaO_2 , a lower diffusing capacity for carbon monoxide, and a higher residual volume (132% vs 107% of predicted value, $P < .01$). On the basis of these observations, the authors concluded that within patients with fixed airflow limitation, there are significant differences on the basis of clinical phenotype. The differences in inflammatory phenotype noted between these groups might have an effect on response to pharmacotherapy for the presence of an active eosinophilic inflammatory process in patients with asthma and fixed airflow limitation, suggesting they derive some benefit from inhaled corticosteroids, even if airflow limitation is fixed. Patients with COPD and fixed airflow limitation are less likely to respond to these drugs given the presence of a predominantly neutrophilic infiltrate. The physiologic evaluations performed as part of this

study suggest that spirometry and airway hyperresponsiveness testing alone might not adequately differentiate patients with COPD from asthma and that lung volume testing can supplement measurement of diffusing capacity and measurement of arterial oxygen tension to distinguish between asthmatic and COPD phenotypes in patients with fixed airflow obstruction.³³

DISEASE STAGE AND SEVERITY OF INFLAMMATION IN COPD

In COPD airway inflammation appears to evolve as the disease progresses. Inflammation begins long before the patient experiences symptoms, and as described previously, even asymptomatic smokers have significant airway inflammation when compared with nonsmokers. In 2003, Amin et al³⁴ compared inflammatory and structural airway changes in 29 asymptomatic smokers and 16 nonsmokers. All subjects were asymptomatic, groups were age matched, and neither group had significant airflow limitation (mean FEV₁ percent predicted of 92% [range, 67%-134%] and 109% [range, 91%-146%], respectively). Endobronchial biopsy specimens from the main carina of asymptomatic smokers demonstrated immunohistochemical evidence of parallel increases in the number of mucosa neutrophils, eosinophils, mast cells, and macrophages (lymphocytes were not evaluated). Increased basement membrane thickness and enhanced epithelial disruption were also observed in the smoking group, and there was a significant inverse correlation between epithelial integrity and numbers of eosinophils, mast cells, and macrophages.

In an evaluation of subjects further along the disease spectrum, Lams et al³⁵ evaluated immunohistochemical markers of small airway inflammation in surgical lung specimens from current ($n = 22$) and former smokers (nonsmokers for ≥ 22 months, $n = 17$) and lifelong nonsmokers ($n = 5$) with and without fixed airflow limitation. The authors demonstrated an increased number of both total and activated eosinophils in the small airways submucosa of smokers when compared with all nonsmokers. Although there were no differences between these groups with regard to median numbers of submucosal neutrophils, macrophages, CD3⁺ lymphocytes (total lymphocytes), CD4⁺ lymphocytes, or CD8⁺ lymphocytes, CD8⁺/CD3⁺ cell ratio was significantly increased in smokers versus nonsmokers. When current smokers were compared with the subgroup of lifelong nonsmokers, increased numbers of neutrophils infiltrating the mucosa of the small airways were seen in smokers. The observed increase in CD8⁺ T lymphocytes as a percentage of total lymphocytes was consistent with previous research demonstrating a similar finding in the large airways of smokers with COPD.²⁴ All between-group differences were independent of the presence of airflow limitation, however, suggesting that these observations are more closely associated with smoking than with physiologic impairment. The authors postulated that a combination of cellular inflammation and other host factors, such as

response to oxidative stress or proteolytic burden, might influence progression to airflow limitation.

When Turato et al³⁶ compared surgical specimens from smokers with severe COPD (FEV₁ 29% $\pm$ 3% of predicted value, $n = 9$) with specimens from smokers with mild or absent COPD (FEV₁ 86% $\pm$ 5% of predicted value, $n = 9$), small airway inflammation was marked by an increased number of leukocytes (CD45⁺), with increased numbers of CD4⁺ and CD8⁺ lymphocytes in the airway wall and increased CD68⁺ macrophages in the airway epithelium. Airway wall area was positively correlated with smoking history in pack-years, and the number of CD45⁺ cells infiltrating the airway wall was negatively correlated with airflow, as measured by using FEV₁ ($r = -0.7$, $P = .005$) and diffusing capacity for carbon monoxide ($r = -0.62$, $P = .05$), and positively correlated with markers of hyperinflation, such as residual volume ($r = 0.71$, $P < .005$). Leukocyte infiltration was also closely associated with the radiologic emphysema score ($r = 0.8$, $P < .005$). These data complimented the previous work of Retamales et al,³⁷ which demonstrated stepwise increases in alveolar inflammation in surgical specimens from patients without COPD versus patients with mild or severe emphysema.

INFLAMMATION IN COPD PERSISTS DESPITE SMOKING CESSATION

Although smoking cessation clearly reduces the rate of decrease in lung function in patients with COPD^{38,39} and is a critical clinical intervention, the structural changes initiated by smoking persist even after smoking cessation has been achieved. Wright et al⁴⁰ compared pathologic airway changes in biopsy specimens from current and former smokers and were not able to demonstrate significant differences between the 2 groups with regard to structural abnormalities, such as airway wall inflammation, fibrosis, and goblet cell hyperplasia. In 2000, Rutgers et al⁴¹ reported the results of a study that characterized airway inflammation in former smokers with COPD and healthy control subjects. They evaluated 18 nonatopic subjects with COPD (FEV₁ = 59% $\pm$ 13% of predicted value [mean $\pm$ SD]) by means of sputum induction, bronchoalveolar lavage, and endobronchial biopsy and compared findings in these subjects with findings in 11 nonatopic healthy control subjects. Despite the fact that patients with COPD had not smoked for 1 year or longer before evaluation, the authors observed evidence of ongoing airway inflammation in these individuals. In comparisons between patients with COPD and control subjects, induced sputum analysis demonstrated a greater median percentage of both neutrophils (77% vs 36%, $P = .001$) and eosinophils (1.2% vs 0.2%, $P = .008$), whereas bronchoalveolar lavage demonstrated a greater median percentage of eosinophils only (0.4% vs 0.2%, $P = .03$). Analysis of subsegmental endobronchial biopsy specimens demonstrated a greater median number of mucosa EG2⁺ eosinophils (40 vs 5 cells/mm², $P = .049$) and CD68⁺ macrophages (1115 vs

590 cells/mm², $P = .03$), with no significant between-group differences observed in numbers of CD4⁺ and CD8⁺ lymphocytes. Although absolute numbers of eosinophils were increased, markers of eosinophil activation (expressed as concentration of eosinophil cationic protein per eosinophil) were not increased.

In contrast to prior studies evaluating mucosa inflammation in current smokers with COPD,^{14,24} the authors of this study were unable to demonstrate an increased CD8⁺/CD4⁺ ratio in the mucosa, a fact that was attributed to the absence of continued acute irritation by tobacco smoke. The authors speculated that CD8⁺ cells characterize the acute tissue inflammation seen in response to tobacco smoke but that these cells do not play a principal role in chronic ongoing inflammation in nonsmokers with COPD.⁴¹ Although absolute numbers of eosinophils were increased, the authors reported that these cells were not activated because of the lack of relative increases in eosinophil cationic protein, a marker of eosinophil activation.

AIRWAY INFLAMMATION IN PATIENTS WITH COPD WHO NEVER SMOKED

Few studies have evaluated airway inflammation in patients with COPD who have never smoked. In 1994, Lusuadi et al⁴² reported the results of an evaluation of airway inflammation in 16 patients with chronic bronchitis (median FEV₁ = 64% of predicted value) who had never smoked and in 17 healthy control subjects. Although overall lavage fluid cell counts were similar in the 2 groups, patients with chronic bronchitis demonstrated an increased median percentage of bronchoalveolar lavage fluid neutrophils (3.5% [range, 1.6%-14.2%] vs 1.3% [range, 0.5%-3.7%], $P = .0001$). In patients with chronic bronchitis, lavage fluid neutrophilia was inversely correlated with FEV₁ ($r = -0.54$, $P = .036$). Although neutrophils were known to be important in the pathogenesis of COPD in smokers, this study suggested that neutrophils might play an important role in COPD pathogenesis independent of smoking history.

CONCLUSION

Airway inflammation is a critical component of the pathogenesis of COPD. The airway inflammatory phenotype of COPD differs from that of asthma, leading to important differences between these disorders with regard to both clinical and physiologic manifestations. Increased understanding of the mechanisms of inflammation in COPD is necessary to facilitate strategies to prevent and modify the progressive nature of this disorder.

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