Eosinophilic Lung Diseases

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KEYWORDS

• Eosinophil • Eosinophilic pneumonia • Interstitial lung disease
• Eosinophilic granulomatosis with polyangiitis • Aspergillus

KEY POINTS

- Eosinophilic lung diseases may present as eosinophilic pneumonia with chronic or acute onset, or as the more transient Löffler syndrome.
- The diagnosis of eosinophilic pneumonia is based on both characteristic clinical-imaging features and the demonstration of alveolar eosinophilia of at least 25% eosinophils at bronchoalveolar lavage.
- Peripheral blood eosinophilia is present in most eosinophilic lung disorders, but can be absent at presentation in idiopathic acute eosinophilic pneumonia and in patients receiving corticosteroid treatment.
- In Europe and North America, chronic eosinophilic pneumonia is most frequently idiopathic, whereas acute eosinophilic pneumonia is often related to drug or tobacco smoke exposure.
- All possible causes of eosinophilia (especially fungus or parasitic infection, drug or toxic exposure) must be thoroughly investigated.

DEFINITION AND CLASSIFICATION

Definition

Eosinophilic lung diseases are a group of diffuse parenchymal lung diseases[1,2] characterized by the prominent infiltration of the lung interstitium and the alveolar spaces by polymorphonuclear eosinophils, with conservation of the lung architecture. As a corollary, a common denominator of eosinophilic lung diseases is represented by a dramatic response to systemic corticosteroid therapy and healing without any sequelae in most cases, despite frequent impressive impairment of lung function at presentation.

Blood *eosinophilia* is defined by an eosinophil blood cell count greater than 0.5×10^9/L, and *hypereosinophilia* by an eosinophil blood cell count of greater than 1.5×10^9 on 2 examinations over at least a 1-month interval.[3–5] Alveolar eosinophilia is defined by differential cell count of at least 25% eosinophils at bronchoalveolar lavage (BAL), and typically greater than 40%.[4]

Classification

Eosinophilic lung disorders can present as acute or chronic pneumonia or as the transient Löffler syndrome, which is most commonly of parasitic origin (**Box 1**). The main causes include exposure to drugs or toxins and fungal infection; however, chronic eosinophilic pneumonia is most often idiopathic, and acute eosinophilic pneumonia most often is related to drugs or tobacco smoking. Eosinophilic lung disorders occurring in the

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Box 1
Classification of the eosinophilic lung diseases in clinical practice

Eosinophilic pneumonias of unknown cause

Solitary idiopathic eosinophilic pneumonias

- Idiopathic chronic eosinophilic pneumonia
- Idiopathic acute eosinophilic pneumonia

Eosinophilic pneumonia in systemic syndromes

- Eosinophilic granulomatosis with polyangiitis
- Idiopathic hypereosinophilic syndromes (lymphocytic or myeloproliferative variant)

Eosinophilic pneumonias of known cause

Allergic bronchopulmonary aspergillosis and related syndromes

Eosinophilic pneumonias of parasitic origin

Eosinophilic pneumonias of other infectious causes

Drug-induced eosinophilic pneumonias

Eosinophilic airways diseases

Eosinophilic asthma

Hypereosinophilic asthma

Idiopathic hypereosinophilic constrictive bronchiolitis

Other pulmonary syndromes with possible eosinophilia

Organizing pneumonia, idiopathic pulmonary fibrosis, Langerhans cell histiocytosis, malignancies, and so forth

context of systemic conditions suggest the diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) or the idiopathic hypereosinophilic syndromes.

PATHOPHYSIOLOGY

Recruitment of Eosinophils to the Lung

Blood and tissue eosinophilia have long been identified as major players in immunity against parasites and in the pathogenesis of allergic diseases.[6] Following differentiation of precursor cells in the bone marrow under the action of several cytokines, including interleukin (IL)-5, IL-3, and granulocyte macrophage colony-stimulating factor (GM-CSF),[7–9] eosinophils are recruited in the blood and tissue, including the lung in response to circulating IL-5, eotaxins, and the C-C chemokine receptor-3 (CCR3). Because recruitment of eosinophils to tissues is organ-specific, tissue and blood eosinophilia are not necessarily associated. The prominence of IL-5 in eosinophil differentiation and recruitment has led to the development of anti–IL-5 monoclonal antibodies to selectively target the eosinophil lineage in humans with asthma.[10–14]

Eosinophils and Immunity

Eosinophils are active participants in innate immunity. They interact with basophils, endothelial cells, macrophages, platelets, fibroblasts, and mast cells through cell membrane signaling molecules and receptors including Toll-like receptors and receptors for cytokines, immunoglobulins, and complement.[7–9,15] Activated eosinophils release proinflammatory cytokines, arachidonic acid–derived mediators, enzymes, reactive oxygen species, complement proteins, chemokines, chemoattractants, metalloproteases, and cationic proteins. The latter are released by degranulation of activated eosinophils and exert a variety of effects, including direct cytotoxicity, upregulation of chemoattraction, expression of adhesion molecules, regulation of vascular permeability, and contraction of smooth muscle cells.[7–9] Activated, degranulated ("hypodense") eosinophils can be found in the bronchoalveolar lavage (BAL)[16,17] and the lung tissue[18] of patients with eosinophilic pneumonias. Tissue damage mediated by eosinophil cationic proteins is exemplified by the cardiac lesions that occur in the hypereosinophilic syndrome or in tropical eosinophilia.[15]

Eosinophils are also involved in adaptive immunity against bacteria, viruses, and tumors through interaction with T-lymphocytes.[7–9] They present antigens to T-helper-2 cells in tissues and in the draining lymph nodes in the context of major histocompatibility complex class II, thereby inducing T cell development, activation, and migration to sites of inflammation. Eosinophils secrete IL-4 and IL-13, amplifying the T-helper-2 response in the lung, and in turn are recruited and activated by T-helper-2 cell-derived cytokines (IL-4, IL-5, and IL-13).

IDIOPATHIC CHRONIC EOSINOPHILIC PNEUMONIA

First characterized by Carrington and colleagues,[19] idiopathic chronic eosinophilic pneumonia (ICEP) is characterized by the onset over a few weeks of cough, dyspnea, malaise, and weight loss, with diffuse pulmonary infiltrates.

Epidemiology and Risk Factors

Although it is a rare disease, representing fewer than 3% of cases of various interstitial lung