Emphysema in COPD

Emphysema in COPD: consequences and causes

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There is still much to be learned about the cellular and cytokine reactions of specific phenotypes in COPD

The current definition of chronic obstructive pulmonary disease (COPD), which has been established by the Global Initiative on Obstructive Lung Disease (GOLD)[1] and also adopted, in large part, by the American Thoracic Society and the European Respiratory Society,[2] is that COPD is a "preventable and treatable disease state characterized by airflow limitation that is not fully reversible". This definition has the virtue of simplicity and clinical applicability but necessarily includes patients with widely varying clinical phenotypes and pathogenic mechanisms. The paper by Boschetto *et al*[3] in this issue of *Thorax* focuses on the role of radiologically identified pulmonary emphysema in a group of patients diagnosed with COPD on the basis of their presenting clinical state and separated into groups for comparison between those with and without radiologically identified emphysema.

Patient selection began with 50 individuals with COPD who then underwent computed tomographic (CT) scanning with a third generation continuous-rotation scanner. The quantitation of emphysema is well described and the quality of the CT scan obtained is considered adequate to rule out the presence of significant emphysema,[3] which is essential for the premises of the study. Importantly, the smoking history between the two patient groups was not significantly different, which suggests varying host factors as causes for the differences observed. The characterisation of patients includes the BODE index, which includes body mass, air flow obstruction, dyspnoea severity, and exercise measured by the 6 minute walk test.[4]

This study shows that patients with CT confirmed emphysema have a higher BODE index and lower IC/TLC ratios than subjects without CT confirmed emphysema. Also, COPD patients with emphysema had lower levels of forced expiratory volume in 1 second (FEV_1), FEV_1/forced vital capacity, and carbon monoxide transfer coefficient and higher functional residual capacity, all of which were associated with an increase in eosinophils and increased matrix metalloproteinase (MMP)-9 concentrations and an increased MMP-9/TIMP ratio in induced sputum.

This paper supports a previous study by Boschetto *et al*[5] which demonstrated the more severely compromised physiological state of lung function in COPD patients with an emphysema phenotype with regard to airflow obstruction, hyperinflation, and reduced transfer factor.

A major strength of the study is the investigation of cell and molecular markers by sputum induction in an attempt to show distinguishing features in patients with and without emphysema. These markers are previously recognised pathogenic factors which have been investigated by bronchoalveolar lavage (BAL),[6 7] but not using the findings in induced sputum to distinguish COPD with and without demonstrable emphysema.

EOSINOPHILIA IN COPD

A new and somewhat surprising finding in this study is the increased numbers of eosinophils in induced sputum in the emphysema group which has not been detected in previous BAL studies[6 7] or in induced sputum of a previous study.[5] Overall, eosinophilic inflammation of bronchi has been well documented in asthma by bronchial biopsies and BAL,[8] and it is also a common finding in the sputum of asthmatic patients.[9 10]

In COPD, previous studies have described significant eosinophilia in bronchial biopsy specimens from patients with chronic bronchitis during exacerbation.[11] Eosinophils were also observed in the sputum of patients with COPD not segregated into emphysema and non-emphysema groups during acute exacerbations.[12] In a study using induced sputum in non-atopic COPD patients in a stable state, eosinophilia was demonstrated and related to mast cell activation.[13] Therapeutically, Brightling *et al* reported an increase in the sputum eosinophil count of patients with COPD in a randomised controlled trial which showed an increased beneficial response to corticosteroids in patients with increased eosinophil counts in blood and sputum.[14] This study suggests that the airway inflammatory state in COPD is related to the eosinophilia. In a later study, Brightling *et al* showed an improvement in FEV_1 post-bronchodilator after a 6 week course of inhaled mometasone in patients with eosinophilia in induced sputum of patients with COPD.[15]

The eosinophilia in the induced sputum of patients in this study must be viewed in the context of the "inflamed lung" in COPD. In this regard, the cellular profile in alveoli and small airways of COPD patients shows increases in macrophages, T lymphocytes (especially CD8 cells), B lymphocytes, and neutrophils.[16 17] Given the multiple possibilities for immunological interactions in the COPD lung parenchyma and airways, it is unclear whether eosinophilia in the emphysema group of this study arises from external antigens or cellular-cytokine reactions in situ. Therapeutically, it would be of interest to determine whether, even in the presence of predominant emphysema, there is increased responsiveness to corticosteroids in this phenotype.

EMPHYSEMA AND MATRIX METALLOPROTEASES (MMPs)

The study by Boschetto *et al*[3] contributes additional evidence for the significant role of MMP-9 (gelatinase-B) among the enzymes which may induce emphysematous destruction. The MMPs are a homologous group of endopeptidases which are capable of degrading many of the constituents of the extracellular matrix including collagen, elastin, proteoglycans, laminin, and fibronectin, and are produced by the macrophages and neutrophils.[18] Previous studies have shown an increase in MMP-9 in BAL fluid in patients with emphysema,[6 7] and this study demonstrates the increase by a non-invasive method in induced sputum which justifies a greater use of induced sputum for such studies. Also, the MMP-9 levels were higher in the COPD patients with emphysema than in those without emphysema, which is consistent with their possibly predominant pathogenic role. However, it is still likely that multiple proteases are involved in parenchymal degradation. In this regard, it should be recognised that MMPs degrade and inactivate α_1-antitrypsin, thus increasing the activity of neutrophil elastase indirectly, together with other enzymes such as cathepsins.[19 20]

ELASTIN DEGRADATION IN COPD

Although desmosine levels in urine, plasma, and sputum were increased, they did not differ between patients with and without emphysema. This

finding is not surprising since elastin is distributed in large measure beyond the alveoli to bronchial and vascular structures. The increased levels of desmosine in the non-emphysematous phenotype indicate that this marker may be useful for detecting tissue degradation in the non-emphysematous COPD phenotype. The improved technical ability to measure desmosine in sputum and plasma, as well as in urine, significantly increases its usefulness as a marker of lung matrix degradation and should be more widely applied in COPD.

IMPLICATIONS OF THE STUDY

Overall, this study presents several significant insights to delineate phenotypes within the broad category of COPD:

- CT scanning is essential for identifying COPD patients with and without a significant component of pulmonary emphysema.
- Induced sputum can yield characterising markers for various COPD phenotypes which may vary from the findings in BAL fluid. Where possible, studies should compare findings in sputum with those from BAL fluid in the same patients.
- While the patients in this study had moderate to severe COPD, studies in patients with mild or early COPD would be worthwhile to determine whether the same enzymatic and inflammatory mediators are detected in early disease.
- The source of increased levels of MMP-9 with respect to neutrophil versus macrophage should be better defined to identify possible therapeutic targets.
- The increase in eosinophils in induced sputum in the emphysema phenotype deserves study in larger series of patients to determine its consistency. Also, the significance of eosinophilia immunologically, functionally and pathologically needs to be better understood in COPD, especially in the emphysema phenotype.

The findings in this study indicate how much more we still need to learn about the cellular and cytokine reactions of specific phenotypes in COPD, and how they differ from the asthmatic state.[21]

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Underdiagnosis of COPD

Underdiagnosed chronic obstructive pulmonary disease in England: new country, same story

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Underdiagnosis or misdiagnosis of COPD is a problem in England too

Chronic obstructive pulmonary disease (COPD) remains one of the leading causes of disability and death in the developed world, and is emerging as increasingly important in the developing world. Despite its importance, COPD is not well recognised by the general public and frequently goes undiagnosed in people who have evidence of it. This underdiagnosis of people with evidence of obstruction on spirometry (generally adults with an FEV_1/FVC ratio <70%) has been previously documented in the United States[1] and Korea.[2]

The paper by Shahab and colleagues in this issue of *Thorax* shows that underdiagnosis and, in all likelihood, misdiagnosis, is a factor in England also.[3] Their key finding was that 13.3% of the population aged 35 and older had evidence of COPD that would, in general, correspond to GOLD stage 1 or more severe disease.[4] Bronchodilator response was not evaluated, so this would not meet strict GOLD criteria and, if this population is similar to the Norwegian adult population,[5] one might expect the ''post-bronchodilator'' prevalence of COPD to be 20–25% lower.