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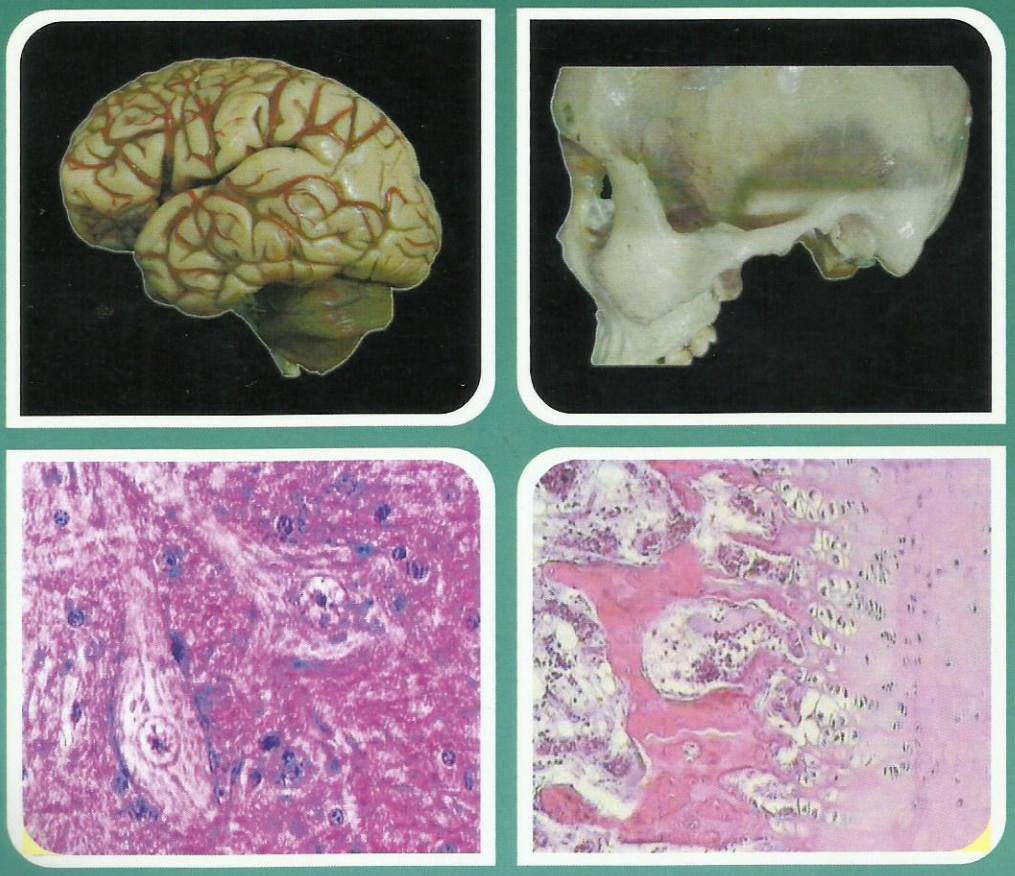

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# THE ROLE OF EOSINOPHILS IN ASTHMA BRONCHIAL ( A STUDY OF LITERATURE )

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## ABSTRACT

**Introduction:** Eosinophils are often found as the dominant inflammatory cells in the airways of asthma patients. but the importance of these white blood cells have been poorly understood. The eosinophil's functional activity, like immune response in general, may be beneficial or harmful for the organism. They could have an important role in the disordered repair. This leads to permanently impaired function of airways tissue in the asthmatic patients. **Objective:** This paper is a review which focused on the relationship of eosinophils and their products with asthma. **Conclusion:** Direct evidence of the role of eosinophils in the pathogenesis of asthma is on the toxic effects of eosinophil granule proteins on bronchial epithelial cells, remodeling and effects of leukotrienes generated bronkokonstriktor eosinophils. Regarding the purpose of eosinophils being actually there, it is not clearly understood.

**Keywords**: Eosinophil, bronchial, asthma, granular, cationic proteins, remodeling.

## INTRODUCTION

Eosinophils play an important role to repair disorders that lead to a permanent non-functioning tissue in asthmatic airways. This paper is a literature review that focused on the relationship eosinophils and their products with asthma.

Eosinophils have a cell nucleus consisting of two lobes. The cell was also called granulocyte eosinophlic because the granulas take dyes granulositic eosin. Eosinofil is a type of leukocyte, and under a light microscope with the outward appearance or MGG staining wright picture shows reddish-yellow granules. Eosinophils have a cell nucleus consisting of two lobes. In the body's defense system, a natural role of eosinophils is to provide a protection against infection-parasitic[1,4].

Terminal differentiation of eosinophils (end-stage) are many in the sub mucosal tissue. The number of eosinophils in tissue is much greater than the number of eosinophils in the blood circulation. In the normal adult circulation, eosinophils have about 1-3% of leucocytes. Blood eosinophils are usually elevated in allergic reactions. Increasing the number of eosinophils in the blood (eosinophilia) clarified as mild eosinophilia when the eosinophils ranged between 351-1500 cells/mm3. According to Rothenberg1, it is categorized as eosinophilia, if the amount > 1500-5000 cells / mm3 and it is categorized as severe eosinophilia when the number of eosinophils> 5000 / mm3[5,6].

The function of eosinophils in immunity is to provide a protection against parasitic infestation, and it also plays a role in allergic reactions and asthma. The involvement of eosinophils in the pathogenesis of asthma has been much discussed, for example, difficult to control asthma without reducing the number of eosinophils in airways tissue. Eosinophils are major cellular mediators in asthma and an integral part in the pathogenesis of asthma, but the function of eosinophils in asthmatic airways is not fully understood. Blood eosinophils are known to be an indirect marker of airway inflammation in asthma[7]. It is known since long that the total number of eosinophils reflects activity in asthma and it is useful to set the dose of steroids and for early detection of exacerbations. Eosinophils are currently considered as effector cells and responsible for the pathology of *asthma*. Eosinophils mediate a damage to the respiratory epithelium and is the main effector cells in the pathophysiology of asthma[8].

Eosinophils also play a major role in the onset and maintenance of bronchial inflammation and tissue injury in asthma. Complete definition of asthma that describes the concept of inflammation as the basic mechanisms of asthma issued by GINA. Asthma is defined as a chronic inflammatory disorder respiratory tract with many cells that play a role, particularly mast cells, eosinophils, macrophages and T lymphocytes in the mucosa and lumen of the respiratory tract. Appearances of these cells are widely associated with the degree of severity of clinical disease. In vulnerable individuals, this inflammation causes episodes, shortness of breath, feeling of chest pressure, and coughing, particularly at night or early morning. These symptoms usually associated with widespread narrowing of the respiratory tract, but which at least partly reversible either spontaneously or with treatment. Inflammation is also associated with hyperactivity of respiratory tract to various stimuli. In line with the process of chronic inflammation, bronchial epithelial injury stimulates the

respiratory tract repair processes that produce structural and functional changes that deviate in the respiratory tract, known as remodeling.

## OBJECTIVE

The objective of the current paper is to describe the role of eosinophils in bronchial asthma. In the circulatory system, eosinophils are recruited to sites of inflammation by specific immune reactions in the network, including allergic reactions. Eosinophils can be observed at the site where the hypersensitivity reaction occurs the airways in asthma. Infiltration of eosinophils is a typical picture of the respiratory tract in patients with asthma who distinguish asthma with airway inflammation due to other reasons.

In bronchial asthma, eosinophils are the major inflammatory cells infiltrate airway wall, in addition to neutrophils, mast cells, macrophages and lymphocytes. In asthma there is a direct correlation between the increased number of peripheral blood eosinophils, eosinophils in bronchial fluids and the excessive airway response to stimuli. Eosinophils are also commonly found in sputum of asthma patients with Charcot-Leyden crystals. Calculate the total number of eosinophils in sputum reflect the process of asthma, and used as a method for early detection for the possibility of exacerbation. Calculating the total eosinophils can also be used as a guide for dosing steroid.

In asthma, although very mild degree, has found that airway inflammation is a fundamental pathogenic factor. Biological markers (BP) in the form of immune system cells or inflammatory cell activation products that can be checked and the results are used as benchmarks to determine the status of allergy and treatment with appropriate doses, especially in the use of steroids. Levels are associated with the degree of inflammation and/ or activation of inflammatory cells. PB has important clinical applications such as in diagnosis, predicting exacerbation of disease, monitor disease and therapeutic intervention. This is possible because the classical criteria for accuracy and provide positive and negative predictive value of high false positives and false negatives that minimal.

### Morphology of Eosinophils

Eosinophils are round or ovoid with a diameter of 12-17 nm, with a core berlobus two. In the cytoplasmic granules, they are found in four populations, namely primary granule, secondary granule-specific or large granules, small granules and lipid bodies. With electron microscopy, large specific granules appear ellipsoidal shape, consisting of dense crystalloid core (electrondense), surrounded by a paler matrix (electrolucent). Small granules do not have a crystalloid core. Primary granules are round and look at the early phase of maturation of eosinophils[9].

### Eosinophil Granules

Large specific granules are used to identify eosinophils. Granules are specific for eosinophils, have a high affinity to eosin dye, and containing four kinds of cationic proteins, the different biological effects. Proteins are: major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil derived neurotoxin (EDN) and eosinophil peroxidase (EPO). MBP found in the core granules, whereas ECP, EDN and EPO contained in matriks.

Proteins are also found fewer of basophils, EDN and ECP are also found in neutrophils. In the large specific granules also contained histaminase and a variety of hydrolytic lysosomal enzymes. Small granules contain the enzyme aryl sulfatase and phosphatase. In addition there are gelatinase, a metalloproteinase which has a molecular weight of 92 kDa. Eosinophil primary granules contain other constituents, namely Charcot-Leyden crystal protein (CLC). Crystals are often found in sputum in asthma. CLC protein has lisofosfolipase activity[9,10].

### Eosinofilopoesis

Eosinophils are produced in bone marrow and progenitor cells derived from basophils. Proliferation and differentiation of progenitor cells in bone marrow is influenced by interleukin-3 (IL-3) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Eosinophils themselves have the ability to release several cytokines, including growth factor that acts in autocrine of eosinophils, including IL-3, GM-CSF and interleukin-5 (IL-5). Interleukin-3 and GM-CSF is active on progenitor cell proliferation in the early stages of eosinophils, whereas IL-5 works as a late differentiation factors and specific to eosinophils. Eosinophil proliferation and differentiation take place in the bone marrow for ± 2-6 days, continuously in a low level when no stimulation is immunologic.

### Activation of Eosinophils

The mechanisms that regulate the activation of eosinophils occurred in three phases. First phase is the regulation of proliferation and differentiation in bone marrow by GM-CSF and IL-3. Activation of Th2 lymphocytes causes the release of IL-5, which increases the proliferation of eosinophils in bone marrow and

promote the release of eosinophils from the bone marrow pool into circulation. Distribution of eosinophil tissues requires chemo attractant such as eotaksin. Eotaksin released by airway epithelium, smooth muscle and fibroblasts under the stimulation of IL-4, IL-13 and TNF-α derived from the Th2 and mast cells. Eotaksin a chemokine specific for eosinofil. The third phase is the degranulation and release of granule proteins. Eosinophil degranulation occurs when exposed to inflammatory mediators such as platelet activating factor (PAF) and the complex molecules of toxic granule proteins imun[10]. Chamber is released causing epithelial damage.

**Functional Activity of Eosinophils**

Eosinophils have the ability for phagocytosis, but weaker than the neutrophil ability, and primarily directed at the antigen-antibody complex precipitates, and not to the particle antigen[10,11]. The enzyme in granule lysosomes are contained in working within fagolisosom to destroy the antigen that has been difagositosis, the granules of eosinophils to work mainly against extracellular targets, such as parasites and inflammatory mediator molecules. The release of eosinophil granule occurs during phagocytosis or following stimuli triggered by PAF and immune complexes. Granule matrix and core points may be released simultaneously or separately. Eosinophil-specific granules wrapped by a membrane (membrane bound). Granule proteins are released out of cells by directed granule membrane fusion with the cell membrane or indirectly incurred by small vacuoles. With degranulation, Charcot-Leyden crystal protein diffuses within the cytoplasm and nucleus, but not released into the extracellular space. The proteins contained in specific granules of eosinophils (MBP, ECP and EPO) are cytotoxic to the epithelium. MBP does not have enzymatic activity, but its effects on epithelial cells occurs through interaction with the lipid membrane of cells that cause changes in the composition of cell membranes.MBP and EPO inhibits muscrinic M2 receptors, which cause neuronal dysfunction and can increase airway hyper-responsiveness through bronchoconstriction vaga[12]. EDN damages myelin coating of nerve fibers[12].

In addition, eosinophils also release various cytokines, including cytokines that have activity against eosinophil growth factors such as GM-CSF, IL-3 and IL-5, and several cytokines that play a role in acute and chronic inflammatory response, such as interleukin-1 alpha (IL- 1α), interleukin-6 (IL-6), interleukin-8 (IL-8), TNF-α, and transforming growth factor (TGF-α and TGF-β). Through stimulation of eosinophils can also be produced and released lipid mediators such as leukotriene C4 (LTC4) daneosinophil derived platelet activating factor (PAF). Both have the effect of causing the airway smooth muscle contraction, increased mucus secretion and cause vascular permeability and attract eosinophil and neutrophil infiltration. Through the mechanism of non-toxic, MBP and EPO stimulates the release of histamine from basophils and mast cells cells. Once stimulated, eosinophils can serve as a source of lipid inflammatory mediators and also induces the release of inflammatory mediators from mast cells and basophils cells, so that the inflammatory process may continue until long time[13-14].

Aryl sulfatase-B which comes from the small granules of eosinophils to work off of slow-reacting substance of anaphylaxis (SRS-A) which is a mixture of leukotrienes-leukotrienes LTC4, LTD4 and LTE4. While the phospholipase-D damage platelet lytic factor, degrade histamine and histaminase work. Lisofofolipase (phospholipase-B) is inactivating cell membrane[15]. Eosinophils participate in the process of fibrosis and is a major source of TGF-β which is a cytokine that stimulates fibrosis. Eosinophils also modulate extracellular matrix deposition and remodeling. In the process of wound healing, eosinophils infiltrate the wound area and in order to express TGF-α and then TGF-β[12].

**Bronchial Asthma**

Asthma is defined as, disorders of chronic airway inflammation with many cells that play a role, particularly mast cells, eosinophils, and lymphocytes T. In some susceptible people this inflammation causes recurrent episodes of wheezing, shortness of breath, feeling of chest pressure, and coughing, particularly at night and early morning. These symptoms usually associated with airway constriction is large but variable, which at least partly reversible either spontaneously or with treatment. Inflammation is also associated with the breath to various. Weighing blown attack varies from time to time within a certain time period, the stand out is the existence of a good response to drugs: beta-agonists and corticosteroids. Allergic reactions to inhaled antigens is a major cause attacks[12,13,16].

**Characteristics of Asthma**

Bronchial asthma is characterized by several characteristics such as the following: (a) The existence of episodes of breathing difficulty accompanied *mengik*, (b) There is narrowing airway lumen and increased resistance to airflow. Airway lumen narrowing occurs due to various combinations of the following factors namely, contraction of smooth muscle around the airway wall and airway wall swelling due to inflammation, (c) Excessive Mucous in the airway lumen, (d) Changes in the level of airway obstruction significant and rapid (peak flow difference varies> = 20%, (e), Episodes nighttime attacks that often and the value of peak flow (peak

flow) is low in the morning, (f) a real response to the administration of beta-2 agonists, (g) a real response to corticosteroids, (h) The existence of symptom-free period, (i) The frequent allergies occur, and lastly, (j) airway inflammation characterized by the presence of eosinophils in the airway wall of bronchi that hyper responsive against non-specific stimuli, such as cold air and histamine, as apparent in the bronchial provocation test[17,18,19,20].

## RESULT

Asthma is a disease primarily of the bronchus. Characterized by the presence of:

1. Mural inflammation with infiltration of eosinophils, mast cells and lymphocytes.
2. Bronchial wall thickening due to edema, and fibrosis
3. Bronchial wall thickening of smooth muscle
4. Blockage of mucus in the lumen
5. Release (shedding) of epithelial cells
6. Goblet cell hyperplasia, usually 20% of epithelial cells. After hyperplasia nearly all epithelial cells are replaced by goblet cells
7. Kolagenosis sub-epithelial, basement membrane thickening

In bronchial asthma, airway smooth muscle layer thickening due to hypertrophy and hyperplasia. Chronic inflammation can further reduce the airway lumen as: infiltration of inflammatory cells into the lumen, especially eosinophils, neutrophil, lymphocytes and mast cells, edema occurs because of vasodilatation and increased capillary permeability, thickened reticular layer and basement membrane under the epithelium, hypertrophy and hyperplasia of glandular structure in the mucosa, often accompanied by increased sputum production, sticky and not easily removed. This is often accompanied by intra-luminal exudate, and thickening of the lining of the airway adventitia, the outer muscular layer.

Asthma is also characterized by spastic contraction of bronchial smooth muscle that causes the patient's breathing hard. A common cause is hypersensitivity bronkhioulus against foreign objects in the air. Reactions that occur in the type of allergic asthma is thought to occur in the following manner: an allergy have a tendency to form abnormal number of IgE antibody in large quantities and these antibodies cause allergic reactions in case of reaction with antigen specifications. In asthma, these antibodies attached to mast cells mainly located in interstitial lung is closely related to brokhiolus and bronkhiolus terminalis. If someone inhaled allergens, the IgE antibody that person will increase, the allergen reacts with antibodies that have been attached to the mast cells and causes these cells to release various substances, including histamine, slow reacting substance of anaphylaxis (which is leukotrient), and eosinophilic kemotaktik factor bradykinin[20].

### Airway Inflammation

In people who presentation of allergens on the surface of the respiratory tract by a cell renderer antigens on the surface of the respiratory tract by a cell renderer antigen (APC) to T cells of CD4 + helper resulted in differentiation phenotype of the cell Th2 which then release cytokines, IL-4, IL-5 and IL-4.13 Interleukin-4 and IL-13 regulate the synthesis of immunoglobulin E IgE), by affecting B cells to perform a "class-switch" from the synthesis of immunoglobulin G (IgG) to IgE. Association of IgE with antigen can cause CrossLink IgE molecules bound to the IgE receptor from cell mast [4-6,13.14]. This sparked the occurrence of mast cell degranulation and release of inflammatory mediators including histamine, prostaglandins, leukotrienes, and several proinflammatory cytokines. T helper cells then organize the inflammatory response. This can be seen with the influx of eosinophils into the airway lumen in response to cytokines/ chemokines.

Eosinophils are recruited into the airway lumen from the bone marrow through several steps that are coordinated by cytokines from Th2. At first the proliferation and differentiation of eosinophils in the bone marrow of progenitor cells occurs under the influence of IL-3, GM-CSF and IL-5 produced by T helper cells. After differentiation, cells that have been involved eosinophils migrate from the bone marrow into the bloodstream through the influence of IL-5. Movement out through the walls of blood vessels to the site of inflammation mediated by Th2 cells and controlled by IL-4 and IL-13. Both these cytokines induce expression of vascular adhesion molecule Cell adhesion molecule-1 (VCAM-1) on endothelial cells that will bind to their partner, i.e. receptor Very Late Activation Antigen-4 ((VLA-4) on the surface of eosinophils. Institute is starting a process of extra-vasasi eosinophils to the site of inflammation. Interleukin-4, IL-13 and TNF-a is released from Th2 cells and mast cells, stimulates the formation of eotaksin by lung epithelial cells, airway smooth muscle cells and fibroblasts. Eotaksin tends to be for eosinophils that cause selective mobilization of these cells from the airway walls of blood vessels into lung tissue and lumen bronkiolus[1,8,15].

Once activated by IL-5 and chemokines such as eotaksin, eosinophils may contribute to the pathogenesis of asthma by releasing proteins toxic to various cells found in the airway wall (epithelial cells, fibroblasts and smooth muscle cells) or cytokine release by Th2 cells. In certain conditions this effect will culminate with the increased sensitivity of airways to various stimuli that produce a hiperesponsif occurrence of respiratory tract, excessive mucus production, increased secretion of excessive mucus, increased mucus secretion and deposition of collagen around the membrane basalis[12].

**Airway Wall Remodeling**

Remodeling is the response of the body to repair tissue damaged by inflammation which then causes changes in tissue that is not terbalikkan in patients with asthma. Remodeling is characterized by the release of epithelial cells in several places leaving only the basal membrane with the basal cell layer. Then came the deposition of matrix proteins such as laminin, tenassin, fibrin, fibronektin and collagen type III and V which cause fibrosis sub epitalial. Also, there is hyperplasia of smooth muscle cells and goblet cells. Vascular changes may occur in angiogenesis.

Many cytokines and growth factors participate in this remodeling process. Among other TG-b-1, GM-CSF, Epidermal Growth Factor (EGF), Platelet-Derived Growth factor (PDGF), endothelin (ET), and insulin-like growth factor 1 (IGF-1). Many of them are products of eosinophils and airway cell constituents. Metalloproteinases such as MMP-2 and MMP-9 produced by both eosinophils and epithelial cells also participated. Mast cells contribute to the release serine proteases and kimase triptase[15-19].

**Eosinophils in Asthma Pathophysiology**

Interleukin-5 eosinofi facilitate infiltration and deployment, along with groups of beta-chemokines, particularly eotaksin, macrophage inflammatory protein-1-alpha (MIP-alpha) and monocyte Chemo attractant Protein-1 (MCP-1).Mobilization of eosinophils requires the bond between molecular adhesion of these cells with their partner (counterreceptor) on endothelial cells of blood vessels. Expression of Adhesion Molecules intracellular (ICAMs) 1 and 2 in endothelial cells regulated by TNF-alpha from mast cells and macrophages, whereas IL-4 and IL-13 regulate expression of VCAM-1 on endothelial cells. This adhesion molecule binds to the ligandnya on eosinophils and T cells are lymphocyte function associatted Antigen-1 (LFA-1) and Very Late activating antigen-1 (VLA-4) which allows the migration of these cells from blood vessels into the tissue. Expression of adhesion molecules and cytokines requires NF-kappa intracellular molecule-B, a protein bound to DNA which is a transcription factor and control reading the genetic code. The genes activated by NF-kappa-B include genes for the cytokines GM-CSF, IL-1-beta and TNF-alpha, the chemokine IL-8 and eotaksin, adhesion molecules VCAM-1 and ICAM-1, and the enzyme NO synthase. Transendotelial eosinophil migration requires the function metaloprotease-9 (MMP-9) which will degrade collagen type IV, entaktin, proteoglycans and elastin to facilitate penetration of eosinophils through basement membrane. Eosinophils have a precursor MMP-9 which will be activated at the time of eosinophils attached to the endothelial cells or epithelial cells.

Eosinophils infiltrate the network in response to inhaled allergens. Activated eosinophils are triggered to release granule proteins and release of cytokines that result in damage to the respiratory tract wall. The presence of eosinophils in the lung tissue causing excessive mucus production, pulmonary edema and bronkospasme[12].

## CONCLUSION

T helper lymphocytes (TH) clearly has a central function in the inflammatory process and the pathophysiology of asthma. The presence of eosinophils in asthmatic airway occurred because of the attraction by the chemokines released during inflammation. Eosinophils may contribute to the pathogenesis of asthma. Direct evidence of the role of eosinophils in the pathogenesis of asthma is on the toxic effects of eosinophil granule proteins on bronchial epithelial cells, remodeling and effects of leukotrienes generated bronkokonstriktor eosinophils. Interestingly, it is not well understood for what purpose eosinophils are actually there. Nevertheless eosinophil cells has remained an important clinical significance as a diagnostic marker and guidelines in the management of asthma or other allergic diseases.

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