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BRONCHIAL INFLAMMATION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: RELATIONSHIP WITH EMPHYSEMA AND SMALL AIRWAYS DISEASE

INFIAMMAZIONE BRONCHIALE NELLA BRONCOPNEUMOPATIA CRONICO-OSTRUTTIVA: RELAZIONE CON ENFISEMA E MALATTIA DELLE PICCOLE VIE AEREE

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Abstract.
Chronic obstructive pulmonary disease (COPD) is a chronic-progressive disease with high prevalence characterized by progressive chronic airflow limitation not fully reversible, its classifications is based on spirometric values and symptoms. Cigarette smoking represents the most important risk factor for the development of COPD. Pathological studies show inflammation in lungs of patients with COPD. The inflammation in the lungs can lead to different pathological alterations and this to a different subtypes of disease: A) Chronic bronchitis, B) Emphysema, C) small airways disease. Current pathogenetic hypothesis for COPD explains chronic airflow limitation with an abnormal inflammatory response to particles and inhaled gases. Radiological tests like High resolution Computerized Tomography can give macroscopic information about lung parenchyma and airways morphology and moreover can estimate the subtype of COPD.

KEYWORDS: COPD, inflammation, lung.

Riassunto.
La broncopneumopatia cronica ostruttiva (BPCO) è una malattia cronica e progressiva con un alta prevalenza e caratterizzata da una limitazione al flusso aereo cronica e progressiva non completamente reversibile. La sua classificazione è basata su indici spirometrici e sui sintomi. Il fumo di sigaretta rappresenta il fattore di rischio più importante per lo sviluppo della BPCO. Studi anatomopatologici hanno mostrato presenza di infiammazione nei polmoni di pazienti con BPCO. L'infiammazione nei polmoni può portare a differenti alterazioni patologiche e questo a differenti sottotipi della malattia: A) bronchite cronica, B) enfisema, C) malattia delle piccole vie aeree. Le attuali ipotesi patogenetiche sulla BPCO spiegano la cronica limitazione al flusso delle vie aeree come una anomala risposta dell'organismo a particelle e gas inalati. Test radiologici come la tomografia computerizzata ad alta risoluzione possono dare informazioni riguardo il parenchima polmonare e la morfologia delle vie aeree e quindi stimare il sotto tipo di BPCO.

PAROLE CHIAVE: BPCO, infiammazione, polmone

Introduction

Chronic obstructive pulmonary disease (COPD) is a illness characterized by progressive chronic airflow limitation, not fully reversible (1). This airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles.
COPD classification is based on spirometric

values and presence of symptoms like cough, dyspnoea and sputum. COPD Stage I is characterized by Forced expiratory volume at 1 second (FEV1) > 80% predicted and Forced expiratory volume at 1 second (FEV1)/ Forced vital capacity (FCV) < 70% , COPD Stage II is characterized by FEV1 > 50%<80% predicted and FEV1/FCV < 70%, COPD stage III is characterized by FEV > 30%<50% predicted and FEV1/ FCV < 70%, COPD stage IV is characterized by FEV< 30% predicted or FEV1< 50% predicted with Chronic respiratory failure or signs of right heart failure

Epidemiology

COPD is a chronic-progressive disease with a high prevalence, in some prevalence surveys up to about one-quarter of adults aged 40 years and older may have airflow limitation classified as stage I COPD (2,3).
This is one of the most important causes of death in most countries.
The Global Burden of Disease Study (4) has projected that COPD, which was ranked sixth as the cause of death in 1990, will become the third leading cause of death worldwide by 2020.
At the moment there aren't any drugs that can alter the natural history of the disease.
There are a lot of risk factors for COPD. Some scientists suppose genetic predisposition as an important risk factor for COPD. Different studies showed a higher risk to develop COPD in siblings with probands affected by COPD. This higher risk, in part, can be due to the sharing of the same environmental risk factors, however data obtained from different population suggest a participation of genetic risk on development of this disease (5-7).
Cigarette smoking represents the most important risk factor for the development of COPD and the most important way how tobacco contributes to determine the onset of the disease (8).
COPD is a functional diagnosis of a disease with different pathologic features in which the common element is the chronic airflow limitation. Pathological studies show inflammation in lungs of patients with COPD. The inflammation in the lungs can lead to different pathological alterations.
So far one can identify, on the basis of the inflammation, and of bronchial remodeling, different subtypes of COPD: A) Chronic bronchitis B) Emphysema C) small airways disease.
This different pathological alterations are characterized by a different kind of bronchial inflammation that plays a pathogenetic role on the development of the pathological alterations of the airways and on the progression of the disease.

A) Chronic bronchitis (CB) is defined on the basis of chronic cough and sputum following inflammation induced by inhalation of gas and particles contained in the cigarette smoke; it involves airways epithelium and mucus secreting sub mucosal glands with mucus hyper secretion, reduction in mucociliar clearance and increased permeability of the airspace epithelial barrier. Hyper secretion of mucus secreting glands can be caused by the release of some proinflammatory cytokines that include IL4 from cells presents on these patients' airways. Jeffery (9-11) showed on CB patients a statistically higher number of CD45 (+) cells in epithelium, subepithelium and glandular areas compared to healthy volunteers and COPD patients. Among these cells there are predominant plasma cells distributed mainly in subepithelium and glandular areas around and within small blood vessels and mast cells distributed mainly on subepithelial compartment. These data show that mucosal glands are highly infiltrated in these patients and that a contribution of a Th1/Th2 type of inflammation, together with increased immunoglobulin secretions are involved in the CB status and mild COPD.
B) Emphysema is defined as an enlargement of the distal airspaces, beyond the terminal bronchioles, caused by destruction of the airway walls (7). Lung destruction due to emphysema reduces the maximum expiratory flows by the reduction of elastic recoil force that allows expiration. The centroacinar emphysema is characterized by the destruction of respiratory bronchioles and is more tightly associated with tobacco smoke. Panacinar emphysema is commonly associated to A1 antitripsin deficit and is characterized by dilatation and destruction of the entire acinus. There is a weak association between severity of emphysema and number of pack years: moreover only 40% of strong smokers develop emphysema. Furthermore the presence of emphysema can be observed in some patients with normal or weakly impaired lung function (3).
In lung parenchyma of patients with mild emphysema there is an increased number of inflammatory cells, in those with mild/moderate emphysema there are prevalently T lymphocytes cells. Severe emphysema is accompanied by a general increase of alveolar inflammatory cells including neutrophils, macrophages and T-lymphocytes. In these patients alteration of proteoglicans has been observed subsequent to fibrillar collagen stabilization, decreased peribronchiolar decorin, increase of proteolitic enzymes as collagenase 1 and matrix metallo protease (MMP)-1 , increased indices of alveolar apoptosis as showed by reduction in alveolar expression of vascular endothe-

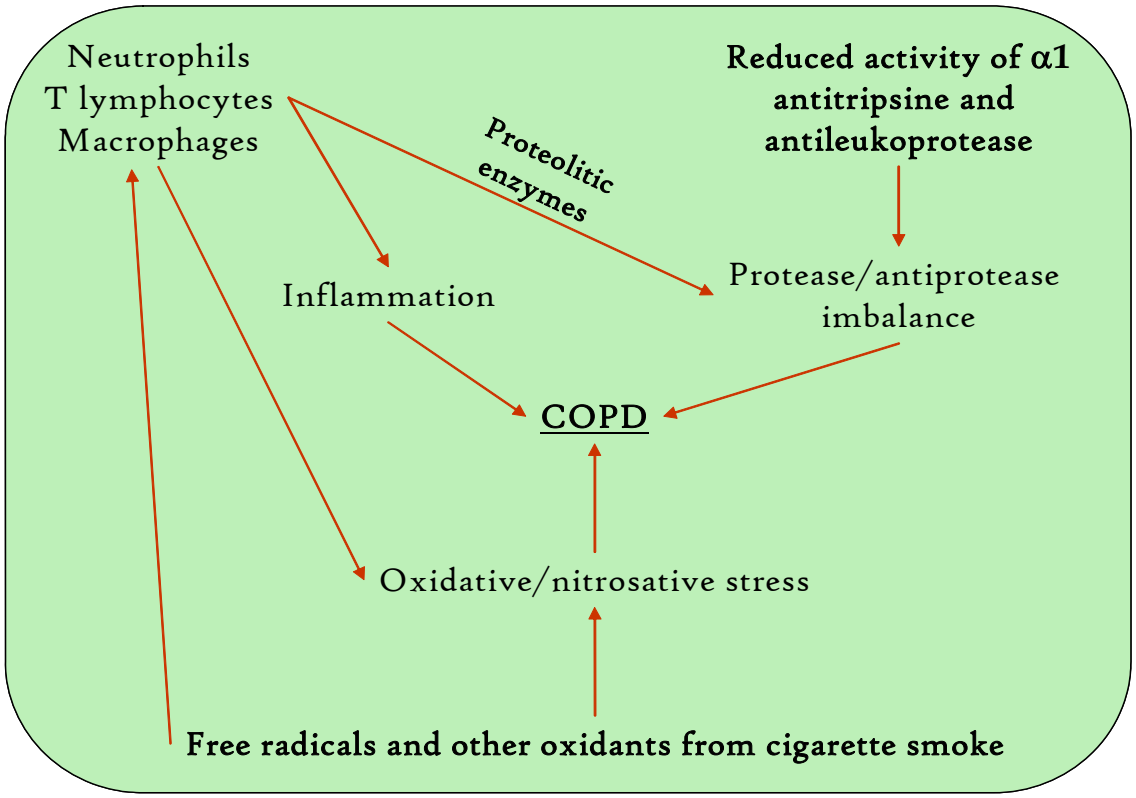
lium growth factor (VEGF-A) and VEGF receptor (VEGF-R)-2. (12). These data suggest that T-cells other than neutrophils can contribute in inducing alveolar septa alterations in mild stages of the disease, while a massive inflammatory cell infiltration and degrading collagen activity becomes prevalent in severe disease states.

C) Small airways disease is caused by occlusion of inflammatory mucous exudates. Inflammation and peribronchial fibrosis contribute to the fixed airway obstruction in the small airways in COPD, and progression of the inflammation, resulting in destruction of the alveolar attachments on the outer walls of the small airways, may also contribute. Airways inflammation rather than increase mucus secretion how happens on central airways of COPD patients and in subjects with CB may favour the increased airway wall thickening, collagen deposition and smooth muscle hypertrophy that determine fixed obstruction of airways. Data regarding inflammation in peripheral airways are conflicting. Many authors (13,14) showed increased total inflammatory cells in the peripheral airways of patients with mild/moderate airflow limitation and near normal lung function. Saetta et al showed increased total inflammation and CD8+ cells and macrophages in the peripheral airways of patients with mild/moderate airflow limitation, however these data are not confirmed by other investigators (15,16). CD4+ and neutrophils were reported as unchanged in mild-moderate COPD patients compared with control smokers. With progression of the disease the following consequences have been reported: decreased mononuclear cell infiltration of the small airways and increasing fibrosis indexes and smooth airways muscles thickening. Increased MCP-1, IL8 and macrophage infiltration has also been reported in bronchiolar epithelium of patients with mild/moderate obstruction in comparison with control smokers. Increased TGFbeta1, a profibrotic protein mainly secreted by epithelial cells, has been reported in moderate disease, suggesting a role for this cytokine in inducing remodelling of peripheral airways.

COPD and inflammation

Current pathogenetic hypothesis for COPD explains chronic airflow limitation with an abnormal inflammatory response to particles and inhaled gases. (Fig.1) Analysis of inflammatory cell infiltration in bronchial biopsies of patients with mild stages of COPD shows an increasing inflammatory cell infiltration in comparison with control non-smokers, among these cells CD8+

Fig. 1: Pathogenetic hypothesis for COPD development: free radicals and other oxidants from cigarette smoke contribute to develop oxidative stress and activate T lymphocytes and neutrophils that release cytokines and proteolytic enzymes that enhance the inflammation and contribute to protease/antiprotease imbalance.



T-lymphocytes, neutrophils and macrophages are prevalent. In patients with severe COPD total inflammatory cells are reduced, the data furthermore show a prevalence in the bronchial tissue of inflammatory cells possessing phagocityc and proteolityc activity like neutrophils and macrophages (12). Another factor involved in the development of COPD is the protease-antiprotease imbalance. Important component of extracellular matrix of the lungs are elastic fibres that contribute to maintain the elasticity and the correct functionality of the lungs. Elastin is the principal component of elastic fibres. In patients with COPD it has been observed an increased degradation of elastic fibres. In the severe stages of COPD there are increased inflammatory cells possessing proteolityc activity like neutrophils and macrophages capable to degrade elastine. On the other hand, it has been observed a reduction of antiproteases activity like Alpha 1 antitripsine and antileukoprotease, that can contribute to elastine degradation (17). Another factor involved in the development of emphysema is the oxidative stress. Cigarette smoke is a mixture of more than 4700 chemical products including high concentration of free radicals and other oxidants. Other sources of reactive oxygen species are those derived by normal cellular respiration or by inhalation of air pollutants such as particulate pollution. In normal lungs there is a balance between toxicity of oxidant agents and protective effect of intra- and extracellular antioxidant defence systems. In COPD patients there is a high evidence of oxidative stress (18) due to a production of oxidants with cigarette smoke and due to increased number of neutrophils and macrophages in the alveolar space. In bronchial biopsies of severely diseased COPD patients an increased presence of MPO+ cells and nitrotyrosine has been reported (19) showing that oxidative and nitrosative stress, mediated by neutrophil activation and MPO production, develops in large airways of severe COPD patients. In vitro studies it has observed that alveolar inflammatory cells from cigarette smokers spontaneously release increased amounts of oxidants, such as O2- and H2O2. Free radicals are responsible for lung emphysema because they act directly on extracellular lung matrix (elastine and collagen) damaging it and moreover they perossidate the airspace surface epithelium lipids leading to an increase in airspace epithelial permeability (20). Once inflammatory process has started it perpetuates itself even if the pathogenic noxa has been removed. This is possible because there are epigenetic modifications of DNA for reduction in activity of histone deacetilase that causes an enhanced transcription of genes involved to inflammation and the activation of proinflammatory transcription factors as STAT4 and NF-kB. Another mechanism involved in the loss of alveolar cells in emphysema is apoptosis. This has been observed in emphysematous lungs (20-23) and is supposed can be mediated by the blockade of VEGF receptor vascular endothelium growth factor.

Conclusion

COPD is a disease characterized by progressive chronic airflow limitation, the diagnosis is functional and is possible by lung function tests. Pathological studies can differentiate COPD on the basis of the inflammation in different subtypes: CB, Emphysema and Small airways disease. Radiological tests like High resolution Computerized Tomography can give macroscopic information about lung parenchyma and airways morphology and moreover can estimate the subtype of COPD prevalent in the damaged lung and the extension of the destruction of lung parenchyma (24). Up to now studies that correlate lung pathology with lung function tests and imaging techniques are needed. Such studies could lead to a better phenotypization of COPD and to a more appropriate use of non-invasive techniques to assess COPD patients and predict a better prognosis and a better therapeutic approach.

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