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Airway pathology in asthma

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ABSTRACT: This review focuses on the major cellular and structural changes present in the airways and lung parenchyma in asthma in comparison with chronic obstructive pulmonary disease (COPD) in an attempt to underline the possible mechanisms contributing to airflow limitation in these two diseases.

Both asthma and COPD are characterized by a thickening of the airway wall and by the presence of an inflammatory process, but the inflammatory cells infiltrating the airway wall differ between the two diseases.

In asthma, the most striking feature is the eosinophilic infiltration, whereas, in COPD, it is the CD8 T-lymphocytic infiltration of the airway wall. In the lung parenchyma, both diseases are characterized by an inflammatory process, whereas destruction and fibrosis of the alveolar walls occur in COPD but not in asthma.

These cellular and structural changes may contribute to the development of airflow limitation (that characterizes both asthma and chronic obstructive pulmonary disease) by inducing either an increase in resistance or a decrease in driving pressure.
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Asthma and chronic obstructive pulmonary disease (COPD) are two diseases characterized by airflow limitation. The airflow limitation is mostly reversible in asthma and mostly irreversible in COPD, at least in the majority of patients. Since flow is the result of a driving pressure that promotes flow and of an opposing resistance that counters flow, a reduction in flow can be due to either a reduced driving pressure (loss of elastic recoil of the lung parenchyma) or an increased resistance (airway obstruction) [1]. This review, therefore, focuses on the major cellular and structural changes present in the airways and lung parenchyma in asthma in comparison with what is known to occur in COPD in an attempt to underline the possible mechanisms contributing to airflow limitation in these two diseases.

Airways

Histopathological studies in asthmatic patients have established that asthma is a process involving both central and peripheral airways. This process includes cellular changes, *i.e.* infiltration of the airway wall by inflammatory cells, and structural changes, *i.e.* thickening of all components of the airway wall (fig. 1).

Cellular changes

Airway inflammation in asthma is a multicellular process involving mainly eosinophils, CD4 T-lymphocytes and mast cells, with eosinophilic infiltration being the most striking feature [2]. Although the inflammatory process occurs in the entire tracheobronchial tree [3–5], it has been recently demonstrated that the distribution of the eosinophilic infiltration within the airway wall varies significantly between large and small airways [6]. The small airways contain a preponderance of eosinophils in the "outer" section of the airway wall (between the smooth muscle and alveolar attachments), whereas the greatest density of eosinophils in the large airways is in the "inner" section of the airway wall (between the smooth muscle and the basement membrane). These regional differences in inflammatory cell density could have important physiological implications in the mechanisms contributing to airflow limitation. In peripheral airways, the increased eosinophil density in the "outer" region would promote airway constriction by decreasing the tethering effects of the parenchyma on the airway wall, whereas, in large airways, the increased eosinophil density in the "inner" region would promote airway constriction by amplifying the effect of bronchial smooth muscle shortening on airway calibre. The fact that the variation in inflammatory cell density seen in patients with asthma was not observed in patients with other inflammatory diseases such as cystic fibrosis suggests that the "inner" *versus* "outer" pattern is not part of a nonspecific pulmonary inflammatory response, but rather may be disease-specific. As pointed out by HALEY *et al.* [6], one possible explanation for this cell distribution is that the cytokine profile produced by local cells within the airway wall may vary within airway regions or within airway size, resulting in the observed differences in

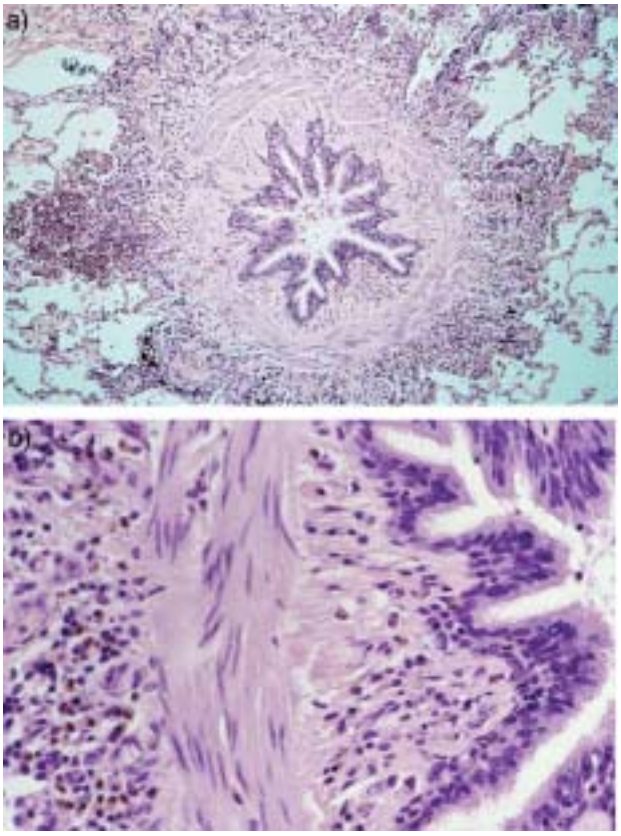

Fig. 1. – Photomicrographs showing a bronchiole from a subject who died during an asthma attack. a) Luminal occlusion caused by muscle constriction, thickening of the airway wall, increased smooth muscle mass and a marked inflammatory process in the airway wall, mainly characterized by eosinophils. b) Detail from a). The distribution of the inflammatory process is more obvious: there is a greater density of eosinophils in the area outside the smooth muscle ("outer" region) than in that inside it ("inner" region). (Haematoxylin and eosin staining).

patterns of inflammatory cells density. The functional consequences of this cell distribution remain speculative. It is possible that different cell localization and different microenvironment influence the local production of mediators by inflammatory cells. For example, factors released immediately adjacent to smooth muscle are likely to exert a greater effect on smooth muscle than factors released distant from it.

Although it is well accepted that asthma is characterized by eosinophilic infiltration, there has been accumulating evidence that prominent neutrophilia occurs in situations associated with severe asthma [7–10]. Neutrophil levels have been shown to be elevated in sputum from exacerbated asthmatics [7], bronchial washes from patients intubated for status asthmaticus [8], autopsy samples from patients who died suddenly of asthma [9] and severe steroid-dependent asthma [10]. It is possible that, in steroid-dependent asthma, the neutrophilia is due to the corticosteroid therapy itself, which has been shown to reduce eosinophil number and to increase neutrophil numbers, by inhibition of neutrophil apoptosis [11]. However, there are other possible explanations for the prominent neutrophilia observed in asthma when the disease becomes severe [10]. The first possible explanation is that the neutrophils are present because the pathology changes when the disease becomes severe. Alternatively, the neutrophils could be present as a response to an altered milieu, perhaps infectious, in the airways. Finally, it is also possible that the neutrophils, although present in the airways, are not contributing in any way to the pathological process but simply represent a marker of severity of the disease.

In severe steroid-dependent asthma, WENZEL *et al.* [10] reported a marked predominance of neutrophils over eosinophils in bronchoalveolar lavage fluid and in bronchial and transbronchial biopsy samples, *i.e.* in the lumen, bronchial wall and alveolar walls. These results suggest that a novel form of inflammation, that is different from that seen in moderate asthmatics, is observed in the majority of severe asthmatics on high doses of corticosteroids. Despite the fact that asthma is not a single disease entity, but rather a complex of conditions that contribute to airflow limitation, clinicians tend to treat all asthmatics in a similar manner. As pointed out by WENZEL *et al.* [10], this may be due to a lack of pathological data, which could help to distinguish between different subgroups of patients. In this context, the finding of different types of inflammation in severe and moderate asthma provides pathological evidence of heterogeneity of the disease that may explain the different response to therapy in individual patients.

WENZEL *et al.* [12] subsequently further analysed the subjects with severe steroid-dependent asthma, and obtained evidence that the phenotype of "severe asthma" is composed of at least two distinct pathological subtypes (based on the presence or absence of eosinophils) with distinct physiological and clinical characteristics. Patients with and without eosinophilia demonstrated similar degrees of airway obstruction and both had persistently elevated neutrophil numbers despite high doses of corticosteroids. However, patients with eosinophilia showed a greater total amount of inflammatory cell infiltrate (including T-lymphocytes and mast cells), thicker subepithelial basement membrane and higher incidence of respiratory failure as compared to patients without eosinophilia. Which specific cytokines are driving the inflammatory process in the two groups of severe asthmatics is still unknown. It is possible that cytokines inducing "classic" asthmatic inflammation (increased numbers of eosinophils, T-lymphocytes and mast cells associated with thickening of the subepithelial basement membrane) are involved in the group with eosinophilia, whereas different cytokines are probably involved in the group without eosinophilia, that showed virtually no evidence of "classic" asthmatic inflammation. As stated by WENZEL *et al.* [12], it is currently impossible to determine whether this latter group had demonstrated a distinct pathology since disease onset or whether eosinophils were lost as a consequence of corticosteroid therapy. Whatever the explanation, the tissue level response appears to be different in the two groups of severe asthmatics.

It is now well accepted that COPD is also characterized by an airway inflammatory process, but that the

inflammatory cells infiltrating the airway wall are different from those observed in asthma [13–16]. In COPD, T-lymphocytes and macrophages are the predominant cells, with CD8 T-lymphocyte infiltration being the most striking feature in both the large and small airways. Interestingly, not only are CD8 T-lymphocytes increased in number but their numbers also correlate with the degree of airway obstruction [15, 16], supporting a role for airway inflammation in the development of airflow limitation in smokers. When COPD becomes severe, prominent neutrophilia occurs [17], confirming that there is an association between neutrophilia and disease severity, as in asthma.

Structural changes

The airway wall of patients with asthma is characterized by increased smooth muscle mass, mucous gland hypertrophy and vascular congestion leading to a thickened airway wall and markedly reduced airway calibre [18–23]. These features may contribute to the development of airflow limitation by increasing airway resistance. The effect on flow is enhanced by the presence of increased amounts of mucus and inflammatory exudate, which not only blocks the airway passages but also causes an increased surface tension favouring airway closure. This excessive mucus secretion is due not only to hypertrophy of mucous glands [21, 22], but also to hyperplasia of goblet cells, which has also been reported in the airway epithelium of asthmatic subjects [24, 25].

The increase in smooth muscle mass may be due to several factors, including proliferation of smooth muscle induced by inflammatory mediators [26], cytokines [27] and growth factors [28, 29]. It has been suggested that an intrinsic abnormality of smooth muscle may underlie asthma severity, but data are lacking to support this hypothesis. The major functional consequence of the increase in smooth muscle mass is that, in an airway with a thickened wall, the same degree of smooth muscle shortening may cause considerably greater luminal narrowing than in a normal airway [30].

An important component of airway wall thickening is vascular congestion. An increased vessel area in the airway wall has been reported in subjects who died during an asthma attack as compared to subjects with mild nonfatal asthma, suggesting a role for vascular congestion in the reduction of airway calibre that characterizes a fatal attack [20]. However, these results were not confirmed in a subsequent study that found no differences in vascular congestion between fatal and mild nonfatal asthma [23].

It is now well accepted that, in asthma, there is increased thickness of the reticular basement membrane [31, 32]. This thickening is due to the deposition of collagen types I, III and V, as elegantly shown by ROCHE *et al.* [31], and so is more properly called "subepithelial fibrosis". Intriguingly, the majority of studies have shown that this thickening correlates with neither the severity nor the duration of asthma [33, 34]. However, one study [35] has shown a correlation between increased thickness of the reticular basement membrane and severity of disease, supporting the role of subepithelial fibrosis in the development of airflow limitation in asthma.

Whereas collagen deposition has been measured in the basement membrane in most studies, only a few have investigated collagen deposition in the rest of the airway wall [31, 32, 36, 37]. Evaluation of this deeper submucosal collagen deposition may be important, since it may contribute (more than the basement membrane) to the total thickness of the airway wall. CHU *et al.* [37] hypothesized that, in severe steroid-dependent asthma, the disease may be refractory to therapy because the airways are more "fibrosed" or "remodelled" than in mild asthma. They, therefore, examined collagen deposition in the deeper submucosa in four groups of subjects: controls, mild asthmatics, moderate asthmatics, and severe steroid-dependent asthmatics. The amount of collagen deposition was similar in the four groups of subjects examined, suggesting that the degree of fibrosis in the deeper submucosa cannot explain the differences in severity of asthma. As both the severe and moderate asthmatics received corticosteroids, it is possible that the lack of differences in collagen deposition among asthmatic groups was secondary to an effect of therapy. Despite similar collagen deposition (whether or not due to corticosteroids), severe asthmatics were clinically different from the other groups, with ongoing symptoms, poor pulmonary function, and oral corticosteroid requirements. As underlined by CHU *et al.* [37], these observations suggest that airway collagen deposition is not a key contributor to the symptoms and pathophysiology of asthma.

Thickening of the subepithelial reticular basement membrane does not occur in COPD, at least in the majority of subjects [38]. By contrast, fibrosis of the total wall has been reported in this disease [39], although more studies are needed to support this observation.

Thickening of the airway wall, hypertrophy of mucous glands, increased smooth muscle mass and hyperplasia of goblet cells have been reported in patients with COPD [16, 40, 41]. Moreover, both thickness of smooth muscle [16] and number of goblet cells [41] correlate with the degree of airway obstruction in this disease, supporting a role for airway remodelling and mucus hypersecretion in the development of airflow limitation in smokers.

Lung parenchyma

Only a few studies have examined the cellular changes in the alveolar walls of patients with asthma, and even less information is available regarding the structural changes that occur in the lung parenchyma of these patients.

Cellular changes

The few studies examining inflammation of the lung parenchyma in asthma have been performed by a group in Denver, CO, USA, who analysed transbronchial

biopsy samples obtained from subjects with nocturnal asthma [42, 43] and from subjects with severe steroid-dependent asthma [10].

In patients with nocturnal asthma, respiratory symptoms worsen considerably at night. Studying inflammatory changes in nocturnal asthma, therefore, provides a model for relating these changes to worsening of the condition in a naturally occurring situation [44]. The inflammatory response in the alveolar walls is considerably greater at night in patients who experience nocturnal asthma. Analyses of transbronchial biopsy samples [42, 43] have shown that the overnight decrease in lung function correlates with increased numbers of eosinophils and CD4 T-lymphocytes in the alveolar tissue, supporting a role for parenchymal inflammation in the acute worsening of the condition.

As has been seen before, patients with severe steroid-dependent asthma demonstrate an inflammatory process in the alveolar walls that is characterized by prominent neutrophilia [10]. Whether this neutrophilia represents an effect of corticosteroids or simply a marker of severity of the disease remains to be investigated.

Inflammatory changes in the alveolar region are also reported in COPD. Lymphocytes, particularly CD8 T-lymphocytes, and macrophages have been demonstrated to form a significant component of this alveolar wall inflammatory infiltrate [45, 46]. The correlation between increased number of CD8 T-lymphocytes in the alveolar walls and reduced expiratory airflow observed in smokers [45] supports a role for these cells in the development of chronic airflow limitation in smokers.

Structural changes

While parenchymal destruction is a characteristic feature of COPD [47], it is uncommon in asthma [18], even though more studies are needed to confirm the lack of parenchymal destruction in asthmatic lungs.

Emphysema, which is one of the major causes of COPD, is defined anatomically as a permanent "destructive" enlargement of airspaces distal to the terminal bronchioles, without obvious fibrosis [47]. However, this last statement (without obvious fibrosis) has been the subject of recent debate. New data have shown that, in emphysema, the destructive process is accompanied by a net increase in the mass of collagen, suggesting that, contrary to the definition of the disease, active alveolar wall fibrosis does indeed occur in emphysematous lungs [48, 49].

Conclusions

From the point of view of the airways, both asthma and COPD are characterized by an inflammatory process, but the inflammatory cells infiltrating the airway wall differ in the two diseases. In asthma, CD4 T-lymphocytes, eosinophils and mast cells are the predominant cells involved, whereas, in COPD, CD8 T-lymphocytes and macrophages are the predominant cells. In asthma, the distribution of the eosinophilic infiltration differs between the central and peripheral airways, and this pattern of distribution may have important functional consequences. When the disease becomes severe, prominent neutrophilia occurs in both asthma and COPD, but the mechanisms underlying the recruitment of neutrophils are still unclear. Thickening of the airway wall, increased smooth muscle mass, hypertrophy of mucous glands and goblet cell hyperplasia have been reported in both asthma and COPD, whereas the extent of the fibrosis differs in the two diseases. In asthma, it is localized in the area just beneath the epithelium even in patients with severe disease, whereas, in COPD, it may involve the entire airway wall.

From the point of view of the parenchyma, both asthma and COPD are characterized by an inflammatory process in the alveolar walls (even though the predominant cell phenotype differs), whereas destruction and fibrosis of the alveolar walls occur in COPD but not in asthma.

These cellular and structural changes may contribute to the development of airflow limitation (that characterizes the two diseases) by inducing either an increase in resistance or a decrease in driving pressure. Whether or not these changes explain the reversible and irreversible component of airflow limitation still remains to be investigated.

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