

CLINICAL APPROACH TO THE PATIENT WITH BLOOD EOSINOPHILIA

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SUMMARY: Increased blood eosinophil count may be caused by a range of diseases, from allergic disorders to malignant tumors. The allergist is often consulted to evaluate patients with this finding and he should not only rule out the presence of allergy, but through a detailed history taking and physical examination, he should provide a list of likely causes of the patient blood eosinophilia. Importantly used drugs capable of inducing blood eosinophilia and common parasitic infections that might be the culprit.

Key-words: Blood eosinophilia - Differential diagnosis.

The allergist is often consulted by other specialists for patients with blood eosinophilia. In western countries allergic diseases are the most common causes of blood eosinophilia. Parasitic infections are the principal sources in developing countries. Additional causes are certain pulmonary conditions, non parasitic infections, skin diseases, inflammatory and autoimmune diseases, and malignancies. Patients who continue to have an elevated eosinophil count after these conditions have been ruled out, may have hypereosinophilic syndrome. Considering the range of underlying disorders that can cause increased blood eosinophil count, the allergist should not only evaluate the presence of allergy, but provide a list of likely causes based on a detailed history taking (eg, travel, environmental and occupational exposure to allergens, used drugs, concomitant symptoms) and physical examination to suggest a practical and cost effective approach.

EOSINOPHIL STRUCTURE AND FUNCTION

The human eosinophil is a polymorphous bilobe granulocyte that has a circulatory life span of 6 to 12 hours before it migrates into tissues. The eosinophil count varies with patient age, time of day, exercise, and environmental stimuli, particularly seasonal allergen exposure. Diurnal variation of blood eosinophil counts (lowest in the morning, highest at night) may be as wide as 40% and is thought to be related to reci-

procal diurnal variation in cortisol levels (highest in the morning) (1). Eosinophils are moderately effective as a phagocyte for bacteria, yeasts, and protozoa but less effective than neutrophils. They are predominantly tissue-dwelling cells; several hundred times more eosinophils are found in tissue than in blood. They are most abundant in tissues that have an epithelial interface with the environment, such as in the respiratory, gastrointestinal, and lower genitourinary tracts. In these tissues, eosinophils may survive for weeks. Production of eosinophils is promoted by a variety of cytokines, especially interleukin-5 (a product of T-lymphocytes), which also acts as a chemotactic factor for eosinophils in tissues (2). In many diseases, eosinophilia appears to be related to a specific type of T-cell response to certain types of antigen, such as external allergens in allergic disease or parasitic allergens in helminthic infection. Eosinophilic anti-inflammatory enzymes help regulate and moderate mast-cell-dependent immediate hypersensitivity reactions. However, eosinophils' major function is as a cytotoxic cell, especially against helminthic infection. Eosinophils can kill a wide variety of helminthic worms, especially in their larval stages, by depositing cationic proteins on the surface of the parasite. Unfortunately, these same cationic proteins may damage host cells. For instance, in idiopathic hypereosinophilic syndrome, eosinophilic granule products are deposited adjacent to cardiac myocytes, producing inflammation and thrombosis, which ultimately results in endomyocardial fibrosis with restrictive cardiomyopathy (3). It is preferable to record the eosinophil count as an absolute count rather than a percentage, because the numbers depend on the total cell

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count. The upper range of the absolute eosinophil count probably extends to $0.5 \times 10^9/L$, so an abnormal count is often considered to be $0.6 \times 10^9/L$ or more. Classification of eosinophilia by degree is helpful when considering a likely cause. Mild eosinophilia has been defined as 0.6 to $1.5 \times 10^9/L$, moderate eosinophilia as 1.5 to $5 \times 10^9/L$, and severe eosinophilia as more than $5 \times 10^9/L$ (3). Table 1 summarizes likely and less likely causes of the three degrees of eosinophilia. The extent of investigation required in patients with mild to moderate eosinophilia remains controversial. Some authorities recommend taking an aggressive approach, possibly including such invasive tests as bone marrow aspiration and skin and muscle biopsies. However, a more practical approach is to consider the degree of eosinophilia along with the clinical setting in which it was discovered (4).

CAUSATIVE CONDITIONS

■ **Allergic rhinitis:** In Western countries allergic rhinitis is probably the most common cause of mild to moderate blood eosinophilia and eosinophil counts often fluctuate with severity of symptoms (5). During the active phase, testing of nasal secretions and biopsy of nasal tissues, including polyps, often reveal large numbers of eosinophils.

■ **Asthma:** Eosinophils predominate among the inflammatory cells in the bronchial mucosa of asthmatic patients. They are present both in extravascular

and intravascular spaces, being in close association with post capillary venules endothelial cells, with which they interact through the mutual expression of specific adhesion proteins. Most patients with asthma have blood eosinophilia which does not reflect the severity of disease (6).

■ **Drugs:** The overall incidence of eosinophilia in patients taking drug therapy is probably less than 0.1%, although a few agents, such as gold compounds, may cause eosinophilia in half of patients receiving them (7). Examples of drug adverse reactions accompanied by eosinophilia are given in table 2. The incidence of drug-induced eosinophilia does not appear to be greatly increased among patients with atopic disease or those with a family history of allergic disease. However, patients with renal or liver failure have a particularly high incidence of drug reactions. Slow-acetylators status appears to be a risk factor and may also account for the relatively frequent eosinophilia and hypersensitivity reactions noted in patients who have underlying liver or renal disease (8). Most adverse drug reactions associated with eosinophilia are accompanied by systemic manifestations (eg, fever, skin rash, adenopathy, signs of hepatic, renal, or cardiac toxicity) that should prompt further investigation (9). When drug-induced eosinophilia is suspected on clinical grounds, cessation of the offending agent usually terminates the problem, often precluding further investigation. Although the approach is not advised, a therapeutic challenge may be necessary when an essential drug is suspected to be the cause of the

Likely causes	Less likely causes
Mild ($0.6-1.5 \times 10^9/L$)	
Atopy Allergic rhinitis Asthma Drug reaction Parasitic disease Occupational lung disease	Neoplasm Gastrointestinal disease Skin disease Certain infectious diseases Long-term dialysis Radiation therapy Immunodeficiency state
Moderate ($1.5-5 \times 10^9/L$)	
Parasitic disease Asthma Drug reaction Pulmonary eosinophilia syndrome	Polyarteritis nodosa Other connective tissue disorders Neoplasm Hypereosinophilic syndrome
Marked ($>5 \times 10^9/L$)	
Parasitic diseases (Visceral larva migrans associated with <i>Toxocara canis</i> or <i>Toxocara cati</i> infestation; tissue migration during larval stage of trichinosis, hookworm infection, ascariasis, strongyloidiasis Hypereosinophilic syndrome	Eosinophilic leukemia Disorder usually associated with moderate eosinophilia Neoplasm Polyarteritis nodosa Drug reaction

Table 1: Likely and less likely causes of blood eosinophilia on the basis of severity (absolute eosinophil count).

hypersensitivity reaction. In this situation, the eosinophilic reaction should recur within 10 days (9).

PULMONARY EOSINOPHILIC SYNDROMES

These syndromes represent a catchall of poorly understood conditions where blood eosinophilia may be associated with respiratory symptoms, together with pulmonary infiltrates that are detectable on chest films (table 3) (10). Allergic bronchopulmonary aspergillosis must be differentiated from asthma and is characterized by a history of infiltrates on chest films, immediate cutaneous hypersensitivity to *Aspergillus fumigatus*, elevation of serum IgE concentration and precipitating antibodies, and possible proximal bronchiectasis (11). In uncomplicated asthma, the eosinophil count is rarely more than $2 \times 10^9/L$. Higher levels, often associated with deteriorating pulmonary function, may indicate allergic bronchopulmonary aspergillosis or the Churg-Strauss syndrome (also called allergic granulomatous angiitis) (12). The Churg-Strauss syndrome is regarded as a variant of polyarteritis nodosa and is characterized by pulmonary infiltrates and eosinophilia along with systemic vasculitis. This entity is relatively rare but can be fatal; however, it may respond well to high-dose corticosteroid therapy (12). Löffler syndrome (also called acute or simple eosinophilic pneumonia) very often is secondary (lung reaction) to other sites parasite infections or drug assumption, exposure to known inhalant aller-

gens or organic compounds and only in a minority of cases the origin is unknown (13). Once the inducing agents (parasites, drugs) have been removed, the pulmonary manifestations resolve spontaneously (usually within a month) or require a short course of oral steroids. The idiopathic form requires always a short course of oral steroids (13). In some patients with eosinophilia and pulmonary infiltration, no underlying disease can be found and the pulmonary infiltrates are long standing. Such patients have a condition called chronic eosinophilic pneumonia. Its cause is unknown. Chest films typically show distinctive peripheral infiltration, which has been described as the "photographic negative" of pulmonary edema. The combination of this characteristic chest-film appearance, eosinophilia, and a predictable response to corticosteroid therapy is considered sufficient to make the diagnosis (14).

PARASITIC DISEASES

Parasitic diseases are the principal causes of eosinophilia in developing world. In established parasitic infections, only moderately high blood eosinophil counts are found, but in the early stages of infection, when parasites are migrating through tissues, very high counts may be noted (15). Stool examination can lead to the correct diagnosis in most cases of intestinal helminthiasis, such as ascarid and hookworm infection. However, some eosinophilia-associated helminthic infections are

Drug reactions	Common agents
Dermatologic manifestations	Any agent, but especially antibiotics (eg, semisynthetic penicillins, cephalosporins), antifungals drugs, allopurinol, anticoagulants
Interstitial nephritis	antibiotics (eg, semisynthetic penicillins, cephalosporins), amphotericin B, phenytoin nonsteroidal anti-inflammatory agents, allopurinol
Pulmonary infiltrates and pleuropulmonary manifestations	Nitrofurantoin, sulfa agents, nonsteroidal anti-inflammatory agents, anticancer drugs, bleomycin sulfate, azathioprine, methotrexate, amiodarone, phenytoin, carbamazepine, antibiotics (cephalosporins, minocycline)
Hepatitis	Phenothiazines, semisynthetic penicillins, methotrexate, allopurinol, carbamazepine, paracetamol, clorpropamide
Hypersensitivity vasculitis	Allopurinol, phenytoin, antibiotics (eg, semisynthetic penicillins, cephalosporins), anticancer drugs, antifungals drugs, ACE inhibitors
Asthma, nasal polyps	Aspirin
Eosinophilia myalgia syndrome	L-tryptophan contaminant
No symptoms (except for eosinophilia)	Gold compounds, any agent (but an uncommon finding)

Table 2: Adverse drug reactions accompanied by blood eosinophilia, with common causative agents.

not diagnosable on the basis of stool examination results and may require blood, urine, and serologic testing; among such infections are trichinosis, several forms of filariasis, anisakiasis, visceral larva migrans, and echinococcosis. Strongyloides infestation may be particularly difficult to diagnose. The parasite may not be readily detectable on the usual serial stool examinations and may persist for decades (16). Duodenal aspiration may be required for diagnosis of strongyloidiasis, and sometimes a trial of antihelminthic therapy may be necessary. In many tropical countries, filariasis is an important cause of persistent eosinophilia and results in lymphangitis and recurrent disability. Visitors to endemic areas are not usually infected unless they

remain for several months. Most common parasitic infections in western world and in travellers are showed in table 4.

NONPARASITIC INFECTION

Fungal infections, especially coccidioidomycosis and aspergillosis, can elicit an eosinophilic response (17). Eosinopenia is common with bacterial and viral infections. In patients with eosinophilia caused by allergic disease, development of intercurrent bacterial or viral infection often suppresses eosinophilia. Some cases of scarlet fever, brucellosis, mycobacterial disease, cat-scratch fever, and

Name	Severity	Radiologic findings	Causes	Diagnosis	Treatment
Allergic bronchopulmonary aspergillosis	Variable	Consolidation, bandlike or glove-finger shadows	<i>Aspergillus fumigatus</i> , candidal infection	Skin testing, precipitins (total and specific)	Oral corticosteroids
Churg Strauss syndrome	Variable; multisystem involvement	Usually resembles chronic eosinophilic pneumonia	Unknown	Biopsy of organs showing vasculitis	Oral corticosteroids +/- immunosuppressive agents
Löffler's syndrome	Mild	Peripheral, rapidly clearing ("fleeting") infiltrates	Parasites, drugs	Minimal symptoms and "fleeting" shadows	Remove inducing agent, treat parasite, oral corticosteroids
Chronic eosinophilic pneumonia	May be severe	"Photographic negative" of pulmonary edema	Unknown	Severity of symptoms and radiologic appearance	Oral corticosteroids
Hypereosinophilic syndrome	Variable; multisystem involvement	Pulmonary infiltrates, cardiomegaly, pleural effusion	Unknown	Often marked eosinophilia, multisystem involvement	Oral corticosteroids +/- immunosuppressive agents +/- chemotherapy

Table 3: Descriptions of conditions classified as pulmonary eosinophilic syndromes.

Infection	Source	Clinical features	Diagnosis	Treatment
Visceral larva migrans (<i>Toxocara canis</i> , <i>Toxocara cati</i>)	Ingestion of eggs with soil (eg, in pica)	Fever, rash, asthma, hepatosplenomegaly, hypergammaglobulinemia	Serologic testing	May be self-limiting or require thiabendazole
Ascariasis	Ingestion of fecally derived eggs	Fever, cough, itch, Löffler's syndrome	Serologic testing, examination for larvae in secretions and eggs in feces	Mebendazole
Trichinosis	Ingestion of poorly cooked pork or wild carnivore meat	Facial and periorbital edema, muscle pain, abnormal muscle enzymes	Serologic testing	May be self-limiting or require corticosteroids
Hookworm disease	Skin infection by exogenous larvae	Pruritic macular papular rash, abdominal symptoms	Examination for eggs in feces	Mebendazole
Strongyloidiasis	Skin infection by exogenous larvae (may be autoinfection cycle)	Acute: skin lesions, hepatomegaly, abdominal pain, diarrhea, acute eosinophilic pneumonia Chronic: urticaria, diarrhea	Serologic testing, duodenal drainage, examination for eggs in feces	Thiabendazole
Anisakiasis (<i>Anisakis simplex</i>)	Ingestion of poorly cooked fish, seafruits	Acute: abdominal pain, diarrhea Chronic: urticaria	Serologic testing	Usually self-limiting, mebendazole Antihistamines or corticosteroids

Table 4: Selected features of common parasitic infections associated with blood eosinophilia in western world and travellers.

chlamydial pneumonia have been associated with eosinophilia (18). In scarlet fever, the eosinophil count reaches maximum by the second or third week and then falls dramatically (19).

SKIN DISEASE

Atopic dermatitis, eosinophilic cellulitis, pemphigoid, dermatitis herpetiformis, and psoriasis may be associated with eosinophilia (20). In addition, some rare skin disorders (eg, vasculitis and granulomatous diseases) may accompany eosinophilia or marked cutaneous eosinophil infiltration (21).

INFLAMMATORY AND AUTOIMMUNE DISEASES

In rheumatoid arthritis, eosinophilia tends to be present only in seropositive patients who have severe long-standing disease accompanied by pleural pericardial involvement (22). Occasionally, Crohn's disease and ulcerative colitis can give rise to moderate and fluctuating eosinophilia (23). Striking eosinophilia can occur in patients who have eosinophilic gastroenteritis, often accompanied by a history of atopy, and may cause abdominal pain without specific features or diarrhea and intestinal obstruction (24). Eosinophilic gastroenteritis may be difficult to diagnose except by radiologic evaluation and small-bowel biopsy. Immunologic causes of eosinophilia include elevated IgE syndrome, isolated IgA deficiency syndrome, Wiskott-Aldrich syndrome (25), and systemic lupus erythematosus or other collagen disease (26). Rarely, eosinophilia may be a sign of graft-versus-host disease (27).

MALIGNANT DISEASE

About 40% of neoplastic diseases are accompanied by a moderate increase in eosinophil count (table 5), and most patients with this finding have metastatic disease with a poor prognosis. Eosinophilia in association with neoplasia may be marked in patients with lung cancer or hematologic disease (eg, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic leukemia) (28,29). Eosinophilia occurring with malignant disease may abate and relapse along with the underlying condition. In lymphoid tumors, eosinophilia has been noted up to a year in advance of the diagnosis (28). After therapy, eosinophilia may recur weeks before detectable relapse of the tumor.

- Myelodysplastic disorders
- Myeloproliferative disorders
- Malignant histiocytosis
- Systemic mast cell disease
- Carcinoma:
 - Lung
 - Colon
 - Pancreas (acinar cell)
 - Cervix
- Plasma cell dyscrasias
- Lymphoma:
 - Hodgkin's disease
 - Non-Hodgkin's (especially T-cell)
 - Angioimmunoblastic lymphadenopathy with dysproteinemia
- Leukemia:
 - Acute lymphoblastic
 - Acute myelomonocytic
 - T-cell leukemia/lymphoma
 - Chronic granulocytic

Table 5: Neoplastic disorders that may be accompanied by blood eosinophilia.

HYPEREOSINOPHILIC SYNDROME

Some patients remain without a diagnosis after all causes of eosinophilia have been excluded. In such instances, the possibility of hypereosinophilic syndrome must be entertained (3,30,31,32). The hypereosinophilic syndrome has been defined as an absolute eosinophil count of greater than $1.5 \times 10^9/L$ for longer than 6 months without clinical evidence of other known cause. More than half of patients have constitutional symptoms (eg, fever, weight loss, night sweats). In addition to peripheral blood abnormalities (eg, anemia, thrombocytopenia), morphologically abnormal eosinophils with marked vacuolation, degranulation, nonlobulation, or hyperlobulation may be noted. A hallmark of hypereosinophilic syndrome is extensive infiltrates of mature eosinophils in multiple organs. In addition, arteritis may be observed in sections of the heart, lung, brain, and kidney. Cardiopulmonary dysfunction is the major cause of morbidity and mortality with the syndrome. Common manifestations include dyspnea, congestive heart failure, mitral regurgitation, T-wave inversion on electrocardiography, and cardiomegaly. Echocardiographic abnormalities include increases in left ventricular wall thickness, left ventricular mass, and left atrial size. As mentioned, the underlying pathology is endomyocardial necrosis, thrombosis, and fibrosis, ultimately resulting in restrictive cardiomyopathy. Thrombi often affect the leaflets of the tricuspid or mitral valves, interfering with function and producing thromboembolic events. It is interesting that similar cardiac manifestations have been seen in association with some of the supposedly benign causes of increa-

sed eosinophils, such as parasitic infections or collagen disease. Both pulmonary infiltrates and pleural effusion may be seen. Although the spleen and liver are often enlarged, hepatic function is usually preserved. Involvement of the central nervous system is common and may manifest as global dysfunction or as a more focal pattern due to cerebral occlusion from cardiac emboli or a hypercoagulable state. The prognosis for hypereosinophilic syndrome has been poor until recently, when aggressive therapy with high doses of steroids or, in case of steroids resistance, combination therapy with various agents (cyclophosphamide, azathioprine, cyclosporin-A, busulfan and ultimately imatinib mesilate) has improved dramatically overall survival (31-33). Whether eosinophilic leukemia exists as a distinct entity separate from hypereosinophilic syndrome has been a topic of considerable debate (33). Although rare, true eosinophilic leukemia can be distinguished from hypereosinophilic syndrome when a marked increase in the number of immature eosinophils in the blood and bone marrow is found, the marrow has more than 10% blast forms, and the clinical course is similar to that of other acute leukemias with anemia and thrombocytopenia. Cardiac and neurologic complications of hypereosinophilia can also develop in acute eosinophilic leukemia, so these clinical findings are not distinguishing features.

CLINICAL APPROACH TO PATIENTS

The initial approach to patients with eosinophilia should be based on history and physical examination results. Collagen, inflammatory bowel, and skin diseases are well-known causes of eosinophilia, and their presence may become apparent during history taking. Patients should be carefully questioned regarding symptoms of allergy, including allergic rhinitis, hay fever, asthma, and history of atopic disease, in themselves and family members. Possible exposure to allergens at work and in the pursuit of hobbies should be elicited by detailed questioning. The next important topic is drug history. Important classes of drugs to consider have been described earlier. A detailed travel history should be obtained, concentrating on tropical or exotic destinations, exposure to mosquitoes, the possibility of contaminated food or water, and symptoms experienced while traveling or immediately after returning home. During physical examination, particular care should be given to the respiratory system, including the nose, and to the skin, lymph nodes, and abdomen. The spleen may be enlarged in several conditions that produce eosinophilia (eg, parasitic disease, drug reaction, primary

hematologic disorder, tumor). The presence of vasculitic lesions in the skin, conjunctivae, or mouth may provide an important clue to collagen disease. The extent of laboratory evaluation required is indicated by results of history taking and physical examination. Recent evidence points toward less exhaustive laboratory evaluation than has been traditionally recommended (34, 35). A reasonable laboratory approach, when there is no obvious underlying clinical condition or apparent cause of eosinophilia, includes fecal examination for helminth eggs, serologic evaluation for endemic parasites that are not detectable by fecal assessment, and testing for atopy using a limited number of common allergens. Skin-prick tests, which are usually cheaper and more effective than radioallergen sorbent testing, may be used for routine evaluation for atopy in the case of eosinophilia (36). If results of these investigations are negative, a follow-up white blood cell count with differential is indicated after 1 to 2 months, to make certain eosinophilia has resolved.

CONCLUSIONS

The vast majority of cases of eosinophilia in western countries are caused by allergic processes. In individual cases, a short differential diagnosis of the most likely causes can be formulated on the basis of the absolute eosinophil count. History taking should emphasize the possibility of drug-induced or helminth-associated eosinophilia. If the history indicates travel, dietary, or other exposure risks, stool examination for ova and parasites is worthwhile. The extensive diagnostic workup previously recommended by some authorities is probably not justified unless detailed history taking and physical examination indicate a need for specific investigations. Although the possibility of missing an occult neoplasm has been used to justify extensive investigation, this is usually not necessary because most tumor-associated eosinophilia is accompanied by widely advanced and metastatic disease. A follow-up white blood cell count with differential is recommended to ascertain whether eosinophilia has resolved. Idiopathic hypereosinophilic syndrome can be diagnosed when an absolute eosinophil count of more than $1.5 \times 10^9/L$ persists for longer than 6 months and other causes are ruled out.

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