Evaluation and differential diagnosis of marked, persistent eosinophilia

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Abstract

High grade eosinophilia in patients can be a diagnostic dilemma, as the etiologies are extensive and varied. Hypereosinophilic syndromes (HES) are a group of heterogeneous disorders, many of which remain ill-defined. By definition, 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, non-infectious causes must be sought including drug reactions, malignancies, and immunologic, inflammatory and allergic diseases.

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 (Table 1). 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 and organ involvement/dysfunction in which other clinical entities have been excluded [1]. This definition of HES has been refined recently [2], and these are largely the subject of this entire issue of Seminars in Hematology. The approach to defining non-HES causes of persistently elevated eosinophilia is the focus of this particular section.

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/µl (or 500/µl in some studies) is normally measured by sampling peripheral blood, although eosinophils are predominantly found in peripheral tissues, [3] 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 [4]. Pyogenic inflammation causes eosinopenia, a process that can mask the presence 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 [5].

Eosinophils, particularly in disease states associated with hypereosinophilia, can have a variety of phenotypic and functional changes felt to reflect cellular activation (see Weller et al, this issue).

HYPEREOSINOPHILIC CONDITIONS

Based on more recent classifications of HES that include idiopathic hypereosinophilic syndrome (IHES), platelet derived growth factor receptor α (PDGFRA)–associated myeloproliferative neoplasms, the lymphocytic variant HES (L-HES), 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 [1]. 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/µl) and/or evidence of organ involvement is discussed. Because there are comprehensive reviews of eosinophilia in general [6], 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 [7]; only a relatively few, however, elicit a sustained, marked increase in eosinophil levels (Table 2) [8]. 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 in infections with a phase of parasite development that involves migration through tissue (e.g., trichinosis, ascariasis, gnathostomiasis, strongyloidiasis, schistosomiasis, and filariasis), but a sustained eosinophilic response is not seen in parasites infections 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 [9]. Those parasites most likely to induce marked eosinophilia are noted in Table 2. Evaluation of helminth etiologies for marked eosinophilia should be guided not only by the clinical findings, but also by the geographic history of potential exposures to infections. Approaches to the diagnosis of parasitic infections are suggested in Table 2 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 [10]. 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 [11].

Ectoparasites, particularly scabies, can also be associated with peripheral blood eosinophilia [12]. While eosinophilia has been noted in myiasis, this association occurs rarely [13]. Although uncommon in HIV infection, modest eosinophilia can be seen. Marked hypereosinophilia has developed in some HIV-infected patients particularly in those with a pustular, exfoliative dermatitis and eosinophilic folliculitis [14]. Crusted or Norwegian scabies, more common in HIV and immunosuppressed patients, had higher mean levels of peripheral blood eosinophils compared to other ectoparasitic infections [15].

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 [16].

B. Atopic/Allergic Diseases

Blood eosinophilia rarely exceeds 1500/µl in allergic rhinitis, non-allergic rhinitis with eosinophilia syndrome (NARES or BENAR), or even in asthma (both allergic and non-allergic) despite respiratory tract eosinophil infiltration [17].

Because many medications (as well as nutritional supplements) 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 elucidated (apart perhaps from some of the cytokines used therapeutically [e.g. IL-2, GM-CSF]) [18, 19], medication-related drug reactions are the most common cause of persistently elevated eosinophil levels in areas of the world where exposure to helminth parasites is uncommon [8]. 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, and 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 with some of the atypical antipsychotics [20]. Eosinophilic pneumonia and peripheral blood eosinophilia have been associated with amiodarone, nitrofurantoin and methotrexate, but also rarely with SSRIs and SNRIs [21]. Interstitial nephritis with eosinophilia and eosinophiluria has been associated with cephalosporins (cefotaxime is most commonly reported, but others such as cefoxitin, cefoperazone, cefotriaxone have also been implicated) and semisynthetic penicillins. Drug reaction with eosinophilia and systemic symptoms (DRESS) can occur with sulfasalazine, hydantoin, carbamazepine, d-penicillamine, allopurinol, hydrochlorothiazide, and cyclosporine, and can be associated with viral infection (human herpesvirus-6, Epstein-Barr virus, cytomegalovirus) [22]. Patients with DRESS present with fever, rash, systemic involvement, and an appropriate medication history. Various drug-associated eosinophilic disorders are listed in Table 3 and a more exhaustive list can be found [6].

C. Hematologic/Neoplastic

1. **Lymphoid malignancies** - Apart from situations where eosinophils or their precursors are malignantly transformed, eosinophilia can be driven by the production of eosinophilopoietic cytokines. For example, eosinophilia is often
2. Solid tumors - In addition to lymphomas, other neoplasms may occasionally be associated with blood eosinophilia. Tumor-associated eosinophilia occurs with large-cell nonkeratinizing cervical tumors, large-cell undifferentiated lung carcinomas [25], squamous carcinomas of the lung, vagina, penis, skin, and nasopharynx [26], adenocarcinomas of the stomach, large bowel, and uterine body, and transitional cell carcinoma of the bladder [27].

3. Mastocytosis - Systemic mast cell disease is accompanied by peripheral eosinophilia in about 25% of those with the disease [28]. Methods for distinguishing between HES (with mast cell involvement) and systemic mastocytosis with eosinophilia have been proposed [29].

D. Immunologic

1. Immunodeficiency Disorders - Among the many primary immunodeficiency disorders only a few are associated with high grade eosinophilia, those being Omenn syndrome [30] HyperIgE (Job’s) syndrome [31], Dock8 deficiency [32], IPEX [33], and Zap70 deficiency [34].

2. Graft-versus-host disease (GVHD) - Marked eosinophilia has also been seen occasionally with acute GVHD and has been associated with milder GVHD and better outcomes [35]. Although chronic GVHD has also been associated with eosinophilia, particularly that which develops following allogeneic stem cell transplantation, the associated eosinophilia has not been shown to be of any prognostic value [36].

E. Endocrine

The loss of endogenous adrenoglucocorticosteroids in Addison's disease, adrenal hemorrhage, or hypopituitarism can cause increased blood eosinophilia. Eosinophilia may help making the diagnosis of adrenal insufficiency in some patients [37].

F. Other

Cholesterol embolization, typically after a vascular or intravascular procedure, can lead to eosinophilia [38]. Eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy (EPPER) is characterized by tumor-associated blood eosinophilia and a cutaneous eosinophilic infiltrate [39]. Sarcoidosis, inflammatory bowel disease and other disorders associated with immune-dysregulation can also be associated with marked eosinophilia [40].

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 Table 4).

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 dermatitis [41]. 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 para-articular nodules, recurrent urticaria with angioedema, and tissue and blood eosinophilia [42].

2. **Eosinophilic Panniculitis** - Eosinophilic panniculitis is characterized by a prominent eosinophil infiltration of subcutaneous fat [43]. Lesions often are nodular and less frequently present as plaques or vesicles. Eosinophilic panniculitis is commonly associated with gnathostomiasis, leukocytoclastic vasculitis and erythema nodosum [43]. 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 [43].

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 marked blood eosinophilia [44]. The level of blood eosinophilia parallels clinical symptoms. This disease is associated with cyclic alterations in serum IL-5 or GM-CSF levels [45]. The clinical course of this disease with its periodic recurrences of angioedema and eosinophilia distinguishes it from other forms of HES it is currently considered within the spectrum of HES [1]. Some patients will develop clonal T cell populations that can progress to lymphocytic-variant HES [46].

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 both [47].

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 exercise [48]. 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 extremities [49]. Although involved skin appears celllulitic, 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 [50]. 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 [51].

**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 have been reviewed [52], and the major categories of pulmonary disorders associated with high-grade eosinophilia are listed in Table 4.

Besides the medication- and toxin-induced eosinophilic pulmonary diseases and ABPA (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) [53]. Moreover, a very rare manifestation of *Wuchereria bancrofti*, termed Tropical Pulmonary Eosinophilia, is a systemic disorder defined by pulmonary infiltrates, nocturnal wheezing, IgE elevations and marked peripheral eosinophilia [54].

1. **Chronic Eosinophilic Pneumonia** - This is a disease of unknown etiology that typically present with cough, fever, dyspnea, and significant weight loss [55]. Laboratory findings include blood eosinophilia in almost 90% of patients [55]. Chronic eosinophilic pneumonia is characterized radiographically by peripheral infiltrates. Mediastinal lymphadenopathy may be present as well.

   Histologically, the lung biopsies show a predominantly eosinophilic infiltrate in the alveoli and interstitium [56]. Response to corticosteroid administration is dramatic, with blood eosinophilia often declining within 24 hours, and complete resolution of symptoms occurs within 2 weeks in two thirds of patients [55]. Radiographic improvement may be seen as early as 60 to 72 hours, and radiologic clearance can be expected to occur within 2 weeks in one half of patients [57]. Recurrences of clinical and radiographic changes were seen in 58% of patients after discontinuation of corticosteroids [55].

2. **Acute Eosinophilic Pneumonia** - Acute eosinophilic pneumonia is a clinical entity distinct from other eosinophilic pneumonias [58]. 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) [58] and rapid response to corticosteroids.

### C. Gastrointestinal

Blood eosinophilia can develop in a number of gastrointestinal and hepatobiliary disorders, but tissue eosinophilia is more characteristic. The eosinophilic gastrointestinal diseases (EGID) are discussed in full by Rothenberg et al [59]. In brief, there are a number of GI diseases that have eosinophil-mediated pathology and marked peripheral blood eosinophilia.

1. **Eosinophilic Gastrointestinal Diseases (EGID)**

   a. **Eosinophilic Esophagitis (EoE)** - Characterized by eosinophilic infiltration of the esophagus, EoE is a disorder, felt to have an unknown pathogenesis, but with increasing evidence of Th2 dysregulation. Adults typically present with dysphagia and/or food impaction and EoE should be considered in patients with these symptoms not improving on a proton pump inhibitor (PPI). Peripheral eosinophilia is common. Strictures may be seen on endoscopy; histopathology reveals mucosal infiltration with eosinophils. EoE was originally considered a symptom of gastroesophageal reflux disease (GERD), but small case studies using PPIs
or H2 blockade failed to demonstrate definitive improvement in GI mucosal eosinophil infiltrates. More large-scale double-blinded studies are still needed to provide a causal link between GERD and EoE. [60].

b. Eosinophilic Gastroenteritis - Eosinophilic gastroenteritis (EGE) is an uncommon disorder characterized by non-specific gastrointestinal symptoms, blood eosinophilia, and eosinophilic infiltration of the gastrointestinal wall. The peak age of onset is in the third to fourth decade and EGE has a male predominance. 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. Suberosal eosinophilic infiltration may result in development of eosinophilic ascites due to eosinophilic infiltration of the pancreas [61].

2. Hepatobiliary Diseases

Eosinophilic hepatitis develops in response to some medications [62] and to helminth parasites (see Table 2). Marked peripheral eosinophilia has been seen in primary biliary cirrhosis (associated with early disease prior to elevated liver function tests [63]), sclerosing cholangitis, eosinophilic cholangitis and eosinophilic cholecystitis [64]. In 90% of cases, there is no evidence of parasitic infection and the peripheral eosinophilia is commonly drug-related or without a clear etiology [65].

D. Neurologic

Eosinophil associated neurologic diseases are uncommon and include the disorders that cause eosinophilic meningitis [66]. Cerebrospinal fluid eosinophilia can be a significant clue to central nervous system infections, ranging from fungal to helminthic (e.g. coccidioidomycosis or Angiostrongylus cantonensis infection), as well as to adverse drug reactions to NSAIDs or antibiotics.

E. Rheumatologic

Marked peripheral blood eosinophilia is not common in connective tissue diseases, although it has been described in association with dermatomyositis [67], rheumatoid arthritis, systemic sclerosis, and Sjögren's syndrome [68]. 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 (EMS) [69] and toxic oil syndrome are both chronic, persisting multisystem diseases in which marked eosinophilia is present [70]. The toxic oil syndrome was due to ingestion of cooking oil adulterated with denatured rapeseed oil [71] and an outbreak of EMS was associated with ingestion of contaminated L-tryptophan. Since 2005, there has only been one new case of EMS [72].

2. Vasculitis - Churg-Strauss syndrome (CSS), among the vasculitides, is the disorder that is most commonly associated with high grade, persistent eosinophilia [73]. Although mild eosinophilia is common, marked eosinophilia is rare in many of the other vasculitides but has been seen in patients with cutaneous necrotizing
vasculitis, thromboangiitis obliterans with eosinophilia of the temporal arteritis [74]
and in Wegener’s granulomatosis. [75]

F. Cardiac

The principal cardiac sequela of eosinophilic diseases is damage to the endomyocardium
[76]). This can occur with hypersensitivity myocarditis and with eosinophilias associated
with eosinophilic leukemia, sarcomas, carcinomas, and lymphomas [77], with GM-CSF [19]
or IL-2 administration [78], with prolonged drug-induced eosinophilia, and with parasitic
infections [79].

G. Genitourinary

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

Eosinophilic cystitis is a rare clinicopathological condition characterized by transmural
inflammation of the bladder predominantly with eosinophils. 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 [80].

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
Table 5 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
complaints, 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 or CT, 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 evaluations based on the initial studies are usually required to distinguish among the myriad of 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 markedly elevated eosinophil count. 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.

**Acknowledgments**

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**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ABPA</td>
<td>Allergic Bronchopulmonary Aspergillosis</td>
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<td>BENAR</td>
<td>Blood Eosinophilic Non-Allergic Rhinitis</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>CSS</td>
<td>Churg-Strauss Syndrome</td>
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<td>CFA</td>
<td>Circulating Filarial Antigen</td>
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<td>DRESS</td>
<td>Drug rash, eosinophilia, and systemic symptoms</td>
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<td>EE</td>
<td>Eosinophilic Esophagitis</td>
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<td>EGID</td>
<td>Eosinophilic Gastrointestinal Diseases</td>
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<td>EPPER</td>
<td>Eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy</td>
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<td>GVHD</td>
<td>Graft-versus-host disease</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>HES</td>
<td>Hypereosinophilic syndromes</td>
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<td>IgE</td>
<td>Immunoglobulin E</td>
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IL        Interleukin
µl        Microliter
Mf        Microfilariae
PDGFRA    Platelet derived growth factor receptor α
SNRIs     Serotonin and norepinephrine reuptake inhibitors
SSRIs     Selective serotonin reuptake inhibitors

References


Table 1

Conditions associated with marked peripheral blood eosinophilia

<table>
<thead>
<tr>
<th>Infectious Diseases</th>
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<tr>
<td>Parasitic infections primarily with helminths (see Table 2)</td>
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<tr>
<td>Certain fungal infections (Allergic bronchopulmonary aspergillosis, Coccidiomycosis)</td>
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<td>Infestations – Scabies, Myiasis</td>
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<th>Allergic or Atopic Diseases</th>
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<td>Drug hypersensitivity or medication-associated eosinophilias</td>
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<th>Hematologic and Neoplastic Disorders</th>
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<tr>
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<td>Leukemia (Acute myelogenous leukemias most commonly, B cell ALL)</td>
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<td>Lymphomas (particularly Hodgkin’s, T- and B-cell lymphomas)</td>
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### Table 2

**Helminth infections associated with marked and/or persistent eosinophilia**

<table>
<thead>
<tr>
<th>Parasitic Disease</th>
<th>Development and duration of Eosinophilia</th>
<th>Main anatomical site(s)</th>
<th>Diagnosis</th>
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<td><strong>Persistent</strong></td>
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<td>+</td>
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<td>Larvae in CSF</td>
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<td>+</td>
<td>GI</td>
<td>Biopsy</td>
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<td>Hepatobiliary</td>
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<td>Hepatobiliary</td>
<td>Eggs in stool, serology</td>
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<td>+</td>
<td>GI</td>
<td>Eggs in stool</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Lymphatic Filariasis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Loa loa</em></td>
<td>+</td>
<td>Subcutaneous, eye</td>
<td>Mf in blood, worm extracted</td>
</tr>
<tr>
<td><em>Mansonella ozzardi</em></td>
<td>+</td>
<td>Blood</td>
<td>Mf in blood</td>
</tr>
<tr>
<td><em>Mansonella perstans</em></td>
<td>+</td>
<td>Blood, body cavities</td>
<td>Mf in blood, adult in tissue</td>
</tr>
<tr>
<td><em>Mansonella streptocerca</em></td>
<td>+</td>
<td>Skin, subcutaneous tissue</td>
<td>Mf in skin snips</td>
</tr>
<tr>
<td><em>Onchocerca volvulus</em></td>
<td>+</td>
<td>Skin, eye, subcutaneous tissue</td>
<td>Mf in skin snips, adults in nodules</td>
</tr>
<tr>
<td><strong>Tropical pulmonary eosinophilia</strong></td>
<td>+</td>
<td>Lung</td>
<td>Serology</td>
</tr>
<tr>
<td><strong>Gnathostomiasis</strong></td>
<td>+</td>
<td>Soft tissue</td>
<td>Serology, worm in specimen</td>
</tr>
<tr>
<td><strong>Hookworm</strong></td>
<td>+</td>
<td>GI, lung (acutely)</td>
<td>Eggs in stool</td>
</tr>
<tr>
<td><strong>Opisthorchiasis</strong></td>
<td>+</td>
<td>Hepatobiliary</td>
<td>Eggs in stool</td>
</tr>
<tr>
<td><strong>Paragonimiasis</strong></td>
<td>+</td>
<td>Lung, CNS, subcutaneous tissue</td>
<td>Eggs in sputum, BAL, stool</td>
</tr>
<tr>
<td><strong>Schistosomiasis</strong></td>
<td>+</td>
<td></td>
<td>Serology</td>
</tr>
<tr>
<td><em>Schistosoma haematobium</em></td>
<td>+</td>
<td>Urinary tract</td>
<td>Eggs in urine</td>
</tr>
<tr>
<td><em>Schistosoma intercalatum</em></td>
<td>+</td>
<td>Hepatic, GI</td>
<td>Eggs in stool</td>
</tr>
<tr>
<td><em>Schistosoma japonicum</em></td>
<td>+</td>
<td>Hepatic, GI</td>
<td>Eggs in stool</td>
</tr>
<tr>
<td><em>Schistosoma mansoni</em></td>
<td>+</td>
<td>Hepatic, GI</td>
<td>Eggs in stool</td>
</tr>
<tr>
<td><em>Schistosoma mekongi</em></td>
<td>+</td>
<td>Hepatic, GI</td>
<td>Eggs in stool</td>
</tr>
<tr>
<td><strong>Strongyloidiasis</strong></td>
<td>+</td>
<td>GI, lung, skin</td>
<td>Larvae in stool, serology</td>
</tr>
<tr>
<td><strong>Trichinosis</strong></td>
<td>+</td>
<td>GI, muscle</td>
<td>Serology, muscle biopsy</td>
</tr>
<tr>
<td><strong>Visceral larva migrants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Toxocara canis; T catis</em></td>
<td>+</td>
<td>Liver, eye, lung</td>
<td>Serology, larvae in tissue</td>
</tr>
<tr>
<td><em>Baylisascaris procyonis</em></td>
<td>+</td>
<td>CNS, eye</td>
<td>Larvae in specimen</td>
</tr>
</tbody>
</table>

*Semin Hematol.* Author manuscript; available in PMC 2013 April 1.
Table 3
Types of Drug Reactions Associated with Eosinophilia

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Commonly Associated Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Penicillins, cephalosporins</td>
</tr>
<tr>
<td>Soft tissue swelling</td>
<td>GM-CSF, IL-2</td>
</tr>
<tr>
<td>Pulmonary infiltrates</td>
<td>Nonsteroidal anti-inflammatory agents</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>Semisynthetic penicillins, cephalosporins</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Ranitidine</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Semisynthetic penicillins, tetracyclines</td>
</tr>
<tr>
<td>Hypersensitivity vasculitis</td>
<td>Allopurinol, phenytoin</td>
</tr>
<tr>
<td>Gastroenterocolitis</td>
<td>Nonsteroidal anti-inflammatory agents</td>
</tr>
<tr>
<td>Asthma, nasal polyps</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Eosinophilia-myalgia syndrome</td>
<td>L-tryptophan contaminant</td>
</tr>
<tr>
<td>DRESS</td>
<td>Sulfasalazine, hydantoin, carbamazepine, allopurinol, hydrochlorothiazide, cyclosporine, nevaripine</td>
</tr>
</tbody>
</table>
Table 4
Diseases with organ-restricted involvement and marked peripheral eosinophilia

<table>
<thead>
<tr>
<th>Skin and subcutaneous diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic angioedema with eosinophilia</td>
</tr>
<tr>
<td>Eosinophilic cellulitis (Well’s syndrome)</td>
</tr>
<tr>
<td>Eosinophilic panniculitis</td>
</tr>
<tr>
<td>Angiolymphoid Hyperplasia with Eosinophilia (and Kimura’s Disease)</td>
</tr>
<tr>
<td>Eosinophilic Pustular Dermatitis</td>
</tr>
<tr>
<td>Cutaneous Necrotizing Eosinophilic Vasculitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug- and toxin-induced eosinophilic lung diseases</td>
</tr>
<tr>
<td>Helminth associated (Loeffler’s syndrome; tropical pulmonary eosinophilia)</td>
</tr>
<tr>
<td>Chronic eosinophilic pneumonia</td>
</tr>
<tr>
<td>Acute eosinophilic pneumonia</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
</tr>
<tr>
<td>Other vasculitides</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophilic Gastrointestinal Disorders (EGIDs)</td>
</tr>
<tr>
<td>Eosinophilic Esophagitis (EE)</td>
</tr>
<tr>
<td>Eosinophilic Gastroenteritis (EG)</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>Sclerosing cholangitis</td>
</tr>
<tr>
<td>Eosinophilic cholangitis</td>
</tr>
<tr>
<td>Eosinophilic cholecystitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurologic diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophilic meningitis</td>
</tr>
<tr>
<td>Ventriculoperitoneal shunts</td>
</tr>
<tr>
<td>Leukemia or lymphoma with CNS involvement (Hodgkin's)</td>
</tr>
<tr>
<td>Nonsteroidal antiinflammatory drugs</td>
</tr>
<tr>
<td>Antibiotics</td>
</tr>
<tr>
<td>Contrast agents</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rheumatologic diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Churg-Strauss syndrome</td>
</tr>
<tr>
<td>Other vasculitides</td>
</tr>
<tr>
<td>Eosinophilia-myalgia syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity myocarditis</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genitourinary disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug induced interstitial nephritis</td>
</tr>
<tr>
<td>Eosinophilic cystitis</td>
</tr>
</tbody>
</table>
### Table 5

**Approach to evaluation of marked eosinophilia**

<table>
<thead>
<tr>
<th></th>
<th><strong>Eosinophil Determinations</strong> – Verify eosinophil count; estimate or get absolute eosinophil count</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td><strong>Medical History</strong></td>
</tr>
<tr>
<td></td>
<td>• Obtain history of previous eosinophil counts</td>
</tr>
<tr>
<td></td>
<td>• Medical History</td>
</tr>
<tr>
<td></td>
<td>• Review medical history with emphasis placed on disorders known to be associated with eosinophilia including atopic disease</td>
</tr>
<tr>
<td></td>
<td>• Medication History</td>
</tr>
<tr>
<td></td>
<td>• Review recent and current medication history</td>
</tr>
<tr>
<td></td>
<td>• Discontinue any drugs known to be associated with eosinophilia</td>
</tr>
<tr>
<td></td>
<td>• Make a detailed list of all medications (including nutritional supplements, vitamins, herbal preparations)</td>
</tr>
<tr>
<td></td>
<td>• Note any history of allergy to medications</td>
</tr>
<tr>
<td></td>
<td>• Travel/Geographic History</td>
</tr>
<tr>
<td></td>
<td>• Review past history of travel to or residence in other countries</td>
</tr>
<tr>
<td></td>
<td>• Review travel within indigenous country with emphasis on regions where particular eosinophilia-associated infections may be common</td>
</tr>
<tr>
<td></td>
<td>• Occupational/Recreational History</td>
</tr>
<tr>
<td></td>
<td>• Review occupational and recreational exposures</td>
</tr>
<tr>
<td></td>
<td>• Dietary History</td>
</tr>
<tr>
<td></td>
<td>• Review carefully; query dietary indiscretions, nutritional supplements</td>
</tr>
<tr>
<td></td>
<td>• Family History</td>
</tr>
<tr>
<td></td>
<td>• Review whether others in family have eosinophilia suggesting a common exposure or familial nature of disease</td>
</tr>
</tbody>
</table>

**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)
- 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.)