Asthma

Non-eosinophilic asthma and the innate immune response

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Pathological heterogeneity of asthma

The concept that there may be heterogeneity of the underlying pathology of asthma has a long pedigree: 80 years ago, Rackemann¹ suggested that a subgroup of patients with intrinsic asthma had disease driven by bacterial infection of the upper and lower respiratory tract and the authors of an early postmortem study² were struck by the heterogeneity of lower airway inflammatory response in fatal asthma. However, since then the prevailing view, largely driven by bronchial biopsy studies of limited numbers of patients with relatively mild disease, has been that there are more similarities than differences in the pathology of subtypes of asthma. Thus, asthma is currently viewed as a condition characterised by TH2 cytokine-mediated eosinophilic airway mucosal inflammation.³⁻⁴

The development of simple methods to assess airway inflammation non-invasively using induced sputum which are applicable to a wide variety of patients⁵ has renewed interest in investigation of the pathological heterogeneity of asthma. Using this technique, Turner *et al*⁶ unexpectedly found that just under half of 34 patients studied during a minor asthma exacerbation had no sputum eosinophilia. Fahy *et al*⁷ made a similar observation in patients studied during a more significant exacerbation; many patients had sputum evidence of neutrophilic airway inflammation. Subsequently non-eosinophilic asthma has been shown to be present in 25% of patients presenting to an adult respiratory clinic with symptomatic asthma,⁸⁻⁹ in patients with occupational asthma¹⁰ and in up to 50% of patients with asthma treated with high doses of inhaled corticosteroids.¹¹ The concept that non-eosinophilic asthma represents a pathologically distinct form of the disease is supported by work by Wenzel *et al*¹² showing that a subgroup of patients with refractory asthma had distinctive, non-eosinophilic pathology and normal basement membrane thickness on bronchial biopsy. Similar bronchial biopsy findings have been reported in patients with non-eosinophilic asthma treated with inhaled

β_2 agonists only.¹³ In a longitudinal study of patients with severe asthma the absence of sputum eosinophils was a stable feature over 12 months in a number of patients¹⁴; other studies indicate that non-eosinophilic pathology can be found in corticosteroid naive patients with symptoms as well as those receiving inhaled corticosteroid therapy.⁵⁻⁶ These observations suggest that, in some patients at least, non-eosinophilic asthma is a stable phenotype. Moreover, the distinctive sputum features cannot be solely due to the effects of corticosteroid therapy.

Non-eosinophilic asthma is of particular interest for several reasons. First, several uncontrolled studies have suggested that it is associated with a poor short-term response to inhaled corticosteroid therapy.⁵⁻⁶ This has been confirmed in a recent double blind placebo controlled study.¹³ There is also evidence that the long-term therapeutic effects of corticosteroid therapy are disappointing: a longitudinal study has shown that patients with persistently non-eosinophilic sputum were able to substantially reduce corticosteroid therapy without any obvious increase in the frequency of asthma exacerbations over 12 months.¹⁴ A lot more work needs to be done before we can conclude that non-eosinophilic asthma is a stable asthma phenotype that does not respond to corticosteroid therapy. However, there does seem to be sufficient data to raise this as a strong possibility and to suggest that non-eosinophilic asthma is a clinically important entity worthy of further research.

A second point of interest is the possibility that an entirely different kind of inflammation to the TH2 driven eosinophilic airway mucosal inflammation normally associated with asthma can be associated with airway hyper-responsiveness and variable air flow obstruction. Many investigators have highlighted the presence of increased sputum markers of neutrophilic inflammation in patients with non-eosinophilic asthma.⁹⁻¹¹ Neutrophilic lower airway inflammatory responses occur in response to a wide variety of stimuli including: viral and

bacterial infection; chronic inflammation of structures embryologically linked to the airways¹⁸⁻¹⁹; and inhaled stimuli such as hypertonic saline,²⁰ endotoxin,²¹⁻²² ozone,²³ cigarette smoke,²⁴ other pollutants²⁵ and occupational irritants.¹⁰⁻²⁶ A common feature of these immune responses is the involvement of innate immunity, and Douwes *et al*¹⁷ have suggested that the interaction between elements of this primitive immune response and the airway might be important in the development of the airway hyper-responsiveness and variable air flow obstruction seen in non-eosinophilic asthma. Tumour necrosis factor (TNF) α might be particularly important in this regard as treatment with the TNF α antagonist etanercept has been shown to be associated with a significant improvement in airway responsiveness and air flow obstruction in patients with severe asthma.²⁷

The concept that activation of the innate immune response in the airway occurs in non-eosinophilic asthma has been investigated in a study reported by Simpson *et al*²⁸ (see p 211) in this issue of *Thorax*. The investigators measured expression of innate immune response receptors and cytokines, the concentration of the proinflammatory cytokine IL8 and the levels of lipopolysaccharide and endotoxin in induced sputum in patients with asthma, bronchiectasis and controls. The group with asthma were subcategorised into inflammatory phenotypes based on the induced sputum differential inflammatory cell count; all were non-smokers. The authors found increased expression of mRNA for several innate immune response receptors and cytokines, increased IL8 and a trend to increased endotoxin concentration in induced sputum in patients who were classified as having neutrophilic asthma. Potentially pathogenic bacteria were identified in 43% of the patients with neutrophilic asthma, a finding that is in keeping with Rackemann's¹ identification of a subgroup with bacterial asthma. Overall, the inflammatory profile seen in neutrophilic asthma was similar to that seen in patients with bronchiectasis, although the sputum endotoxin concentration tended to be higher and the proportion with bacterial colonisation lower in patients with neutrophilic asthma. These findings strongly support the hypothesis that activation of the innate immune response occurs in non-eosinophilic asthma. The observations are cross-sectional, and it is important to investigate the effect of interventions such as bacterial eradication or removal of sources of inhaled endotoxin on the clinical and inflammatory expression of the disease before we can conclude that

there is a direct link between these inflammatory mechanisms and airway dysfunction. The recent demonstration that treatment with telithromycin improves outcome in patients with exacerbations of asthma²⁹ provides some support for this view, but more studies on the role of infection in both stable and acute asthma are required before we can be sure.

One third of the patients with asthma studied by Simpson *et al*²⁸ had normal sputum neutrophil and eosinophil differential cell counts. The authors suggest the term paucigranulocytic asthma for this subgroup. Whether neutrophilic and paucigranulocytic asthma can be distinguished reliably and consistently, and to what extent sputum findings reflect stable differences in the underlying lower airway immunopathology or the cause of the pathology, remains to be determined. None of the inflammatory parameters assessed in induced sputum differed between normal controls and the patients with paucigranulocytic asthma, suggesting that airway hyper-responsiveness and variable air flow obstruction can occur independently of airway inflammation as measured by induced sputum. This finding, together with evidence that the patterns of lower airway inflammatory responses associated with other airway conditions such as cough^{30–32} and chronic obstructive pulmonary disease^{33–34} are heterogeneous, implies that it might be other factors such as the intrinsic characteristics of the airway or the site of the inflammatory response^{35–36} that determine the functional consequences. One key factor leading to airway hyper-responsiveness might be mast cell localisation within the airway smooth muscle as this has been observed in eosinophilic and non-eosinophilic asthma but not eosinophilic bronchitis.^{13–35}

A final point of interest is to speculate on the consequences of the coexistence of inflammatory stimuli leading to neutrophilic airway inflammatory responses with the more usual eosinophilic inflammatory response. An elegant series of studies on smoking and asthma shows quite clearly that this combination leads to a number of features associated with more severe airway disease including: more troublesome symptoms; more frequent exacerbations; a more neutrophil dominated lower airway inflammatory response; physiological evidence of involvement of the small airways; an accelerated decline in lung function; and evidence of airway and systemic corticosteroid resistance.^{37–42} Importantly, many of these features improve with smoking cessation.^{40–41} Could the effect of multiple inflammatory stimuli be an important and potentially modifiable factor leading

to more severe airways disease?¹⁸ If so, then investigating the mechanisms of chronic neutrophilic airway inflammation, and the way it interacts with airway function and other airway inflammatory responses, has a wider importance.

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