

Pathology of asthma and its clinical implications

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Although detailed histopathologic studies have described the inflammatory processes present in fatal asthma, until recently the pathology of less severe forms of the disease has been less well understood. Now a series of important studies has extended our understanding of the pathophysiology of mild asthma. Studies that examine sputum or fluid obtained by bronchoalveolar lavage from mildly asthmatic subjects revealed findings consistent with an active inflammatory process within the airways. The histopathologic examination of endobronchial biopsy specimens from stable asthmatic patients has shown that inflammatory cell infiltration of the mucosa is a distinctive feature of mildly asthmatic subjects requiring only intermittent inhaled β -agonist therapy. These studies have also shown that marked tissue disruption may occur early in the natural history of mild asthma. These investigations have demonstrated that asthma is a disease characterized by acute and chronic inflammatory changes within the airways and that in many respects the histopathologic features of mild allergic asthma are similar to those observed in fatal asthma. The therapeutic implications of these findings are that management of mild asthma should be directed toward resolving this inflammatory process. There is now sufficient evidence to suggest that anti-inflammatory drugs such as cromolyn sodium, inhaled corticosteroids, and nedocromil sodium be used earlier in the course of the disease and that the use of these therapeutic agents should not be limited to patients with severe forms of asthma. This may be particularly important in view of the increasing awareness of the potential problems associated with the overreliance on β -agonist therapy in patients with asthma. (J ALLERGY CLIN IMMUNOL 1993;92:148-54.)

Despite improved understanding of the pathogenesis of asthma, increased diagnostic awareness and the development and use of highly potent and specific therapies, morbidity and mortality from this disease have increased during recent decades. Consequently it is important to review what is known about the pathology of asthma and to determine whether this knowledge can improve our approach to the management of this common disorder.

FATAL ASTHMA

It has long been recognized that patients who die of asthma have a marked inflammatory process occurring within their airways.¹⁻³ This inflammation has been shown to be both highly specific

Abbreviations used:

BAL: Bronchoalveolar lavage
DAB: D-methylaminobenzene
MBP: Major basic protein

and restricted to the airways (Fig. 1). The airway lumina are filled with thick, tenacious mucus plugs. These obstructions may be so extensive that the lungs remain inflated when the pleural cavities are opened at autopsy, and they may not collapse, even with the use of pressure. On microscopy the mucus plugs that contain eosinophils, macrophages, plasma cells, and ciliated epithelial cells may completely occlude the bronchial lumen. Detachment of the bronchial epithelial cells may be marked, exposing a layer of basal cells and indicating damage to an extensive area of mucosa (Fig. 1).

In fatal asthma the submucosa shows massive inflammatory cell infiltration, mainly with eosinophil leukocytes. Extensive deposition of collagen is seen beneath the true epithelial basement

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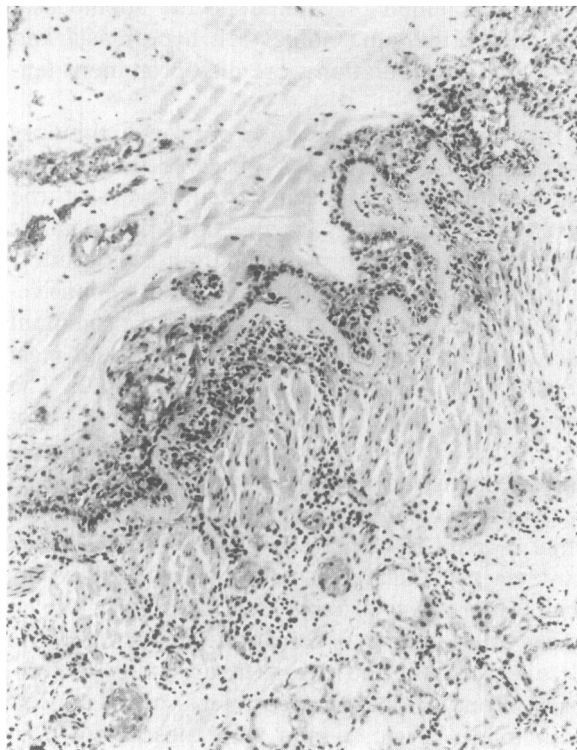


FIG. 1. Fatal bronchial asthma. Mucus and cellular debris are present in bronchial lumen. Pronounced inflammatory infiltrate is present in bronchial wall. This wall is mainly composed of eosinophils. Band of hyaline material is beneath epithelium, giving appearance of thickened basement membrane. (Hematoxylin-eosin stain; original magnification $\times 112$.)

membrane, leading to an apparent increased thickness of the basement membrane when viewed by light microscopy.⁴ The entire bronchial wall also appears thickened because of the tissue edema associated with vascular congestion and increased smooth muscle thickness. The increased prominence of the bronchial smooth muscle is probably due to hyperplasia, not hypertrophy, of the muscle bands.⁵ Hyperplasia also occurs in the submucosal glands and is similar to that observed in patients with chronic bronchitis. Because these pathologic changes are found in the airways of patients with both atopic and intrinsic asthma, it is natural to assume that some common inflammatory process activated by a wide variety of inciting stimuli may be responsible.

SPUTUM AND BRONCHOALVEOLAR LAVAGE

In contrast with the information obtained from detailed histopathologic studies of the airways in

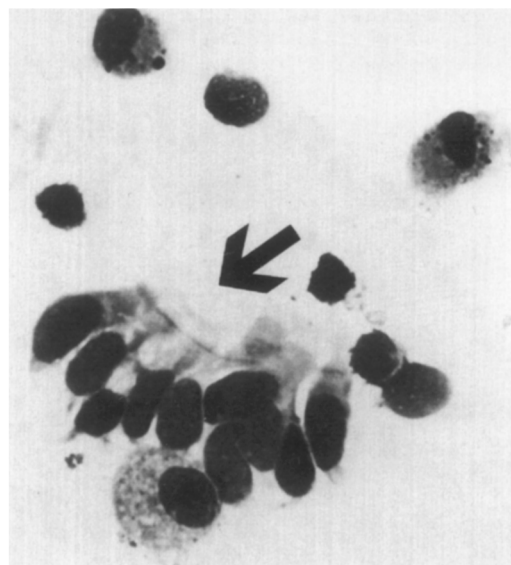


FIG. 2. Bronchial lavage fluid in patient with allergic asthma. Cluster of shed ciliated bronchial epithelial cells is present (arrow). This phenomenon is due to increased fragility of bronchial epithelium in asthma. (May-Grundwald-Giemsa stain; original magnification $\times 450$.)

fatal asthma, the inflammatory events that characterize less severe forms of the disease are less clear. One fundamental approach to a better understanding of this issue has been to examine the sputum of asthmatic patients. The significance of this approach was first demonstrated in 1883 by Curschmann,⁶ who described spiral mucoid casts in asthmatic sputum and proposed that mucus within airways can cause airflow obstruction. At about the same time, Vierordt noticed that large clusters of epithelial cells were present in the sputum of asthmatic patients. The presence of bronchial epithelial cells in sputum reflects extensive damage to, and denudation of, the respiratory epithelium. This detachment occurs almost exclusively in asthmatic patients and increases considerably during asthma attacks.⁷

Another key feature of asthmatic sputum is the presence of eosinophils, reflecting eosinophil infiltration within the bronchial mucosa. The findings of Charcot-Leyden crystals⁸ and increased concentrations of eosinophil-derived major basic protein in the sputum of asthmatic patients⁹ provide evidence for eosinophil activation.

An alternative approach to sputum analysis is to evaluate fluid obtained by BAL in subjects with mild to moderate asthma (Fig. 2). With this method an increased number of epithelial cells,¹⁰ mast cells,¹¹ eosinophils,¹² and T lymphocytes,¹³

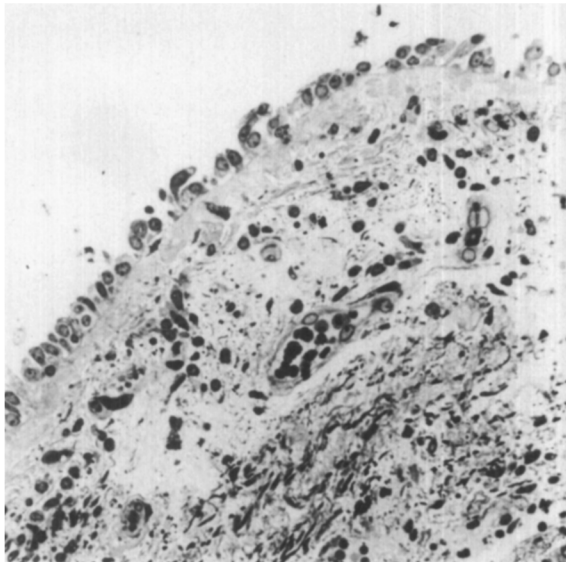


FIG. 3. Bronchial biopsy from subject with allergic asthma. There is partial denudation of bronchial epithelium, an artifact induced by biopsy forceps. Thickening of subepithelial collagen is apparent, and inflammatory cell infiltrate in adjacent submucosa. Margination of leukocytes is seen in small venule. (Azure II–methylene blue–basic fuchsin stain; original magnification $\times 280$.)

have been demonstrated in asthmatic patients compared with normal subjects.

Furthermore, the use of BAL after local allergen challenge in segmental airways permits examination of the probable inflammatory changes that occur in allergic asthma.^{14, 15} During the early asthmatic response to locally instilled allergen, marked increases in mast cell–derived prostaglandin D₂ occur in BAL fluid.¹⁵ During the late asthmatic response to allergen, there is a cellular inflammatory reaction characterized by significant increases in lymphocytes, neutrophils, and eosinophils in BAL fluid.¹⁴ Nevertheless, despite careful attempts to limit the site of lavage to the airways, neither the origin of these cells nor their relevance to events occurring in the airway wall itself is completely clear.¹⁶

BRONCHIAL BIOPSIES

A more definitive approach to the study of nonfatal asthma is the histopathologic examination of endobronchial biopsy specimens from asthmatic patients. This type of study was first done with rigid bronchoscopy, and leukocyte infiltration of the mucosa was the dominant finding by light microscopy.^{17, 18} In particular, eosinophils were found at all sites throughout the airway wall:

within the lumen of capillaries, the submucosa, and the epithelium. Goblet cell hyperplasia and mast cell degranulation were also prominent features.

In a clinicopathologic study of bronchial biopsy specimens Laitinen et al.¹⁹ observed that epithelial destruction can occur at all levels of the airways in asthmatic patients. Epithelial damage and denudation were seen in patients with mildly to severely increased bronchial hyperresponsiveness. The abnormality was considered prominent enough to expose the epithelial nerves and mast cells to both specific and nonspecific stimuli. The investigators postulated that the resulting exposure of afferent nerves could explain bronchial hyperresponsiveness in patients with asthma. In a scanning electron microscopic study of the bronchial mucosa in asthma, Lundgren²⁰ also showed large areas of damage to the ciliated epithelium, including regions of complete ciliary loss.

To extend these observations we undertook a detailed cellular and ultrastructural study to compare bronchial biopsy specimens from subjects with mild allergic asthma with those from non-asthmatic control subjects.¹⁰ In this study asthmatic subjects requiring only intermittent inhaled β -agonist treatment were deliberately chosen for two reasons: (1) to identify the abnormalities that were present in the mildest form of asthma and (2) to avoid the effects of antiinflammatory treatment that might modify the appearance of biopsy specimens. As a result, all subjects had clinically mild asthma with normal spirometry (mean forced expiratory volume in 1 second 98% predicted) and moderate hyperresponsive (geometric mean, provocation concentration causing a 20% fall in forced expiratory volume in 1 second [PC₂₀]; methacholine, 0.90 mg/ml). All subjects also had positive skin prick tests to common allergens.

The most distinctive finding from this study was the inflammatory cell infiltration into the bronchial mucosa (Fig. 3). This infiltration was observed in all the asthmatic subjects to varying degrees. In particular, the presence of large numbers of eosinophils throughout the airway wall clearly differentiated asthmatic biopsy specimens from normal ones. Eosinophils viewed by transmission electron microscopy showed morphologic features suggesting activation with electron lucency of the granule matrix, loss of the major basic protein central core of the granules, and the presence of extracellular granule material. In addition to these morphologic changes, there was functional evidence of activation, including the

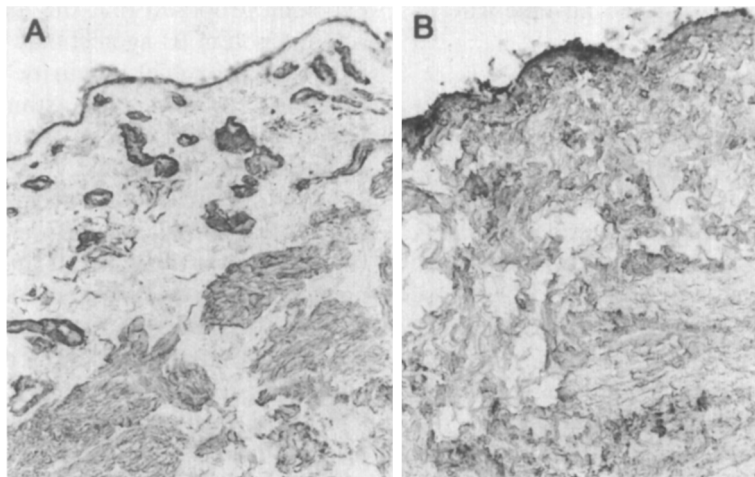


FIG. 4. Bronchial biopsy specimens from a subject with allergic asthma. **A**, Distribution of collagen IV. This basement membrane component is confined to bronchial epithelial basement membrane, basement membrane of blood vessels, and smooth muscle. In contrast, collagen III is present in interstitium and in thickened collagen band beneath bronchial epithelium. **B** (Immunoperoxidase-D-methylaminobenzene stain; original magnification $\times 280$.)

adherence to and emigration of eosinophils from vessel walls, and the presence of eosinophils within the dense subepithelial collagen layer and among the bronchial epithelial cells (Fig. 3).

Another difference between the asthmatic and control subjects was the appearance at biopsy of mast cells in the bronchial lamina propria. In the asthmatic biopsy specimens these mast cells appeared activated, showing varying degrees of degranulation. Their appearance could not be attributed to the biopsy procedure itself because the mast cells in the nonasthmatic subjects were fully granulated and the fine detail of their granule matrices was preserved. These findings suggest that mast cell activation, with the subsequent release of inflammatory mediators, may occur continuously within the airways of atopic asthmatic subjects. This possibility is supported by the observation that histamine H_1 -receptor blockade results in bronchodilation in patients with stable atopic asthma.²¹ Thus the activation of mast cells is probably an ongoing process in asthma and contributes to airway dysfunction even in mild forms of the disease.

Another feature of the biopsy specimens from asthmatic subjects was an extensive deposition of collagen beneath the bronchial epithelium. The demonstration of abundant interstitial structural proteins, collagen types III and V, and fibronectin in this thickened subepithelial band indicates that their origin from the fibroblasts, not the epithelial cells (Fig. 4).²² These findings illustrate that se-

vere tissue disruption may occur early in the natural history of mild asthma. The subepithelial fibrosis may be related to the progressive development of the irreversible airway obstruction that accompanies chronic asthma.²³

CLINICAL RELEVANCE

These studies indicate that asthma is a disease characterized by marked acute and chronic inflammatory changes within the airways and that the inflammatory changes in the airways of subjects with mild allergic asthma are similar in nature to the features described for fatal asthma. This similarity suggests that pharmacologic treatment directed toward modifying the underlying inflammatory process should be an essential component of the management of all forms of asthma and not just reserved for the more severe forms of the disease.

However, before such a change is proposed in the therapeutic emphasis of treatment, it is important to consider whether current management practices, particularly overreliance on bronchodilator drugs, are less than ideal and may have contributed to observed increases in morbidity and mortality. There is no doubt that inhaled β -agonist drugs have improved the quality of life in asthmatic persons and should be available to all asthmatic patients for use to relieve episodes of symptomatic airflow obstruction. However, could their regular use make asthma worse in the long term, or could their overuse during an acute

severe attack contribute in some adverse way to the risk of a fatal outcome?

ASTHMA MORTALITY

A review of mortality rates in the twentieth century reveals a gradual increase in asthma mortality since the 1940s, interrupted by an epidemic of asthma deaths occurring in a number of countries during the 1960s, and a second epidemic that occurred in New Zealand in the 1970s.²⁴ The most likely explanation for the first epidemic is that it relates to the introduction and use of the high-dose isoprenaline inhaler,^{25, 26} although this hypothesis is still the subject of debate.

The evidence is stronger for the use of the high-dose preparation of the potent β -agonist fenoterol as a cause of the second New Zealand epidemic. The fenoterol hypothesis was originally proposed after the identification of an association between the sales of fenoterol by metered dose inhaler and asthma mortality,²⁷ and after the findings from two mortality surveys showing a disproportionate use of fenoterol among patients dying from asthma.^{28, 29} Subsequently, evidence came from three case-control studies of prescribed drug therapy and death from asthma in New Zealand.^{27, 30, 31} In these three studies, each of which used different methods and incorporated different data sources, an increased risk of asthma death was noted in persons for whom fenoterol was prescribed. Although the possibility was raised that fenoterol may have been preferentially prescribed to patients with more severe asthma, there was little evidence to support this hypothesis, and certainly this could not account for the case-control findings.³² In particular, the observation that the relative risk associated with fenoterol use in each study increased in subgroups defined by markers of severity indicated that the case-control findings were not due to confounding by chronic asthma severity. No other antiasthma drugs that were examined appeared to increase the risk of death disproportionately in patients with severe asthma. More recently, a Canadian study specifically designed to address the fenoterol hypothesis has also found that the prescription of fenoterol is associated with an increased risk of death compared with the more commonly prescribed β -agonist salbutamol.³³

The mechanisms by which the high-dose preparations of fenoterol and isoprenaline increase the risk of death have not yet been determined but are likely to relate either to their regular long-term use or to overuse in a severe attack. It

has been proposed that the long-term, high-dose use of a potent β_2 -agonist may lead to tolerance,³⁴ increased bronchial reactivity,³⁵ reduced baseline function,³⁶ or worsening asthma.³⁵ On the other hand, their overuse in an acute attack may result in increased hypoxemia,³⁷ hypokalemia,³⁸ or a delay in seeking medical help.³⁹ The use of high doses of a less selective β_2 -agonist that is also a full β_1 -agonist may result in cardiac toxicity,³⁸ particularly in the presence of hypoxemia.⁴⁰ Regardless of the exact mechanism, this phenomenon, which has been identified with isoprenaline and fenoterol, demonstrates the potential problems that exist when treatment is based on a reliance on potent but poorly selective β -agonist drugs, which are marketed in high-dose ("forte") preparations.

ASTHMA MORBIDITY

The possible role of β -agonist drugs in contributing to increased asthma morbidity is less conclusive. The many studies of asthma prevalence undertaken at different times in both Western and developing countries suggest a real increase in asthma prevalence.⁴¹ The factors responsible for such a change are unknown, although they are unlikely to be related solely to disease labeling or changes in environmental factors (e.g., airborne allergens or pollution). Evidence from prevalence studies and from those studies demonstrating dramatic increases in the number of severe asthma patients requiring hospital admission,^{42, 43} also indicate an increase in disease severity.

Recent studies have demonstrated that regular inhaled β -agonist therapy increases bronchial responsiveness.⁴⁴⁻⁴⁶ Although the clinical relevance of these changes in bronchial hyperresponsiveness is unclear, it is possible that β -agonists make individual patients more vulnerable to provoking stimuli during exacerbations. This worsening in bronchial hyperresponsiveness also has potential significance when applied to the entire population of patients with asthma. This was illustrated by Mitchell,⁴¹ who demonstrated that a very small change in bronchial hyperresponsiveness within the population results in a small increase in the number of patients with mild or moderate asthma, but a substantial increase in the percentage of patients with severe disease. It is thus possible that the increasing widespread use of β -agonist drugs may be causing an increase in the severity of asthma within a population of asthmatic persons, but further studies are needed to confirm or refute this hypothesis.

CONCLUSION

Although it may not be recognized clinically, bronchial asthma is an inflammatory disease. Consequently, instead of simply alleviating symptoms with bronchodilators such as β -agonists, management should be directed toward resolving the underlying disease process with pharmacologic agents that are known to be active against the inflammatory component. There is now sufficient evidence to suggest that drugs such as cromolyn sodium, inhaled corticosteroids, and nedocromil sodium should be used earlier in the course of the disease and should not be limited to patients with severe asthma. Certainly this approach is strengthened by the increasing evidence that the emphasis on bronchodilator treatment may not only have been partially responsible for the asthma mortality epidemics but may also have affected the natural history of asthma, leading to an increase in the prevalence of severe asthma.

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