

EDITORIAL

Are eosinophils still important in asthma?

Asthma is characterized by chronic airway inflammation, reversible airway obstruction and airway hyperresponsiveness [1]. Although airway inflammation along with eosinophil accumulation and activation can be associated with airway obstruction and hyperresponsiveness, some studies in asthmatics and animal asthma models have suggested contradicting roles of eosinophils in asthma pathogenesis [2–9].

In this issue of the journal, Ishiura and colleagues evaluate the associations between airway eosinophil accumulation induced by repeated intranasal polymyxin-B treatment in guinea pigs and bronchial responsiveness to methacholine, acetylcholine and histamine challenges. Interestingly, they found that airway eosinophilia coexisted with actual reduction in airway responsiveness to all three challenges [10]. Thus, the question that has been brought to the forefront is the role(s) of eosinophils in the pathogenesis of asthma.

Pros for involvement of eosinophils in asthma

Airway eosinophilic inflammation has been recognized for nearly 100 years in asthmatic lung tissue [11]. Typically, the airway wall of fatal asthmatics is thickened and the airway lumen is occluded by mucus plugs with large numbers of eosinophils [12,13] (Fig. 1a). These pathologic findings may well explain the severe airflow obstruction in fatal asthma attacks. Increased numbers of activated eosinophils have also been extensively reported in various airway samples from living asthmatics with different severity of the disease. These samples include bronchial biopsy tissue, alveolar tissue, bronchoalveolar lavage (BAL) and induced sputum [14–18]. Since eosinophils are known to produce, store and release many proinflammatory cytokines and mediators, they are considered to play a critical role in the pathophysiology of asthma. For example, mediators from eosinophils such as major basic protein, eosinophil cationic protein (ECP) and cysteinyl leukotrienes (CLTs) have been demonstrated to contribute to bronchoconstriction and airway hyperresponsiveness [19–22]. In fact, allergen challenge in atopic asthma has been shown to induce a significant eosinophil infiltrate into the airways in the late asthmatic reaction (Fig. 1b), which is accompanied by increased levels of ECP and leukotriene C₄ (LTC₄) in BAL, and a significant drop in forced expiratory volume in 1 s (FEV₁) [23]. Strong correlations between baseline airway eosinophils and airway hyperresponsiveness as well as FEV₁ have also been reported in patients with asthma, especially mild

asthma [4–6,24]. In animal models of asthma, eosinophils were also shown to be associated with increased airway responsiveness to methacholine challenge [9]. IL-5 is one of the key cytokines in the recruitment, activation and survival of eosinophils. IL-5 knockout mice and anti-IL-5 antibody-treated mice demonstrated significantly lower numbers of lung eosinophils and reduced airway responsiveness to methacholine challenge [25–27]. These animal studies suggest that IL-5 elimination from airways could attenuate eosinophilic inflammation with consequent improvement in pulmonary function.

Cons for involvement of eosinophils in asthma

Although eosinophils are likely to play important roles in asthma, some studies suggest that asthma and/or airway hyperresponsiveness/obstruction could exist without significant eosinophil accumulation in the airway [8,28–31]. Fatal asthma can be presented as a ‘sudden-onset’ or ‘slow-onset’ process. In contrast to slow-onset asthma, sudden-onset fatal asthma is characterized by large numbers of neutrophil accumulating in the airway mucosa with minimal numbers of eosinophils [32]. Additionally, studies in severe living asthmatics suggested that a subgroup of patients demonstrated no obvious eosinophil infiltration in the large airway mucosa. Neutrophils were the predominant cells in this subgroup of asthmatics, which showed a lower FEV₁ than those severe asthmatics with airway eosinophils [28,29]. A recent study also indicated that clinically unstable severe corticosteroid-dependent asthmatics had decreased numbers of eosinophils in the airway mucosa compared with mild asthmatics [33]. These results suggest that eosinophils may not be essential in certain populations of severe asthmatics. It is important to note that some studies in mild and moderate asthmatics failed to establish a significant inverse relationship between pulmonary function and eosinophil numbers or ECP levels in bronchial biopsy tissue and BAL samples [2,3]. Moreover, a recent clinical study using a single dose of humanized anti-IL-5 antibody treatment in mild asthmatics did not show an improvement in the early or late asthmatic reaction following an allergen challenge, although reduction of eosinophil levels was found in both peripheral blood and induced sputum [34]. Furthermore, another recent study even demonstrated that airway hyperresponsiveness could not be observed in the late asthmatic reaction, although there was an airway eosinophilic inflammation [35]. These human studies suggest that eosinophils may not necessarily be involved in the

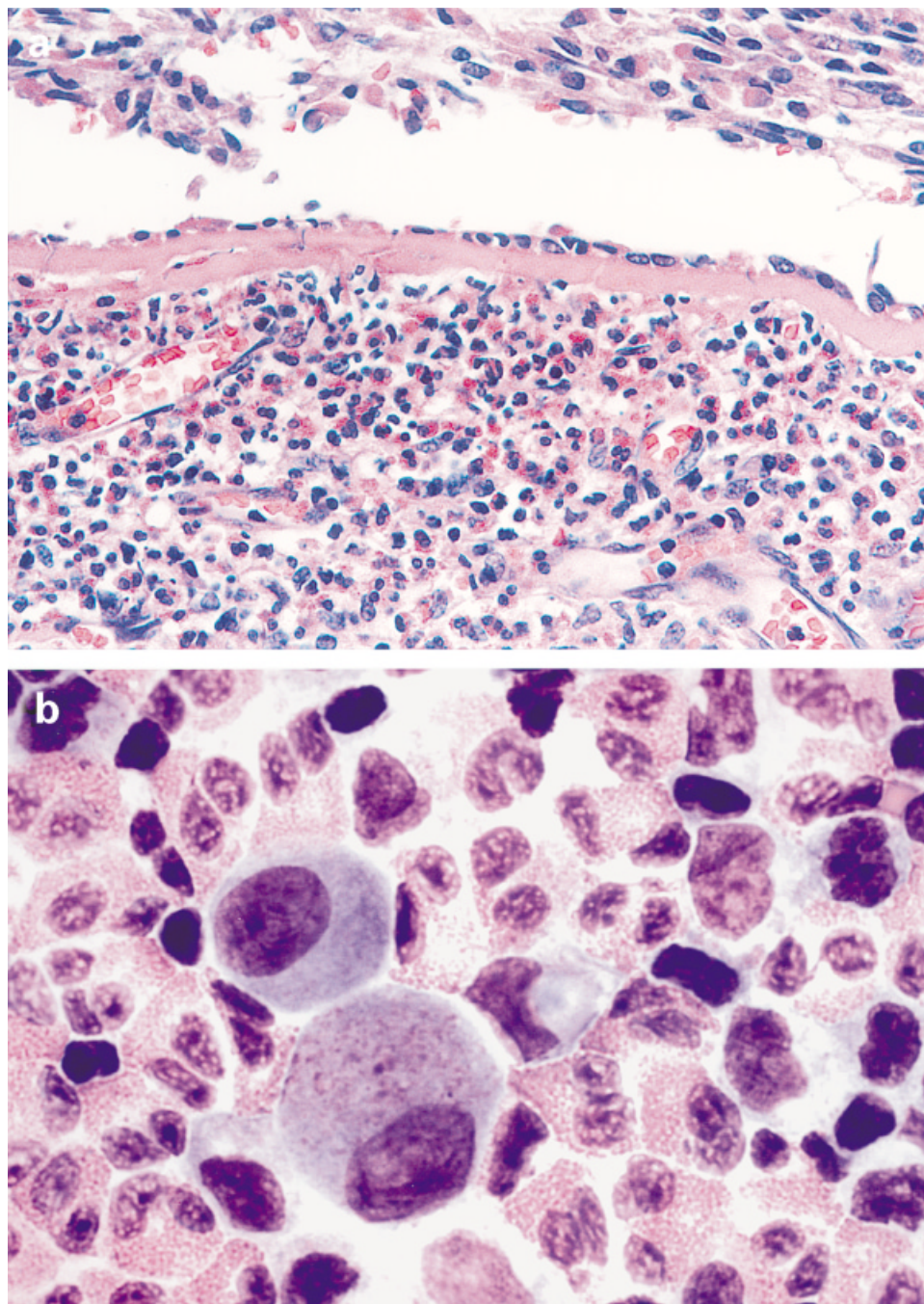


Fig. 1. (a) Fatal asthmatic bronchial tissue demonstrating a large amount of eosinophil accumulation with a marked bronchial epithelial desquamation. (H-E staining, original mag. $\times 400$.) (b) Allergen challenge in atopic asthma causing significant eosinophil influx into the bronchoalveolar lavage. (Diff-Quick staining, original mag. $\times 1000$.)

pathophysiology of a subgroup of asthmatics with different severity of the disease.

Some animal studies also suggest that airway eosinophilia may not be important in the development of allergen-induced airway hyperresponsiveness. For example, Tournoy *et al.* [8] demonstrated that airway hyperresponsiveness could occur

with or without airway eosinophil influx and elevated serum allergen-specific IgE in a murine asthma model induced by house dust mite allergen. Additionally, IL-5-deficient mice could present a similar airway hyperresponsiveness compared with the wild-type mice after nasal inoculation with nematode *Nippostrongylus brasiliensis*

[30]. In this issue of the journal [10], results from Ishiura *et al.* further support the concept that eosinophils may not be required for the development of airway hyperresponsiveness. The specific point from this study is that airway eosinophilia may be associated with reduced airway responsiveness to methacholine, acetylcholine and histamine challenges in polymyxin-B-treated guinea pigs. It is interesting to note that another study demonstrating the lack of airway eosinophil accumulation to increase airway hyperresponsiveness was also conducted in guinea pigs [36]. It is not clear if the genetic background of guinea pigs could contribute to this specific phenomenon. It is important to determine if this observation could be duplicated in mouse asthma models in future studies. As for the potential mechanisms of eosinophils in the reduction of airway hyperresponsiveness, study from Ishiura and colleagues suggests that cyclooxygenase pathway products of arachidonic acids, such as prostaglandins E_2 (PGE_2) and I_2 (PGI_2), could play a role. Eosinophils are one of the major cellular sources for 5-lipoxygenase products of arachidonic acids such as CLTs. It has been shown that levels of CLTs were increased in asthmatic airways after allergen challenge [37]. In contrast to PGE_2 and PGI_2 [38,39], CLTs are able to cause significant bronchoconstriction and airway hyperresponsiveness [22]. Therefore, it is very intriguing why 5-lipoxygenase products from eosinophils seem to be suppressed in Ishiura's guinea pig model.

Are pros and cons of eosinophils in asthma reconcilable?

How can the pros and cons story of eosinophils be reconciled? We suggest the following two points to reconcile the contradictory stories of eosinophils in asthma. First, asthma should be considered as a syndrome rather than a single disease. In this context, there may be several or many subgroups/phenotypes of asthma with different aetiologies or triggers. Some populations of asthmatics may be eosinophil-associated and some may not. Second, asthma pathogenesis is very complex and still uncertain. Current studies suggest that both chronic airway inflammatory and remodelling processes are involved [1]. Eosinophil accumulation may be only part of the processes which produce chronic changes in the airway. Eosinophil accumulation may also only exist intermittently as a result of different endogenous and exogenous stimulants. In the absence of airway eosinophils, the other inflammatory components (e.g. neutrophils and mast cells) and airway remodelling may be sufficient to contribute to the disease process [1,40]. When eosinophils appear in the airway, they may or may not exacerbate asthma.

In conclusion, the significance of eosinophils in asthma

may be much more complicated than we thought several decades ago. We may need to realise that there is a heterogeneity issue for asthma and certainly for eosinophils (both the amount and activity) in asthmatic airways. Different types of airway inflammation such as eosinophilic and non-eosinophilic inflammation may characterize different phenotypes of asthma. In the future, these concepts need to be considered in research designs and in the selection of asthma therapy.

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