Eosinophilia in Pulmonary Disorders

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KEYWORDS

• Asthma • AFAD • Eosinophilic pneumonia
• Eosinophilic granulomatosis with polyangiitis (EGPA) • Hypereosinophilic syndrome

KEY POINTS

- The presence of lung disease can aid in the diagnosis, investigation, and management of eosinophilic disorders.
- Sputum eosinophilia has been shown to be associated with persistent airway inflammation, uncontrolled asthma, lung function decline, future risk of exacerbations, and asthma severity.
- Eosinophilic pneumonia (EP) may represent a relapse of chronic EP and is rarely simple or acute unless caused by a defined and avoidable trigger (usually a drug reaction).
- A better classification of EP in the authors' opinion would be by cause: parasitic migration, allergic (including drug allergy) or idiopathic (the most common form).
- The boundaries between nonatopic eosinophil-predominant asthma, EP, eosinophilic granulomatosis with polyangiitis (EGPA), and hypereosinophilic syndrome (HES) with respiratory involvement are blurred, and they may all be part of the same condition, possibly driven by Type 2 innate lymphoid cells (ILC2) cells in response to an unknown antigen.

GENERAL CONSIDERATIONS

Introduction

Lung disease associated with marked peripheral blood or tissue eosinophilia is an unusual event and almost always points toward a diagnosis. For example, florid allergic fungal airway disease (AFAD) with pulmonary masses, upper lobe shadowing, or large airway collapse is commonly misdiagnosed as lung cancer or tuberculosis but invariably is associated with a peripheral blood eosinophilia that is unusual in these other conditions. The peripheral blood eosinophil count is a balance between eosinophil

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production and the rate of entry of eosinophils into the tissue. If there is a strong inflammatory stimulus in the lung recruiting eosinophils into the tissue, then the tissue eosinophilia may be marked to a modest or even normal peripheral blood eosinophil count. In other situations such as drug allergy in which there is a systemic stimulus for eosinophilopoiesis, the latter may be the case with a modest tissue eosinophilia in the context of a marked peripheral blood eosinophilia. This review is written from the perspective of expertise gained in a tertiary level specialist clinic for people with an unexplained peripheral blood eosinophilia (>1.5 $\times$ 10^9/L), set within a respiratory and allergy department with an ethnically mixed catchment of about 1,000,000 and a regional catchment of about 5,000,000. The most common causes of an eosinophilia affecting the respiratory system seen in this clinic are severe asthma, AFAD, HES, EGPA, and chronic idiopathic EP. The patient's medical history including a detailed drug history and geographic background is therefore important in guiding investigations when trying to elicit a cause.

Eosinophilia has been associated with several diseases that affect the small and large airways. It can be detected as an increased percentage of the differential cell count on peripheral blood, induced sputum and bronchoalveolar lavage (BAL) samples, or as eosinophilic infiltration seen on lung biopsy specimens. Its presence or absence is used to endotype patients and guide treatment intensity during exacerbations and stable state in asthma[1] and chronic obstructive pulmonary disease (COPD)[2,3] and is likely to form part of the criteria for treatment with new drugs, such as mepolizumab, an anti-interleukin (IL)-5 antibody developed for treatment of asthma.[4] The common causes of an eosinophilia associated with respiratory disease seen in the authors' clinic are listed in **Table 1**. The degree of eosinophilia seen in each condition varies and is not helpful for diagnosis, although an eosinophil count of greater than 5 $\times$ 10^9/L is not often seen in severe asthma without another complication such as fungal allergy. This list does not include conditions such as eosinophilic bronchitis or idiopathic pulmonary fibrosis in which there is a sputum or BAL eosinophilia without a peripheral blood eosinophilia.

Mechanisms of Eosinophil Migration into the Lung

Eosinophils are one of the key effector cells of allergic inflammation. Their maturation, recruitment, and survival are closely associated with cytokines and chemokines generated in the context of the immune pathway involving T_H2 lymphocytes in the adaptive system and ILC2 cells in the innate system, with IL-5 and IL-13 being central to the process. Epithelial-derived Thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 seem to orchestrate this pathway to a significant extent.[5,6] Differentiation of eosinophils also occurs in the lung with increased numbers of $CD34^+$ Interleukin 5 receptor, alpha (IL5Rα) cells seen in sputum in response to allergen challenge, although the physiologic importance of this is uncertain.[7,8]

Although IL-3 and Granulocyte macrophage colony-stimulating factor (GM-CSF) are involved in the eosinophil maturational pathway, IL-5 is essential for the late differentiation of eosinophils. Eosinophilia is reactive in most cases (as opposed to being due to a malignant transformation of the eosinophil) and has been shown to be responsive to antibody therapy directed against IL-5, which causes a marked decrease (although not a complete ablation) in the peripheral blood eosinophil count.[9,10] Antieosinophil therapies are much more effective at reducing the eosinophilia in the blood than in the tissue. Thus, mepolizumab, an antieosinophilic antibody that binds IL-5, preventing it from binding to the IL-5 receptor, reduced the blood eosinophil count by 90% but the eosinophil count in the bronchial mucosa by only 50%.[11] A marked reduction in the blood eosinophil count by mepolizumab is associated with a prevention of asthma