The Role of Mucus in Fatal Asthma

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Although the number of deaths from asthma (~5000 per year in the United States) (1) is small relative to other causes of mortality, it is important to note that these deaths frequently occur in young people and are preventable. A history of near fatal asthma is the best predictor of asthma mortality. In fact, it has been reported that 23% of patients discharged from the intensive care unit following treatment for asthma die of recurrent asthma within 6 years (2). Physicians managing patients with a history of near fatal asthma should therefore recognize that these patients are at an increased risk of death, and that close follow-up is warranted, as is aggressive treatment with anti-inflammatory treatments when their asthma shows signs of instability.

Arrhythmias and cardiac arrest due to electrolyte abnormalities, hypoxia, and asthma medications have been considered possible causes of death in severe asthma. However, rigorous studies of serum electrolytes and electrocardiograms have not supported this hypothesis (3,4). It is more likely that mortality results from asphyxiation. Airway narrowing from contraction of concentric smooth muscle almost certainly occurs in severe asthma, although it is debatable whether muscle contraction by itself is sufficient to cause death. Evidence suggests that airway narrowing results from a combination of factors, including smooth muscle contraction, airway wall edema, and mucus hypersecretion (5). Mucus hypersecretion has been underappreciated as a cause of respiratory failure in severe asthma; indeed there is strong evidence that it may be the principal cause. For example, Huber documented mucus plugging of the airways in patients with fatal asthma in 1922 (6), and Dunhill later provided graphic descriptions in 20 cases (7). Dunhill noted that in a typical case of fatal asthma, "both lungs are acutely distended. They fill the chest, completely covering the pericardium, nearly meeting at the midline, and failing to collapse once the negative pressure has been released." He also found that "the cut surface of the lung showed a striking picture with numerous grey, glistening, mucous plugs scattered throughout the airway passages." In brief, "pathologically the outstanding feature of the asthmatic lung lies in the failure of clearance of the bronchial secretions." Although other investigators (8) have confirmed this observation, there have been isolated reports since the 1960s of deaths not associated with airway mucus impaction (9). The lack of airway mucus could be because of washout of mucus during lung fixation; however, it is more likely that these cases are a specific subset of asthma deaths without mucus hypersecretion.

In this issue of the *Journal*, Kuyper et al (10) present a morphological analysis of the nature of airway narrowing in fatal asthma in a large number of subjects who died of asthma in New Zealand. The authors measured the degree of airway narrowing and the lumenal content of mucus and cells in lungs from 93 cases of fatal asthma and from lung segments from nonasthmatic subjects. They found that substantial airway plugging occurred in the vast majority of asthma cases and that airway narrowing was greater in larger airways and in older patients. Thus, the subset of asthma deaths with no evidence of mucus hypersecretion is very small.

An acute severe episode of airway narrowing is a characteristic feature of asthma. In contrast, other airway diseases such as chronic obstructive pulmonary disease, cystic fibrosis, and bronchiectasis are characterized by subacute deteriorations in lung function and are rarely associated with life-threatening sudden-onset attacks. Our understanding of the mechanisms of mucus hypersecretion in asthma, although improved, is still rudimentary. The sources of mucin glycoproteins in the airway are goblet cells in the surface epithelium and mucus cells in submucosal glands. Although the number of goblet cells is increased in mild and moderate asthma (11), it appears that enlargement of submucosal glands is characteristic of more severe forms of the disease (12). The mechanism of airway mucus cell hyperplasia must be separated from those of mucus cell degranulation, although both mechanisms could be targeted to provide novel therapies. Recently discovered candidate mediators of mucus cell metaplasia include interleukin 13, ligands for the epidermal growth factor (EGF) receptor, and a calcium-activated chloride channel (CLCA1). Candidate mucin secretagogues include neutrophil elastase, chymase, leukotrienes, and eosinophil cationic protein (13). Interestingly, airway inflammation in acute severe asthma is also qualitatively different than in mild asthma. Mild and moderate asthma are characterized by eosinophilic airway inflammation, whereas acute severe asthma is characterized by intense neutrophilic inflammation and increased levels of neutrophil elastase (14,15). Thus, neutrophil elastase may be an important mediator of goblet cell and submucosal gland cell degranulation in fatal asthma.

Each airway disease is characterized by differences in the cellular and biochemical constituents of mucus, resulting in varying physical characteristics of mucus.

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Kuyper et al found that the mucus plugs in fatal asthma comprised mucins, plasma proteins, and cells. Sputum or tracheal aspirates from asthma patients are not purulent but can be quite tenacious. Conversely, sputum in cystic fibrosis has more neutrophils and higher concentrations of deoxyribonucleic acid (DNA) than in asthma, with fewer differences in mucin and albumin content (16), which may explain sputum quality in these two diseases, as the interaction between albumin and mucin may be important in determining the physical properties of mucus plugs in asthma. For example, List et al (17) explored the interaction of serum albumin and mucin glycoprotein using rotary viscometry, and found that mixing albumin and mucin yielded a markedly viscous solution. Viscosity enhancement was proportional to albumin concentration and was considerably greater than the additive or multiplicative viscosity values calculated from albumin or mucin solutions measured separately.

Although mucus plugs are involved in airway obstruction in severe asthma, there are no specific mucolytic treatments, and treatment is therefore largely supportive. Beta-agonists are given to relieve airway obstructions due to smooth muscle contraction, and corticosteroids are used to reduce airway inflammation. Corticosteroids may also decrease mucin secretion by mucus cells (18). N-acetylcysteine is not effective in asthma (19), and rhDNAse is unlikely to be effective in asthma because DNA concentration in airway secretions is much lower than in cystic fibrosis. Consequently, there is a great need for mucolytic treatments that either prevent mucus cell metaplasia or speed the breakdown and clearance of mucus plugs, precluding the need for hospitalization or mechanical ventilation in some patients.

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