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Evaluation and differential diagnosis of marked, persistent eosinophilia

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Synopsis:

Hyperosinophilic syndromes (HES) are a group of heterogeneous disorders many of which remain ill-defined. By definition, the HES must be distinguished from other disorders with persistently elevated eosinophilia with a defined cause. Although marked eosinophilia worldwide is most commonly caused by helminth (worm) infections, the diagnostic approach must include non-infectious (non-parasitic) causes of marked eosinophilia as well.

Keywords

eosinophilia; parasitic; helminth; hypersensitivity

INTRODUCTION

Elevations in the levels of peripheral blood and tissue eosinophils can occur in a wide variety of disease processes that include infectious, allergic, neoplastic, primary hematologic disorders, and other, often less well-defined entities 102,110,131. Worldwide, multicellular helminth (worm) parasites are most commonly associated with significant eosinophilia, followed in frequency by drug hypersensitivity and atopic diseases. Hypereosinophilic syndromes (HES), in contrast, are a set of relatively rare, heterogeneous disorders characterized by persistent eosinophilia (defined as >1500/ul for 6 months) and organ involvement/dysfunction in which other clinical entities have been excluded 70. The approach to defining these non-HES causes of persistently elevated eosinophilia is the focus of this review.

BIOLOGY OF THE EOSINOPHIL AND EOSINOPHILIA

Eosinophils are bone marrow-derived leukocytes whose development and terminal differentiation are under the control of several cytokines (IL-3, GM-CSF, and IL-5), with IL-5 being the cytokine that is primarily responsible for eosinophilopoiesis. Eosinophilia, defined as > 450 eosinophils/ul (or 500/ul in some studies) is normally measured by sampling peripheral blood, although eosinophils are predominantly found in peripheral tissues 127 particularly in those tissues with a mucosal-environmental interface such as the respiratory, gastrointestinal and lower genitourinary tracts. Physiologically, eosinophil levels in the peripheral blood have a diurnal variation with a peak in the morning, a time at which endogenous steroids are the lowest 120. Pyogenic inflammation causes eosinopenia, a process that can mask the presence

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of eosinophilia or eosinophil-mediated inflammation. Hypoadrenalism is associated with eosinophilia because of low levels of endogenous glucocorticoids. Eosinophil levels can also be lowered by exogenous administration of medications, including corticosteroids, estrogen, and epinephrine 14,16.

Eosinophils, particularly in disease states associated with hypereosinophilia, can have a variety of phenotypic and functional changes felt to reflect cellular activation. In these situations, the eosinophil on a peripheral smear can appear vacuolated with alterations in granule size, and, on flow cytometric analysis, the eosinophil has characteristic changes in surface molecule expression 81. By electron microscopy, eosinophils demonstrate piecemeal degranulation 42 when activated.

HYPEREOSINOPHILIC CONDITIONS

Based on more recent classifications of HES that include idiopathic hypereosinophilic syndrome (IHES), platelet derived growth factor receptor α (PDGFRA)–associated HES, the lymphocytic variant HES (LHES), familial hypereosinophilia, Churg-Strauss Syndrome (CSS), and eosinophil-associated gastrointestinal disease (EGID), HES have been classified as heterogeneous group of uncommon disorders characterized by marked eosinophilia in the peripheral blood, tissues, or both, often without an identifiable cause 70,108,110). It is against this backdrop that an approach to the differential diagnosis of those non-HES (with identifiable causes) associated with persistent, marked eosinophilia (>1500 eosinophils/ul) and/or evidence of organ dysfunction is discussed. Because there are comprehensive reviews of eosinophilia in general 89,102,125, the focus herein is on those disorders that could be confused with HES.

A. Infectious Diseases

A wide variety of infectious agents, almost exclusively helminth (worm) parasites, elicit eosinophilia 89,126,131; only a relatively few, however, elicit a sustained, marked increase in eosinophil levels (Box 1) 130. The pattern and degree of eosinophilia in parasitic infections is determined by the development, migration, and distribution of the parasite within the host as well as by the host's immune response. In general, it is useful to remember that parasites tend to elicit marked eosinophilia when they or their products come into contact with immune effector cells in tissues, particularly during migration. When barriers are erected between the parasite and host or when the parasite no longer invades tissue, the stimulus for eosinophilia is usually absent. Therefore, eosinophilia is highest among parasites with a phase of development that involves migration through tissue (e.g., trichinosis, ascariasis, gnathostomiasis, filarial parasites), but a sustained eosinophilic response is not seen among parasites that are wholly intraluminal (e.g., adult tapeworms) or contained in a cystic structure (e.g., hydatid cysts) unless there is disruption of the integrity of the cyst wall with leakage of cyst contents and exposure to the immune system 89,126. Those parasites most likely to induce marked eosinophilia are noted in Table 1. Evaluation of helminth etiologies for marked eosinophilia should be guided not only by the clinical findings, but most often by geographic histories of potential exposures to infections. Approaches to the diagnosis of these infections are suggested in Table 1 provided there is an appropriate exposure history.

Infections with protozoa rarely result in peripheral eosinophilia. However, the intestinal coccidian *Isospora belli* can be associated with eosinophilia 23,119. Less commonly, eosinophilia can result from infection with the protozoan *Dientamoeba fragilis*. Rarely,infection with *Sarcocystis hominis*, a cause of eosinophilic myositis, has been accompanied by marked peripheral eosinophilia 7,33,121.

Ectoparasites, particularly scabies, are also associated with peripheral blood eosinophilia36. While eosinophilia can be associated with myiasis, this association occurs rarely 113. Although

uncommon in HIV infection, modest eosinophilia can be seen 40,111,112,118. Marked hypereosinophilia has developed in some HIV-infected patients particularly in those with a pustular, exfoliative dermatitis 40,62,82,118. Two fungal diseases have been also been associated with hypereosinophilia: coccidiomyocosis and aspergillosis (when presenting as ABPA). Although the eosinophilia is typically mild in coccidial infections, marked eosinophilia may develop with disseminated coccidioidomycosis 43,53,106.

B. Atopic/Allergic Diseases

Blood eosinophilia rarely exceeds 1500/ul in allergic rhinitis, nonallergic rhinitis with eosinophilia syndrome (NARES) or even in asthma (both allergic and non-allergic) despite respiratory tract eosinophil infiltration.

Because so many medications (as well as nutritional supplements and alternative therapies) have been associated with eosinophilia, a detailed history of current and past medications should be obtained from all patients with eosinophilia. Although the mechanisms underlying the drug-associated rise in eosinophil levels have not been determined (apart perhaps from some of the cytokines used therapeutically [e.g. IL-2, GM-CSF] 38,57,100 medication-related drug reactions are likely the most common cause of persistently elevated eosinophil levels in areas where exposure to parasites is uncommon 89. Medication-associated peripheral blood eosinophilia may present without accompanying symptoms or may be associated with specific signs and symptoms. Asymptomatic eosinophilia has been associated most often with quinine, penicillins, cephalosporins, or quinolones. Pulmonary infiltrates with peripheral eosinophilia have been particularly associated with NSAIDs, sulfas, and nitrofurantoin. Drug-induced hepatitis with eosinophilia is most often induced by the tetracyclines or the semisynthetic penicillins, although, more recently this has been seen by some of the newer SSRIs 41. Interstitial nephritis with eosinophilia has been associated with cephalosporins (cefotaxime is most commonly reported but others such as cefoxitin, cefoperazone, cefotriaxone have also been described) and semisynthetic penicillins. Drug reaction with eosinophilia and systemic symptoms (DRESS) can occur with sulfasalazine, hydantoin, carbamazepine, d-penicillamine, allopurinol, hydrochlorothiazide, and cyclosporine, associated with viral infection (human herpesvirus-6, Epstein-Barr virus, cytomegalovirus) 69,125,133. Patients with DRESS present with fever, rash, systemic involvement, and an appropriate medication history. Various drug-associated eosinophilic disorders are listed in Box 2 and a more exhaustive list can be found 125.

C. Hematologic/Neoplastic

1. Lymphoid malignancies—Apart from situations where eosinophils or their precursors are malignantly transformed 8-10, eosinophilia can be driven by the production of eosinophilopoetic cytokines. For example, eosinophilia is often associated with Hodgkin's disease, and the generation of IL-5 by Reed-Sternberg cells has been demonstrated 52,105. In primary cutaneous T-cell lymphoma and Sezary syndrome, blood and dermal eosinophilia are also frequently observed 22. Other types of lymphoid malignancies (acute lymphoblastic leukemia 56 and B cell ALL99) have been associated with eosinophilia.

2. Solid tumors—In addition to lymphomas, other neoplasms may occasionally be associated with blood eosinophilia. Tumor-associated eosinophilia 79occurs with large-cell nonkeratinizing cervical tumors, large-cell undifferentiated lung carcinomas 71, squamous carcinomas of the lung, vagina, penis, skin, and nasopharynx 19,77, adenocarcinomas of the stomach, large bowel, and uterine body, and transitional cell carcinoma of the bladder 78.

3. Mastocytosis—Systemic mast cell disease is accompanied by peripheral eosinophilia in about 25% of cases94and rarely by features and organ involvement typical of HES87. Recently,

methods for distinguishing between HES (with mast cell involvement) and systemic mastocytosis with eosinophilia have been proposed 80.

D. Immunologic

1. Immunodeficiency Disorders—Among the many primary immunodeficiency disorders only a few are associated with high grade eosinophilia, those being Omenn syndrome 4 and the HyperIgE syndrome 50,51.

2. Graft-versus-host disease (GVHD)—Chronic GVHD, particularly that which develops following allogeneic stem cell transplantation, most commonly affects the skin, liver, and GI tract59,86. Marked eosinophilia has also been seen occasionally with acute GVHD 12.

E. Endocrine

The loss of endogenous adrenoglucocorticosteroids in Addison's disease, adrenal hemorrhage, or hypopituitarism can cause causes increased blood eosinophilia. Eosinophilia may be a clue to adrenal insufficiency in some patients, including those whose illnesses require intensive care 17.

F. Other

Cholesterol embolization, typically after a vascular or intravascular procedures, can lead to eosinophilia 129. Radiation therapy has also been linked to eosinophilia, although high grade eosinophilia is rare in this setting 29. Sarcoidosis, inflammatory bowel disease and other disorders associated with immunodysregulation, can also be associated with marked eosinophilia98.

HYPEREOSINOPHILIA WITH ORGAN-RESTRICTED INVOLVEMENT

It is most important to be able to distinguish between HES and those conditions with overlapping clinical presentations. Because, historically, HES has required organ dysfunction associated with high grade eosinophilia, known disorders of specific organ systems accompanied by eosinophilia are those most often confused with HES (see Box 3).

A. Skin and Subcutaneous Tissues

1. Atopic and blistering diseases—Eosinophils participate in the inflammatory infiltrate in numerous dermatologic conditions. Blood and tissue eosinophilia are common in atopic dermatitis74. Tissue eosinophils are seen in blistering diseases, such as bullous pemphigoid, pemphigus vulgaris, dermatitis herpetiformis, and herpes gestationis, and can be prominent in drug-induced lesions. An uncommon disorder, characterized by the association of nodules, eosinophilia, rheumatism, dermatitis, and swelling (NERDS), includes prominent paraarticular nodules, recurrent urticaria with angioedema, and tissue and blood eosinophilia27.

2. Eosinophilic Panniculitis—Eosinophilic panniculitis is characterized by a prominent eosinophil infiltration of subcutaneous fat 3. Lesions often are nodular and less frequently present as plaques or vesicles. Eosinophilic panniculitis is commonly associated with gnathostomiasis, leukocytoclastic vasculitis and erythema nodosum 3. Other disorders associated with eosinophilic panniculitis include atopic and contact dermatitis, eosinophilic cellulitis, arthropod bites, toxocariasis, polyarteritis nodosa, injection granuloma, lupus panniculitis, malignancy, diabetes, and chronic recurrent parotitis 3,64.

3. Episodic Angioedema with Eosinophilia—Although blood eosinophilia does not usually accompany angioedema, a distinct entity, episodic angioedema with eosinophilia, is

characterized by recurrent episodes of angioedema, urticaria, pruritus, fever, weight gain with oliguria, elevated serum IgM, and leukocytosis with Imarked blood eosinophilia47.The level of blood eosinophilia parallels disease activity. This disease is associated with cyclic alterations in serum IL-5 or GM-CSF levels11,21,26. The clinical course of this disease with its periodic recurrences of angioedema and eosinophilia and its lack of association with cardiac damage distinguishes it from HES although some consider it an overlapping syndrome with HES 70. Indeed, some patients will develop clonal T cell populations and progress to HES.

4. Kimura's Disease and Angiolymphoid Hyperplasia with Eosinophilia— Kimura's disease presents as large subcutaneous masses on the head or neck of Asian men, whereas angiolymphoid hyperplasia with eosinophilia occurs in all races and is characterized by generally smaller and more superficial lesions. Eosinophilia is common to both2,37,55.

5. Eosinophilic Fasciitis—Eosinophilic fasciitis (Shulman's syndrome) has an acute onset of erythema, swelling, and induration of the extremities, often with a history of antecedent exercise39,109. Skin lesions are accompanied by elevated blood eosinophil counts. Histologically, unlike scleroderma, the epidermis and dermis are normal with most pathology located in the subcutaneous tissue, fascia, and muscle.

6. Wells' syndrome (eosinophilic cellulitis)—Eosinophilic cellulitis is marked by recurrent swellings on the extremities1,44.Although involved skin appears cellulitic, minimal tenderness, absence of warmth, and failure to respond to antibiotics distinguish it from bacterial cellulitis. It resolves spontaneously leaving a granulomatous infiltration. Blood eosinophilia is present in 50% of cases.

7. Eosinophilic Pustular Folliculitis—Mixed eosinophilic and neutrophilic infiltrates occur in affected follicles, and blood eosinophilia may be present 85. Although described in healthy individuals, it also occurs in those infected with HIV and less commonly in HIV-negative patients being treated for hematologic malignancies or following bone marrow transplantation 13,25.

B. Pulmonary

Eosinophilic lung diseases are a heterogeneous group of disorders unified by the presence of large numbers of eosinophils in the inflammatory cellular infiltrates in the airways or parenchyma of the lungs with a clinical presentation that usually consists of symptoms referable to the respiratory system accompanied by abnormal chest radiograph/CT and peripheral blood eosinophilia. These eosinophilic lung diseases are reviewed extensively by Wechsler 124 and the major categories of pulmonary disorders associated with high grade eosinophilia are listed in Box 3.

Besides the medication- and toxin-induced eosinophilic pulmonary diseases and allergic bronchopulmonary aspergillosis (discussed above), Churg-Strauss Syndrome and helminth infections (particularly in the migratory phase early in the infection) have been associated with transient pulmonary infiltrates and marked eosinophilia (Loeffler's syndrome) 76. Moreover, a very rare manifestation of *Wuchereria bancrofti*, termed Tropical Pulmonary Eosinophila, is a systemic disorder defined by pulmonary infiltrates, nocturnal wheezing, IgE elevations and marked peripheral eosinophilia 92.

1. Chronic Eosinophilic Pneumonia—This is a disease of unknown etiology that typically present with cough, fever, dyspnea, and significant weight loss 60. Laboratory findings include blood eosinophilia in almost 90% of patients 60. Chronic eosinophilic

pneumonia 28 is characterized radiographically by peripheral infiltrates. Mediastinal lymphadenopathy may be present as well 28.

Histologically, the lung biopsies show a predominantly eosinophilic infiltrate in the alveoli and interstitium 91. Response to corticosteroid administration is dramatic, occurring within 24 hours. Blood eosinophilia can decline within 24 hours 60, and complete resolution of symptoms occurs within 2 weeks in two thirds of patients60. Radiographic improvement may be as early as 60 to 72 hours, and clearance can be expected to occur within 2 weeks in one half of patients 84. Recurrences of clinical and radiographic changes were seen in 58% of patients after discontinuation of corticosteroids 60.

2. Acute Eosinophilic Pneumonia—Acute eosinophilic pneumonia is a clinical entity distinct from other eosinophilic pneumonias5,54,96. Patients commonly present with acute onset of cough, dyspnea, and fever. Diagnostic criteria for acute eosinophilic pneumonia have been defined and require both exclusion of other causes and the presence of a febrile illness of short duration, hypoxemic respiratory failure, diffuse alveolar or mixed alveolar-interstitial infiltrates on radiography, either bronchoalveolar lavage eosinophils >25% (or biopsy confirmation of lung tissue eosinophilia) 5,116and rapid response to corticosteroids.

C. Gastrointestinal

Blood eosinophilia can develop with a number gastrointestinal and hepatobiliary disorders, but tissue eosinophilia is more characteristic. The eosinophilic gastrointestinal diseases (EGID) are discussed in in full by Rothenberg et al 103. In brief, there are a number of GI diseases that have eosinophil-mediated pathology and marked peripheral blood eosinophilia.

1. Eosinophilic Gastrointestinal Diseasese (EGID)

a. Eosinophilic Esophagitis (EE) Characterized by eosinophilic infiltration of the esophagus, EE is a disorder, felt to have an allergic etiology. Adults typically present with dysphagia and/or food impaction while children have a more variable clinical presentation. Peripheral eosinophilia is common. Strictures may be seen on endoscopy; histopathology reveals mucosal infiltration with eosinophils 20,123.

b. Eosinophilic Gastroenteritis Eosinophilic gastroenteritis is an uncommon disorder characterized by gastrointestinal symptoms, blood eosinophilia, and eosinophilic infiltration of the gastrointestinal wall67,73,104,115. The peak age of onset is in the third decade. Although allergies to foods, including milk, contribute in some children; in adults, allergic etiologies are uncommon. Different layers of the GI tract may be involved, and as a consequence, different types of symptoms may occur. Mucosal involvement can result in abdominal pain, nausea, vomiting, diarrhea, weight loss, anemia, protein-losing enteropathy, and intestinal perforation. Patients with muscular layer involvement have symptoms of pyloric or intestinal obstruction and early satiety. Subserosal eosinophilic infiltration may result in development of eosinophilic ascites 73,115.

2. Hepatobiliary Diseases—Eosinophilic hepatitis develops in response to some medications 34,46,93,95 and to helminth parasites (see Table 1). Marked peripheral eosinophilia has been seen in primary biliary cirrhosis117, sclerosing cholangitis 49, eosinophilic cholangitis101 and eosinophilic cholecystitis 35.

D. Neurologic

Marked tissue eosinophilia occurs within organizing chronic subdural hematomas48. Other eosinophil associated neurologic diseases are uncommon and include the disorders that cause eosinophilic meningitis 128. Cerebrospinal fluid eosinophilia can be a significant clue to

central nervous system infections with coccidioidomycosis or *Angiostrongylus cantonensis* as well as to adverse drug reactions to NSAIDs or antibiotics.

E. Rheumatologic

Marked peripheral blood eosinophilia is not common in connective tissue diseases 63, although it has been described associated with dermatomyositis 63, rheumatoid arthritis 132, systemic sclerosis45, and Sjögren's syndrome 15. It should be remembered that many of the drugs used to treat these disorders can cause hypersensitivity reactions with eosinophilia (e.g. NSAIDS).

1. Eosinophilia-Myalgia Syndrome and Toxic Oil Syndrome—The eosinophilia-myalgia syndrome arose from ingestion of contaminated L-tryptophan 18 and toxic oil syndrome was due to ingestion of cooking oil adulterated with denatured rapeseed oil 68,83, 97,114. Both are chronic, persisting multisystem diseases in which marked eosinophilia developed 65.

2. Vasculitis—Churg-Strauss syndrome (CSS), among the vasculitides, is the disorder that is associated with high grade, persistent eosinophilia (see Wechsler et al for fuller treatise). Although mildly eosinophilia is common, marked eosinophilia is uncommon in many of the other vasculitides but has been seen in patients with cutaneous necrotizing vasculitis 30-32, thromboangiitis obliterans with eosinophilia of the temporal arteritis 75 and unusual cases of Wegener's granulomatosis 72,134.

F. Cardiac

The principal cardiac sequela of eosinophilic diseases is damage to the endomyocardium (see Ogbogu et al90). This can occur with hypersensitivity myocarditis 66 and with eosinophilias associated with eosinophilic leukemia, sarcomas, carcinomas, and lymphomas 88, with GM-CSF 38 or IL-2 administration 61,107, with prolonged drug-induced eosinophilia, and with parasitic infections 6,24,58.

G. Genitourinary

Interstitial nephritis with eosinophilia is typically drug-induced. Agents known to induce nephritis include: semisynthetic penicillins, cephalosporins, NSAIDs, allopurinol, rifampin, and ciprofloxacin, among others.

Eosinophilic cystitis is a rare clinicopathological condition characterized by transmural inflammation of the bladder predominantly with eosinophils, associated with. It has been associated with bladder tumors, bladder trauma, parasitic infections and some medications. The most common symptom complex consists of urinary frequency, hematuria, dysuria and suprapubic pain 122.

APPROACH TO THE EVALUATION OF A PATIENT WITH HIGH GRADE EOSINOPHILIA

The approach to identifying the cause of marked, persistent eosinophilia is a challenging problem. Nevertheless, the prevention of morbidity by identifying the cause of the eosinophilia and intervening therapeutically is an important task that should be approached systematically. Although this article assumes that the presence of marked eosinophilia has been established, it should be borne in mind that some of the earlier automated methods used to assess leukocyte populations resulted in inaccuracies in establishing the presence of eosinophilia.

To evaluate a patient with persistent and marked eosinophilia, the approach suggested in Box 4 is recommended. A careful history should be taken directed specifically at the nature of the

symptoms (if present) with an emphasis placed on disorders known to be associated with eosinophilia, previous eosinophil counts (if available), travel, occupational and dietary history. A complete medication history should be taken that includes over the counter medications, supplements, herbal preparations, and vitamins; any medication known to induce eosinophilia should be discontinued. Patients should be asked about diseases commonly found in their family; previous allergies to medications or to environmental allergens must also be addressed.

Physical examination with special attention to skin, soft tissues, lungs, liver, and spleen as well as an additional directed examination based on the patient's specific symptoms or chief complaint is obviously important.

Initially, the approach to the evaluation of marked eosinophilia must be to assess general health status and to assess whether there is underlying organ dysfunction. The eosinophilia must be confirmed, and an estimation of the absolute eosinophil count (if not measured directly) must be made. Routine studies to assess hematologic status (CBC, platelet count, PT/PTT), studies to assess organ function (liver function tests, renal function tests, urinalysis, chest radiograph, electrocardiogram), markers of inflammation (CRP/ESR) and immunologic status (quantitative immunoglobulins and IgE) should also be performed routinely. The presence of particular symptoms or physical findings may direct other laboratory studies.

Further diagnostic evaluation based on the initial studies is usually required to distinguish among the myriad disorders underlying hypereosinophilia. When a parasitic infection is suspected, the laboratory evaluation should be based on information gleaned from the history and physical examination, in order to avoid going on a “fishing expedition” by ordering needless laboratory tests; however, a minimum set of diagnostic tests directed toward establishing the presence of a particular parasite should be obtained (Table 3). The localizing clinical findings in symptomatic patients as well as laboratory evidence of organ involvement must guide the subsequent evaluation. Access to tissue (biopsies) or material (e.g. CSF, sputum, bronchoalveolar lavage, stool, urine) that can identify the underlying problem is often necessary. CT and MRI to define better focal lesions should be employed. Bone marrow aspirates and biopsies will often be necessary to assess fully the nature of the process underlying the high-grade eosinophilia. Additional disease-defining tests may be necessary to exclude particular diagnoses (e.g. serum tryptase/assessment of cKIT mutations for systemic mastocytosis, antineutrophil cytoplasmic antibodies (ANCA) for CSS and other vasculitides, serologies for helminths).

CONCLUSION

The approach to the identifying the cause of marked, persistent eosinophilia is a challenging problem. Excluding many of these non-HES causes of marked peripheral blood eosinophilia is required for making the diagnosis of HES. Moreover, the prevention of morbidity by identifying the cause of the eosinophilia and intervening therapeutically is an important task that must be approached systematically.

Box 1. Conditions associated with marked peripheral blood eosinophilia

Infectious Diseases

- Parasitic infections primarily with helminths (see Table 1)
- Certain fungal infections (Allergic bronchopulmonary aspergillosis, Coccidiomycosis)
- Infestations – Scabies, Myiasis

Allergic or Atopic Diseases

- Drug hypersensitivity or medication-associated eosinophilias
- Atopic diseases

Hematologic and Neoplastic Disorders

Hypereosinophilic syndromes (HES) including chronic eosinophilic leukemia

Leukemia (Acute myelogenous leukemias most commonly, B cell ALL)

Lymphomas (particularly Hodgkin's, T- and B-cell lymphomas)

Tumor associated

Adenocarcinomas

Squamous carcinomas

Large cell lung carcinomas

Transitional cell carcinoma of the bladder

Systemic mastocytosis

Immunologic

Primary Immunodeficiency Diseases (HyperIgE syndrome, Omenn's syndrome)

Graft-versus-host-Disease

Endocrinologic Disorders

Hypoadrenalism

Other

Irradiation

Atheroembolic Disorders

Sarcoidosis

Box 2 – Types of Drug Reactions Associated with Eosinophilia

Manifestations	Commonly Associated Drugs
Asymptomatic	Penicillins, cephalosporins
Soft tissue swelling	GM-CSF, IL-2
Pulmonary infiltrates	Nonsteroidal anti-inflammatory agents
Interstitial nephritis	Semisynthetic penicillins, cephalosporins
Myocarditis	Ranitidine
Hepatitis	Semisynthetic penicillins, tetracyclines
Hypersensitivity vasculitis	Allopurinol, phenytoin
Gastroenterocolitis	Nonsteroidal anti-inflammatory agents
Asthma, nasal polyps	Aspirin
Eosinophilia-myalgia syndrome	L-tryptophan contaminant
DRESS	Sulfasalazine, hydantoin, carbamazepine, allopurinol, hydrochlorothiazide, cyclosporine, nevirapine

Box 3. Diseases with Organ-restricted involvement and marked peripheral eosinophilia

Skin and subcutaneous diseases

Episodic angioedema with eosinophilia

Eosinophilic cellulitis (Well's syndrome)

Eosinophilic panniculitis

Angiolymphoid Hyperplasia with Eosinophilia (and Kimura's Disease)

Eosinophilic Pustular Dermatitis

Cutaneous Necrotizing Eosinophilic Vasculitis

Pulmonary diseases

Drug- and toxin-induced eosinophilic lung diseases

Helminth associated (Loeffler's syndrome; tropical pulmonary eosinophilia)

Chronic eosinophilic pneumonia

Acute eosinophilic pneumonia

Churg-Strauss syndrome

Other vasculitides

Gastrointestinal diseases

Eosinophilic Gastrointestinal Disorders (EGIDs)

Eosinophilic Esophagitis (EE)

- Eosinophilic Gastroenteritis (EG)
- Primary biliary cirrhosis
- Sclerosing cholangitis
- Eosinophilic cholangitis
- Eosinophilic cholecystitis
- Neurologic diseases
  - Eosinophilic meningitis
  - Ventriculoperitoneal shunts
  - Leukemia or lymphoma with CNS involvement (Hodgkin's)
  - Nonsteroidal antiinflammatory drugs
  - Antibiotics
  - Contrast agents
- Rheumatologic diseases
  - Churg-Strauss syndrome
  - Other Vasculitides
  - Eosinophilia-myalgia syndrome
- Cardiac diseases
  - Hypersensitivity myocarditis
  - Churg-Strauss syndrome
- Genitourinary disease
  - Drug induced interstitial nephritis
  - Eosinophilic cystitis

Box 4 - Approach to evaluation of marked eosinophilia

1) Eosinophil Determinations – Verify eosinophil count; estimate or get absolute eosinophil count

2) Medical History

- Obtain history of previous eosinophil counts
- Medical History
  - ○ review medical history with emphasis placed on disorders know to be associated with eosinophilia including atopic disease
- Medication History
  - ○ review recent and current medication history
  - ○ discontinue any drugs known to be associated with eosinophilia
  - ○ make a detailed list of all medications (including nutritional supplements, vitamins, herbal preparations)
  - ○ Note any history of allergy to medications
- Travel/Geographic History
  - ○ Review past history of travel to or residence in other countries
  - ○ Review travel within indigenous country with emphasis on regions where particular eosinophilia-associated infections may be common
- Occupational/Recreational History
  - ○ Review occupational and recreational exposures
- Dietary History
  - ○ Review carefully; query dietary indiscretions, nutritional supplements
- Family History
  - ○ Review whether others in family have eosinophilia suggesting a common exposure or familia nature of disease

Physical Examination

- Do a careful physical examination
- Close attention paid to skin, soft tissues, masses, lymphadenopathy

Initial Laboratory Evaluation

- Routine studies to assess general hematologic status (CBC, platelet count)
- studies to assess organ function (liver function tests, renal function tests, urinalysis, chest radiograph), inflammation (CRP/ESR), immune status (immunoglobulins, IgE).

Further Diagnostic Evaluations (based on initial laboratory findings or localizing symptoms)

- Tissue examination (biopsies) if necessary
- Specimen collection (CSF, sputum, bronchoalveolar lavage, stool, urine) that can identify the
- CT and MRI to define better focal lesions.
- Bone marrow aspirates and biopsies to assess fully the nature of the process underlying the eosinophilia.
- Additional disease-defining tests to exclude particular diagnoses (e.g. serum tryptase/cKIT mutations for systemic mastocytosis, antineutrophil cytoplasmic antibodies (ANCA) for CSS and other vasculitides, serologies for helminths

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Abbreviations

APBA, Allergic Bronchopulmonary Aspergillosis; CNS, Central Nervous System; CSS, Churg-Strauss Syndrome; CFA, Circulating Filarial Antigen; DRESS, Drug rash, eosinophilia, and systemic symptoms; EE, Eosinophilic Esophagitis; EGID, Eosinophilic Gastointestinal Diseases; GVHD, Graft-versus-host disease; HES, Hypereosinophilic syndromes; HIV, Human Immunodeficiency Virus; IgE, Immunoglobulin E; IL, Interleukin; ul, Microliter; Mf, Microfilariae; PDGFRA, Platelet derived growth factor receptor α; SSRIs, Selective serotonin reuptake inhibitors.

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Table 1

Helminth infections associated with marked and/or persistent eosinophilia

Parasitic Disease ***Organism(s)***	**Development and duration of Eosinophilia**		**Main anatomical site(s)**	**Diagnosis**
	Acute	**Persistent**		
Angiostrongyloidiasis				
Angiostrongylus cantonensis	+		CNS	Larvae in CSF
Angiostrongylus costericensis	+		GI	Biopsy
Ascariasis	+		GI	Eggs in stool
Clonorchiasis	+	+	Hepatobiliary	Eggs in stool, serology
Fascioliasis	+	+	Hepatobiliary	Eggs in stool, serology
Fasciolopsiasis	+		GI	Eggs in stool
Filarial infections				
Lymphatic Filariasis				
Brugia, Wuchereria	+	+	Blood, lymphatics	Mf in blood, serology, CFA
*Loa loa**	+	+	Subcutaneous, eye	Mf in blood, worm extracted
*Mansonella ozzardi**	+	+	Blood	Mf in blood
*Mansonella perstans**	+	+	Blood, body cavities	Mf in blood, adult in tissue
*Mansonella streptocerca**	+	+	Skin, subcutaneous tissue	Mf in skin snips
*Onchocerca volvulus**	+	+	Skin, eye, subcutaneous tissue	Mf in skin snips, adults in nodules
Tropical pulmonary eosinophilia*	+	+	Lung	Serology
Gnathostomiasis	+	+	Soft tissue	Serology, worm in specimen
Hookworm*	+	+	GI, lung (acutely)	Eggs in stool
Opisthorchiasis	+	+	Hepatobiliary	Eggs in stool
Paragonimiasis	+	+	Lung, CNS, subcutaneous	Eggs in sputum, BAL, stool
Schistosomiasis	+			Serology
Schistosoma haematobium	+		Urinary tract	Eggs in urine
Schistosoma intercalatum	+		Hepatic, GI	Eggs in stool
Schistosoma japonicum	+		Hepatic, GI	Eggs in stool
Schistosoma mansoni	+		Hepatic, GI	Eggs in stool
Schistosoma mekongi	+		Hepatic, GI	Eggs in stool
Strongyloidiasis	+	+	GI, lung, skin	Larvae in stool, serology
Trichinosis	+	+	GI, muscle	Serology, muscle biopsy
Visceral larva migrans*				
Toxocara canis; T catis	+	+	Liver, eye, lung	Serology, larvae in tissue
Baylisacaris procyois	+	+	CNS, eye	Larvae in specimen