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Eosinophils and Airway Inflammation

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Abstract

Respiratory diseases which are associated with the presence of eosinophilia include: asthma, rhinitis, chronic rhinosinusitis, nasal polyposis, ASA triad (Acetil Salicilic (aspirin) ASA triad: nasal polyposis, asthma, and non-steroid anti-inflammatory analgesic intolerance), fungal airway infections and systematic self-immune vasculitis (Churg-Strauss syndrome). The airway inflammation mediated by eosinophils appears in a metachronous form in the superior and inferior airways during the chronic phase of the disease. The association between asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) is more frequent in patients with higher tissue eosinophilia and the disease is more severe, both in the upper and lower airways. Moreover, a high degree of eosinophilia is associated with a favorable response to corticosteroid treatment. The purpose of this work is to review the relation between eosinophils and airway respiratory diseases, as well as their clinical consequences.

Keywords Asthma; Rhinosinusitis; Nasal polyps; Rhinitis; Systematic self-induced vasculitis; Churg Strauss syndrome; Fungal infections

Introduction

Eosinophils are polymorphonuclear leukocytes that, unlike other leucocytes, show a weak phagocytic activity, so they have been historically considered as cells with a homeostatic function responsible of moderating the damage provoked by mast cells. However, this concept changed as a result of the discovery regarding the capacity of their granule proteins to produce tissue damage. Recent molecular studies have emphasized again the importance of their homeostasic functions, since eosinophils have the ability to synthesize a variety of inflammatory mediators. In addition, they have also allowed insight into the mechanisms involved in eosinophil's maturation, migration, activation and elimination [1].

The determination and quantification of eosinophils soon became part of clinical medicine since, in 1889, Gollasch realized the association between eosinophilia and asthma [2]. Perhaps, the best studied features concerning eosinophils are their role in allergy and in defence against parasites. Nevertheless, many other diseases show eosinophilic infiltrates [3].

Respiratory diseases associated with the presence of eosinophilia include, asthma, rhinitis, chronic rhinosinusitis, nasal polyposis, ASA triad (Acetil Salicilic Acid (aspirin) triad: nasal polyposis, asthma, and non-steroid anti-inflammatory analgesic intolerance), fungal airway infections and systematic self-immune vasculitis (Churg-Strauss syndrome). The airway inflammation mediated by eosinophils appears in a metachronous form in the superior and inferior airways during the chronic phase of the disease [4].

Regarding the treatment of airway and other eosinophil mediated diseases, is of high interest to know that current data suggest that deficiency of eosinophils is not associated with any characteristic abnormality. So, the reduction of eosinophils appears to have no characteristic ill effects on normal health, and monoclonal antibodies that deplete eosinophils have the potential to be widely employed in the treatment of eosinophil-associated diseases [5].

The purpose of this work is to review the relation between eosinophils and airway respiratory diseases, as well as their clinical consequences.

Asthma

Asthma is a chronic inflammatory disease of the lower airways, characterized by hyper-reactivity that is translated into bronchial constriction episodes and increased secretions in response to one or more trigger factors. Classically, asthma can be classified into two groups: extrinsic or allergic asthma (Ig E mediated) and intrinsic asthma. Both types involve the predominance of the TH2 cytokines with increased levels of IL-4, IL5 and IL13 [6]. Eosinophilia is characteristic of the two types of asthma, both in tissue and in exudates, so it is thought that eosinophils play an important role in its pathogenesis. In eosinophilic asthma refractory to treatment with corticosteroids, treatment with anti-IL5 antibody reduces asthma exacerbations together with a corticosteroid-sparing effect [7]. In asthma and allergic inflammation, the role of interleukin (IL)-25, IL-33 and thymic stromal lymphoprotein (TSLP) have been evidenced, and activation states of eosinophil β1 and β2 integrins have been found to correlate with the measurement of eosinophil recruitment and pulmonary function in asthma [8]. In the majority of asthmatic patients there is an increasing amount of eosinophils, both in the tissue and in the secretions, and the degree of eosinophilia is related with the degree of the symptoms. These cells have also been implicated in the underlying mechanisms of tissue remodeling in asthma and in chronic rhinosinusitis [9]. The association between asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) is more frequent

in patients with higher tissue eosinophilia, and the disease is more severe, both in the upper and lower airways [10].

Corticosteroids are probably the most effective treatment for airway inflammation with eosinophilia. No wonder that several studies have shown that sputum eosinophilia is associated with a favorable response to treatment with corticosteroids in both asthma and chronic obstructive pulmonary disease (COPD), and tailored strategies aimed to normalize sputum eosinophils have resulted in a significant reduction of the exacerbation rates [11].

Rhinosinusitis

Eosinophils are possibly the most important inflammatory cells in the pathogenesis of CRSwNP [12] and eosinophil degranulation is the mechanism by which these cells exert their inflammatory action. Cytolysis and piecemeal degranulation are the principal degranulation modes of eosinophils in nasal polyposis, in contrast to apoptosis, which is very infrequent. Nasal polyposis shows a correlation between the eosinophil degranulation mode, the clinical and radiological stage and the degree of tissue eosinophilia of the case of origin [13]. In the case of CRSwNP, but also extrapolated to other eosinophilic inflammatory diseases, chronicity could result from the creation of a micro-ambient in the affected tissue as well as from the autocrine capacity of the cells involved [14]. Nasal polyposis could be an inflammatory reaction, self-perpetuated by growth factors and cytokines produced within the same polyps, which would create a micro-environment that would extend the life of the eosinophil and where it would be available to participate in immune reactions with structural cells, such as epithelial cells and fibroblasts. In normal conditions tissue eosinophils are programmed to die by apoptosis within a few days, but some cytokines can inhibit this process. For example GM-CSF is produced in significant amounts in nasal polyps [15], where it can prolong the survival, proliferation, differentiation and activation of granulocytes. A micro-ambient that is rich in GM-CSF would delay eosinophil's apoptosis and would also enhance antigen presentation, which increases the sensitivity to small amounts of allergens that in normal conditions would not elicit a response [16].

The rhinosinusal polyposis can be initiated by an immunologic recognition error [17]. Fungus or bacteria, which are not normally pathogenic, could generate an inflammatory process in which eosinophils predominate, that might result in the formation of a micro-environment, where autocrine cell effects can provoke the perpetuation of the inflammatory process. A key function of the eosinophil is related to its involvement in immunity to parasitic helminths. The nasal mucosa seems to react as it would do it if it was colonized by parasitic worms. The immunologic error provokes the release of cytokines and chemokines that recruit eosinophils, setting up a local eosinophilic inflammatory reaction. The eosinophils arrive from the vessels, travelling throughout the chorion, reaching the epithelium and finally arriving to the mucosal surface, without finding parasites. Although the majority of them are cleared with mucociliary clearance, some of them release their cytotoxic granule proteins generating more inflammation and leading to the chronicity of the symptoms.

Clinically, the eosinophilia in tissues and in polyp exudates correlates with the severity of the disease and to polyp resurgence following surgical excision [13,18]. In this disease, the colonization of the nasal mucosa by bio-films is also related with severity, although the precise pathogenic mechanism is not known with certainty.

Non-Allergic Eosinophilic Rhinitis

(NARES: non allergic rhinitis with eosinophilia syndrome), which was described in 1979 by Jacobs and Mullarkey [19], is characterized by permanent nasal congestion, rhinorrhea, sneezing, pruritus, and elevated nasal eosinophilia (higher to 20%). The possibility that the evolution of NARES could be driven by nasal polyposis-related genes was not confirmed by an epidemiologic study [20], although occassionally micropolyps are observed in NARES. The pathogenic mechanism could be initiated by an alteration in the regulation of the autonomous nerve system in the nasal mucosa, which would then introduce neurogenic inflammation that would facilitate eosinophil migration. Epithelial damage may stimulate the sensitive unmyelinated nerve fibers resulting in the release of P substance by an antidromic reflex. The newly recruited eosinophils in the epithelium would release further quantities of cytotoxins and pro-inflammatory substances, thereby maintaining and amplifying the inflammation [21].

Eosinophilic Fungal Sinusitis or Allergic Fungal Sinusitis

The eosinophilic fungal sinusitis or allergic fungal sinusitis shows histological resemblance with allergic bronchopulmonary aspergillosis. Sinusitis due to aspergillus infection of the sinus maxillary was described by Millar in 1981 [22] and Katzenstein in 1983, who observed the presence of groups of necrotic eosinophils, crystals of Charcot-Leyden and noninvasive fungal hyphae in the sinus mucosa of patients affected by chronic sinusitis [23], designating it as allergic sinusitis by aspergillus.

It was thought that it was a pathology mediated by IgE, in response to diverse fungi mainly aspergillus, that can proliferate in the eosinophilic sinus mucosa. The theory was supported by the observation of specific IgE in the crops. Today the most accepted hypothesis excludes an allergic factor and suggests the importance of eosinophilic fungal sinusitis [24,25]. This is based on the negative results of the skin-prick test observed in many of these patients. In fact, the quantification of the specific fungal serum IgE does not differ among patients with chronic rhinosinusitis compared with healthy individuals. This contradiction might be explained by the importance of local IgE in the absence of systemic IgE. Most of these patients are young and allergic. Half of them are asthmatic and frequently show a unilateral affectation. The TC shows opacification with heterogenic densities, with a more dense and wide mucosa. Polyp recurrence after surgery is frequent and some authors have reported improvement after immunotherapy [26].

Systematic Self-Immune Vasculitis such as the Churg-Strauss Syndrome

In some forms of systematic self-immune vasculitis such as the Churg-Strauss syndrome (CSS), there is a nasal and bronchial inflammation with abundant eosinophilia [27]. CSS is a multisystemic medium and small-vessel autoimmune vasculitis of unknown etiology. It can appear at any age, although it most frequently affects middle-aged patients of both sexes fairly equally .It is characterized by the onset of asthma in adulthood, hypereosinophilia, and extravascular eosinophilic granulomas [28]. The American College of Rheumatology [29] established six diagnostic criteria: a history of asthma, eosinophilia of >10%, mono- or polyneuropathy, migratory

pulmonary infiltrates, paranasal pathology, and extravascular eosinophils in biopsy samples. The presence of four of the six criteria is sufficient for the diagnosis of CSS. The most common manifestations of CSS are allergic rhinitis, recurrent rhinosinusitis, and sinonasal polyposis, thus affecting the ENT area. Some studies have observed the presence of sinonasal polyposis in up to 50% of cases [30]. The involvement of the paranasal sinuses and sinonasal polyposis is typically found in radiological studies. Fifty percent of patients with CSS have p-ANCA–MPO+ antibodies [31], although the presence of c-ANCAS–PR-3 also exists. When no positivity for this type of antibody is found, the diagnosis is not excluded if there is an elevated clinical suspicion. Histological study is not necessary, but nasal biopsy specimens are useful for diagnosis. Compatible findings are necrotizing vasculitis, extravascular granulomas, and tissue eosinophilia [30].

Eosinophils and Infection by a Respiratory Syncytial Virus

The syncytial virus is an RNA virus that belongs to the family of the paramyxovirus (paramyxoviridae, subfamily) and provokes bronchiolitis and pneumonias in neonates and young children. Accumulated and degranulated eosinophils are found within the pulmonary tissue with abundant eosinophils and their degranulation products in bronchial washes from infected individuals [32]. In vivo studies performed in rats have implicated several molecular mechanisms that lead to a pulmonary eosinophilia, and there is evidence pointing out to a potential role of eosinophils in clearing virally-infected cells [9].

Conclusion

The airway inflammation mediated by eosinophils, which appears in a metachronous form in the superior and inferior airways evolving to chronicity, shows a favorable response, although temporary and not curative, to corticosteroid treatment.

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