

Eosinophilia: An Ode to Lesser Known Facts

Santosh Kondekar* and Pravin Pillai

Associate Professor, Department of Pediatrics, TN Medical College, Mumbai, India

*Corresponding Author: Santosh Kondekar, Associate Professor, Department of Pediatrics, TN Medical College, Mumbai, India.

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Abstract

Eosinophils are deeply pink staining granulocytes with bilobed nuclei. Unlike neutrophils, eosinophils have a longer life span and can also recirculate from tissues. These cells have a crystalline core composed of an arginine-rich protein called Major Basic Protein with histaminase activity, which plays an important role in host defense against parasites. It also contains cationic proteins, some of which bind to heparin to negate its anticoagulant effects. Did you observe that? Eosinophils are like arch rivals to mast cells and basophils, because of its histaminase and heparinase effects that nullify the histamine and heparin released by the latter. Mast cells also facilitate this balance by releasing eosinophil chemotactic factors.

Keywords: Eosinophilia; Asthma; Peripheral Blood

Eosinophilia is defined as an absolute count of ≥ 500 eosinophils/ μL of blood. In no case should a finding of eosinophilia be ignored. Even if it is an incidental finding in a healthy individual seen in an outpatient setting, a clinician should elicit a complete history, perform a physical examination to rule out signs of organ dysfunction and get baseline lab test results.

There are innumerable diseases, which can be broadly grouped into helminthic infections, allergies (most commonly associated with asthma), malignancies, collagen vascular diseases, skin manifestations, microbial infections and genetic... The list is endless. This further emphasizes how important is eosinophilia as a clinical finding.

Local deposition of eosinophils in a particular tissue results in the release of toxic proteins like eosinophilic cationic protein, major basic protein and eosinophil-derived neurotoxin. Such tissue damage in the heart can be in the form of thrombosis, endocardial fibrosis or restrictive endomyocardialopathy.

Significant tissue eosinophilia is possible without an elevated blood count.

The eosinophil-derived neurotoxin is responsible for a syndrome of muscular rigidity and ataxia, progressing to severe paralysis, in laboratory animals when it was injected intracerebrally or intrathecally- an effect known as the "Gordon phenomenon" [1].

Terminology

Absolute eosinophil count	No. of circulating eosinophils in the peripheral blood (in cells/ μL)
Mild eosinophilia	500 - 1500 eos/ μL
Moderate eosinophilia	1500 - 5000 eos/ μL
Severe eosinophilia	> 5000 eos/ μL

Methods of detection of eosinophilia

Direct methods

- **Absolute eosinophil count in peripheral blood:** This is probably the most accurate method theoretically to measure eosinophils and detect eosinophilia. However, it has a disadvantage: diurnal variation in blood eosinophil counts [2]. It is inversely related to blood glucocorticoid levels, which explains why such a variation would be observed in any individual. To avoid this and standardize these counts, a clinician should order blood draws at, for instance, 8 am.
- **Relative eosinophil percentage:** It is difficult to define a normal range of relative eosinophil percentage because of a wide variation in absolute neutrophil counts between ethnic groups [3] and also because of variations in absolute eosinophil counts in an individual at different times of the day and on different days [4-6]. In addition, one cannot determine eosinophilia based on this alone, as it is a relative number that depends on the total WBC count and the relative percentages of other WBCs.

Indirect methods

- Eosinophiluria: Eosinophiluria is considered a useful marker of drug-induced acute interstitial nephritis, and is also seen in a variety of acute disorders of the genitourinary tract.
- Eosinophil peroxidase assay.
- Immunofluorescence of eosinophil granule major basic protein in tissue specimens.
- Eosinophil detection in hypertonic saline-induced sputum.
- Measurement of exhaled nitric oxide: The level of exhaled nitric oxide might be a useful tool for the clinician in understanding the nature of underlying airway inflammation, whether it is eosinophilic or not, and also help decide whether inhaled corticosteroids dose needs to be adjusted or not [7].

Molecular markers (Indirect)

- CD44 expression on blood eosinophils: The level of CD44 expressed on blood eosinophils is a novel marker indicative of whether the treatment for bronchial asthma is effective. The density of CD44 markers on blood eosinophils is higher in a well-controlled asthma patient, as compared to a poorly controlled one.
- ICAM-1 and HLA-DR on sputum eosinophils.
- An improved immunomagnetic procedure to isolate highly purified human blood eosinophils. CD16 is a molecule found on neutrophils but not on eosinophils. By negative selection involving superparamagnetic particles coupled to monoclonal anti-CD16 antibodies, an isolate consisting of highly purified eosinophils can be obtained.
- CD52 expression on eosinophils using anti-CD52 monoclonal antibodies. This study [8] also points out the clinical relevance of this interaction in inhibiting the production of reactive oxygen species by eosinophils in a dose-dependent manner.
- CD69, CD81 and CD23 expression on eosinophils using whole-blood immunostaining and flow cytometry [9].

Common diseases presenting with eosinophilia that can be easily missed

There are a number of diseases presenting with eosinophilia, and yet, what is fascinating is the fact that depending on the specialty the clinician belongs to, the clinical finding of eosinophilia attracts their attention only to a few of the most notable diseases within that specialty.

Eosinophilic infestations

Some of the helminth worms are endemic all over the world, e.g. *Strongyloides stercoralis*, *Toxocara canis* and *cati*, *Trichinella* species and *Ancylostom aduodenale*, and should be considered in every clinician's differential diagnoses, irrespective of whether the individual has a recent travel history or not.

The other helminth infestations presenting with eosinophilia that are more geographically restricted (more probable in India and other tropical countries) are filariasis, schistosomiasis and ascariasis. *Strongyloides* and filarial worms can cause eosinophilia for years, but *Ascaris* worms causes marked eosinophilia only when the larva migrate transpulmonary into the bloodstream. Eosinophilia is often absent in ascariasis when the worms are mature [10].

Hyper-IgE Recurrent Infection Syndrome (Job Syndrome)

If a child comes to a pediatrician with recurrent bouts of infections, and on lab testing, shows a high count of eosinophils, then Job syndrome should be the first to cross his/ her mind (after obviously ruling out major parasitic infestations).

Some of the common clinical manifestations are coarse facies, cold abscesses due to staphylococcal infection, retained primary teeth, high levels of IgE antibodies, dermatological complaints like eczema and brittle bones. Lab results also show a low IFN- γ level.

It can occur due to numerous mutations, one of which is STAT3 mutation that leads to a deficiency of T_h17 cells.

Eosinophilic Leukemias

It is a rare form of acute myeloid leukemia caused by chromosome 16 aberrations (pericentric inversion or a reciprocal translocation that involves both chromosome 16 homologs), with immature eosinophils on peripheral blood smears [11-13]. It is clinically relevant because patients with inv (16) or t (16, 16) abnormalities and abnormal marrow eosinophils have a better prognosis with the standard treatment protocol [14].

Chronic eosinophilic leukemia is another type of rare myeloid neoplasm showing clonal multiplication of dysplastic eosinophils [15].

Patients may present with symptoms like severe fatigue, bleeding and infections in case of acute eosinophilic leukemia, or may be asymptomatic or have constitutional symptoms if they have the chronic variant.

Neoplasia

Such a small space will not do justice to the vast number of neoplasia's that can cause eosinophilia.

A few examples of hematological cancers are:

- Primary hypereosinophilic syndrome.
- Chronic myeloid leukemia: High neutrophil counts is the predominant finding, but eosinophilia is also commonly seen [16].
- Systemic mastocytosis: Signs and symptoms are manifested because of multi-organ infiltration by clonally proliferating mast cells. Peripheral blood can show eosinophilia in less than a quarter of these cases [17].
- Lymphoid neoplasms like B cell lymphoma, T cell lymphoblastic leukemia, adult T cell leukemia/lymphoma and Sézary syndrome.

Examples of solid tumors that can cause eosinophilia are adenocarcinomas of the gastrointestinal tract (e.g. stomach, large intestine), lung, and squamous epithelium (e.g. cervix, vagina, penis, skin, nasopharynx and bladder).

Eosinophilic cellulitis

Also known as Wells syndrome, patients show recurrent lesions on their extremities, with around 50% of cases having high eosinophil counts [18]. There are several clinical subtypes. This diagnosis should be suspected when patients do not respond to antibiotics for bacterial cellulitis.

Eosinophilic cystitis

Of unknown etiology, eosinophilic cystitis presents with hematuria, dysuria, increased urinary frequency and suprapubic pain [19]. It is more commonly seen in children than adults. It can be confused with hemorrhagic cystitis due to chemotherapeutic agents like cyclophosphamide, and transitional urothelial carcinoma.

Pulmonary eosinophilia

It is a heterogeneous group of disorders that commonly have an abnormally high eosinophil count in the pulmonary airways and parenchyma. Peripheral blood eosinophilia is not seen in all of them, and standard chest radiographs may fail to detect disease in lung parenchyma.

A few of these will be listed below:

- **Idiopathic Acute Eosinophilic Pneumonia:** It usually involves sudden development of acute respiratory failure in a previously healthy adult. Recently starting or resuming cigarette smoking, and heavy inhalation of smoke, dust or sand seems to play a role in its initiation [20-25].
- **Chronic Eosinophilic Pneumonia:** CEP occurs more commonly in women and nonsmokers, and a few cases reported after radiation therapy for breast cancer [26-28]. It is a subacute disease with symptoms like cough, fever, progressive dyspnea, weight loss, wheezing and night sweats.
- **Eosinophilic Granulomatosis with Polyangiitis:** It is the only type of vasculitis that is associated with both eosinophilia and frequent lung involvement. Patients present with sinusitis, asthma and hypereosinophilia in peripheral blood. The skin and cardiovascular, gastrointestinal, renal and neurologic systems can also be affected [29].

Significant eosinophilia in unusual diseases

It is known to us in which diseases is eosinophilia commonly seen. Helminthic infections are the most common cause of eosinophilia in developing countries, whereas allergies e.g. hay fever, allergic rhinitis and asthma are the commonly seen causes of eosinophilia in developed nations. But there are innumerable more diseases contributing to eosinophilia, some of them being very unusual as well. Let us have a look at a few of them.

Infections

1. **Retroviral infections:** Human T-lymphotropic virus HTLV-II infection is commonly associated with eosinophilia [30]. Eosinophilia is also seen in late-stage HIV disease associated with cutaneous disease [31].
2. **Fungal infections:** Eosinophilia in peripheral blood is often seen in allergic bronchopulmonary aspergillosis (ABPA) caused by *Aspergillus fumigatus* [32]. Primary coccidiomycosis is frequently accompanied by eosinophilia in the range of 5% - 10% of the peripheral WBC count. However, disseminated coccidiomycosis is associated with severe eosinophilia [33].
3. **Scabies mites:** Eosinophilia can be seen in severe cases of scabies with inherited disorders of keratinization, or with underlying immunodeficiency [34,35].
4. **Post-infectious 'rebound' eosinophilia:** Neutrophil leukocytosis accompanying acute infections is frequently followed by a drop in eosinophil counts. But during convalescence, when leukocytosis subsides, eosinophil count returns to normal or temporarily slightly raised above normal.

Idiosyncratic

1. **Cholesterol embolization:** Isolated blood eosinophilia may occasionally be seen [36]. However, there are other more definitive and specific clinical findings that help in diagnosing cholesterol embolism, e.g. livedo reticularis, blue-toe syndrome, acute renal failure, acute onset of diffuse neurological deficit, amaurosis fugax, high ESR or CRP levels, hypocomplementemia etc.
2. **Gold therapy:** Data from this study suggests that eosinophilia may be the most common side effect of gold therapy (used for managing rheumatoid arthritis) [37].

Neurological manifestations

Hypereosinophilic syndromes, eosinophilic granulomatosis with polyangiitis (EGPA) and eosinophilic meningitis (etiologies include parasitic, e.g. *Angiostrongylus cantonensis*, or Coccidioidomycosis) [38, 39] are some of the diseases of nervous system due to neurotoxicity of eosinophils.

High risk for spontaneous preterm delivery

Women in preterm labor with a high ratio of eosinophils in the amniotic fluid are found to be at a greater risk for spontaneous preterm delivery [40].

Diffuse fasciitis with eosinophilia

This is a separate clinical entity that is sometimes confused with scleroderma. In contrast to scleroderma, proximal parts of extremities are more often affected than are the hands and feet. Indurated skin appears woody and dimpled, instead of being bound down as in scleroderma. Peripheral blood eosinophilia, elevated ESR levels and sometimes hypergammaglobulinemia are other findings. It can be diagnosed by doing a deep biopsy of affected regions of the skin, which would show an inflammatory infiltrate consisting of eosinophils and mononuclear cells, and thickening of deep fascia overlying muscle [41].

Is asthma always associated with eosinophilia?

Asthma is commonly associated with an eosinophilic pattern of airway inflammation, and hence induced sputum is frequently assessed to look for eosinophils or markers suggesting its presence. However, sputum eosinophilia has been found to be absent in a certain set of patients across the range of asthma severity. The authors found sputum neutrophilia and high sputum supernatant IL-8 concentration in this phenotype, but this finding was inconsistent and hence cannot be generalized for non-eosinophilic variant as a whole. However, they did find evidence that short- and long-term response to inhaled corticosteroids was significantly reduced in non-eosinophilic asthma [42].

Genetics and eosinophilia

Genetic control of eosinophilia

Inbred NIH and B10 genetic variants of mice were observed to have varying capacity to develop peripheral blood eosinophilia on exposure to parasitic antigens either by infection or parenteral injection in Freund's complete adjuvant. NIH mice showed a good eosinophilic response, whereas the B10 strain showed a poor response [43-57].

Conclusion

Eosinophil count is one of the neglected blood cells while interpreting complete blood count. A recheck of eosinophilia by a hematologist is essential as machines cannot give correct eosinophil count. Often there is marginally increased eosinophil count in children or those who are on medications. In developing countries, parasite infections is a common cause. Though eosinophilia is known manifestation in allergic diseases in asthma; only a count substantially high warrants a detailed investigations. At times it can be the only early marker of some serious diseases like Job syndrome or eosinophilic leukemia.

This article summarizes vast possibilities that may get overlooked in a case of persistent eosinophilia in children.

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